

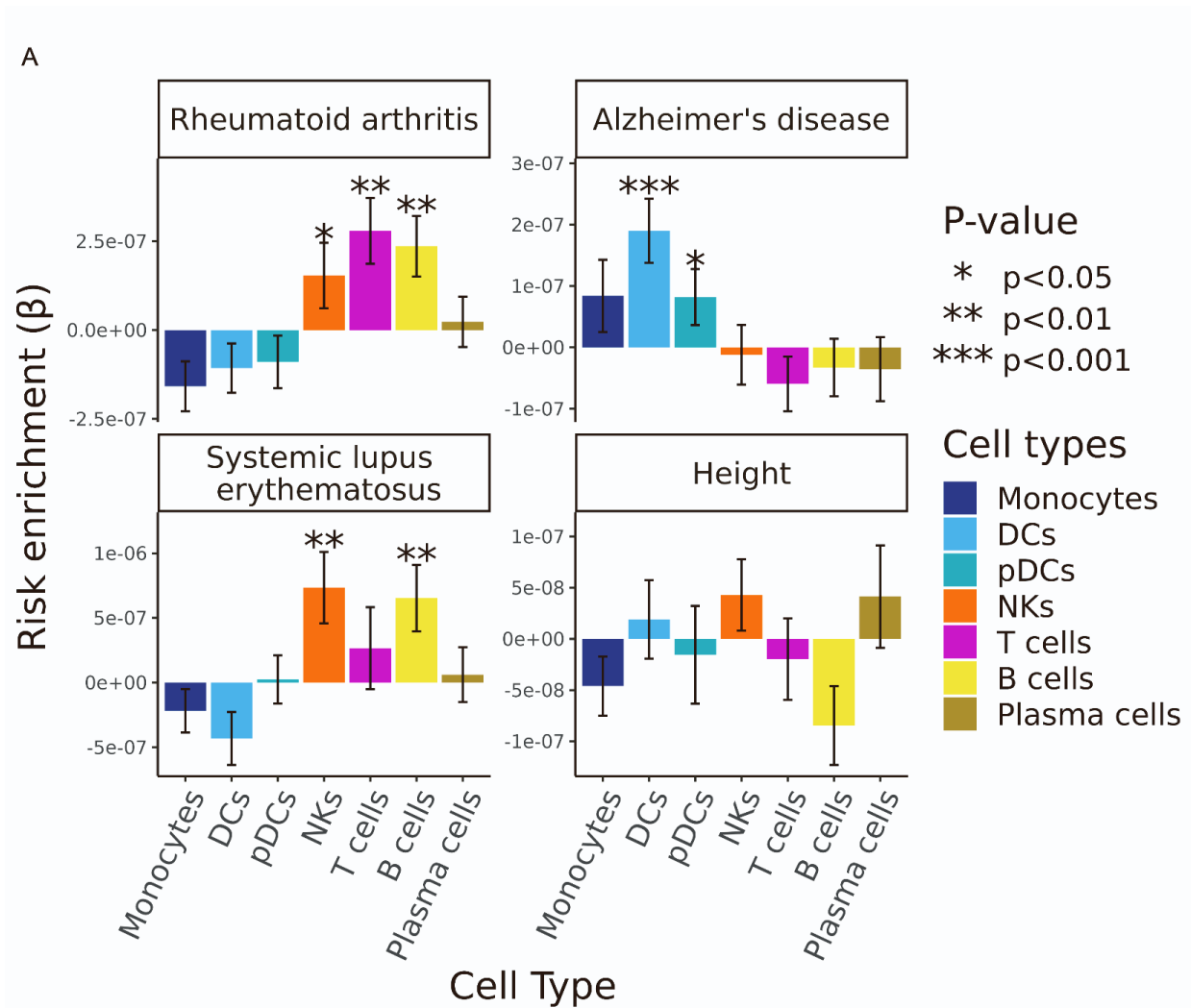
**HGGA, Volume 6**

**Supplemental information**

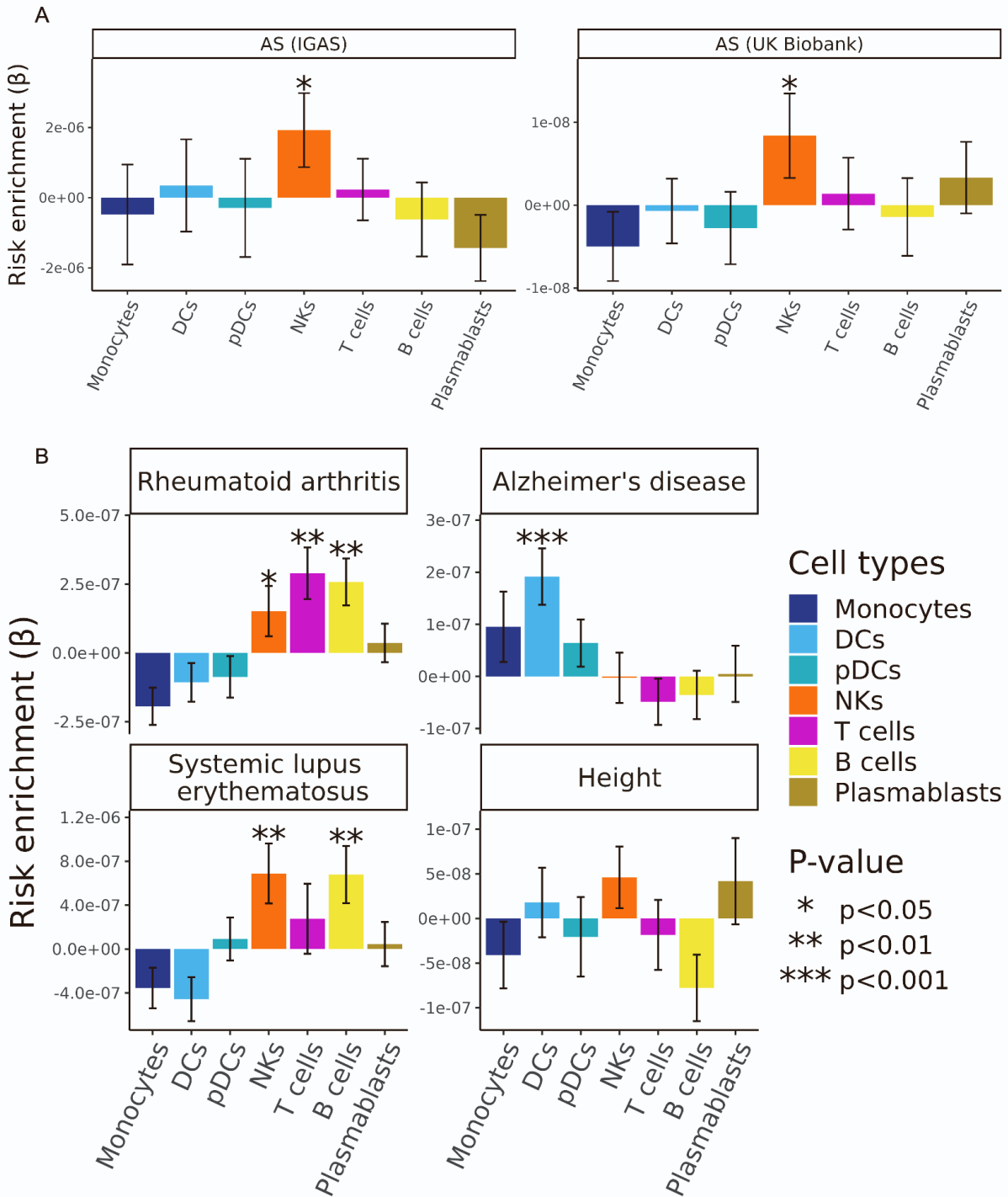
**Functional genomics implicates natural killer  
cells in the pathogenesis  
of ankylosing spondylitis**

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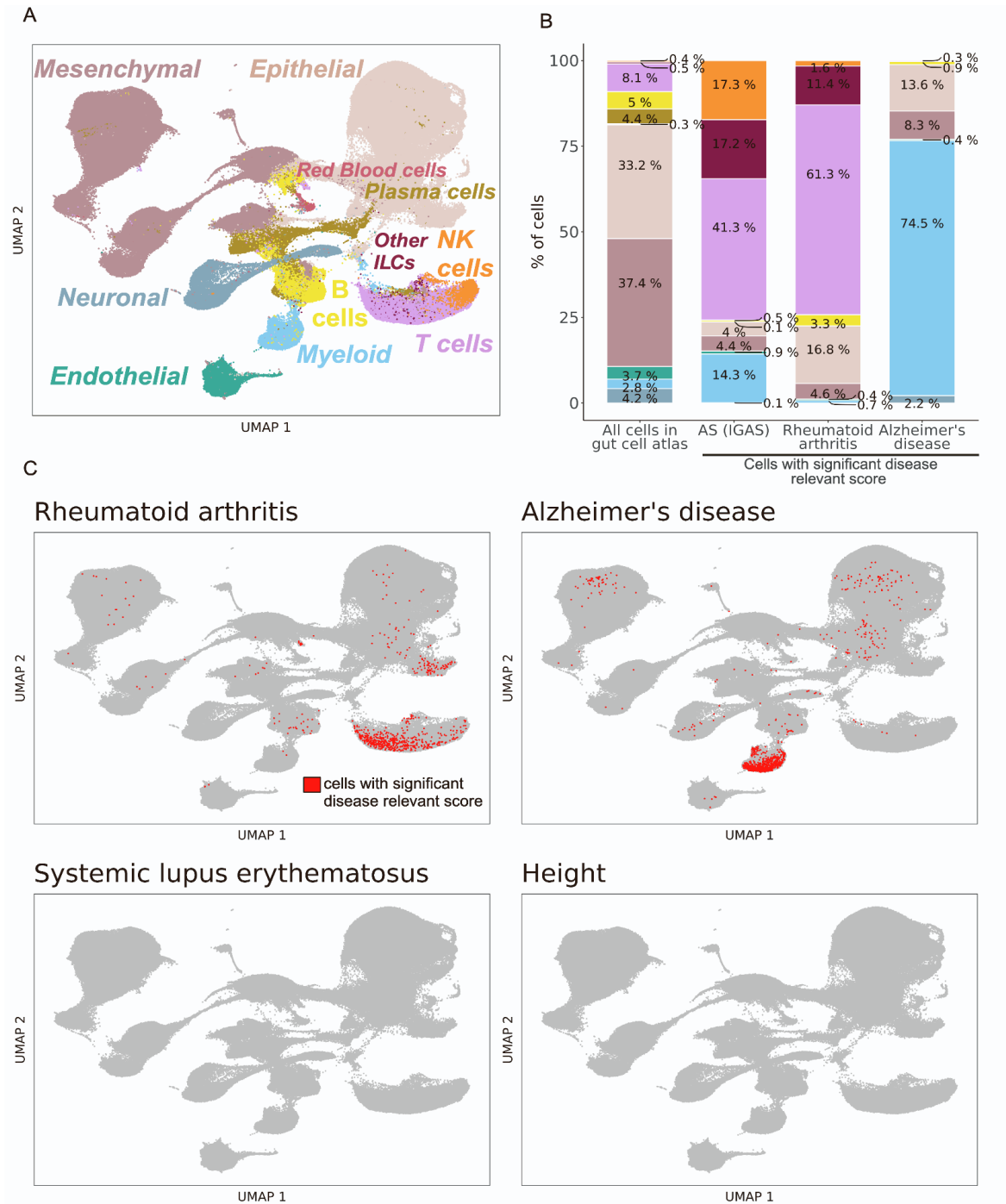
## Supplemental figures



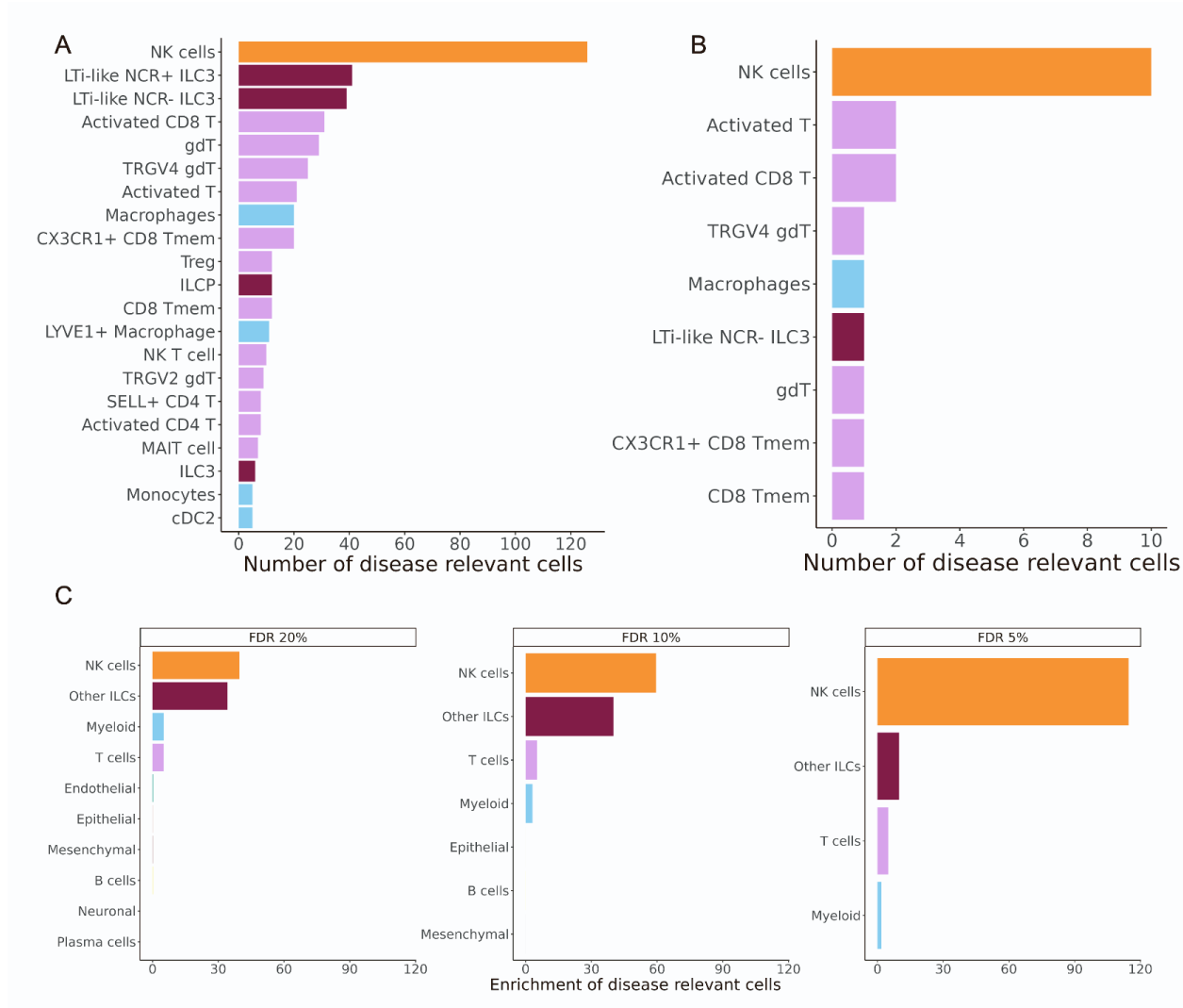
**Figure S1. Heritability enrichment results for control traits. (A)** Bar graphs display the genetic risk enrichment coefficient (y-axis) and standard error for cell-type specific open chromatin accounting for control peaks and baseline annotations. Open chromatin data were taken from the Calderon *et al.* study. Risk enrichment was assessed using GWAS summary statistics for the positive control traits rheumatoid arthritis, Alzheimer's disease, systemic lupus erythematosus, and the negative control trait height. Bars marked with “\*” indicate  $P < 0.05$ , “\*\*” indicates  $P < 0.01$ , “\*\*\*” indicates  $P < 0.001$ .



**Figure S2. Heritability enrichment results for cell type-specific open chromatin controlling for stimulation status.** (A) Bar graphs displaying the AS genetic risk enrichment coefficient  $\beta$  and block jackknife standard error for cell type-specific open chromatin accounting for control peaks and baseline annotations. Here differentially accessibility analysis was performed controlling for donor as a random effect and stimulation status as a fixed effect. Summary statistics from the International Genetics of Ankylosing Spondylitis Consortium (IGAS) (left) and UK Biobank (right) GWAS were used. (B) Same as (A) but for control traits. Bars marked with “\*” indicate  $P < 0.05$ , “\*\*” indicates  $P < 0.01$ , “\*\*\*” indicates  $P < 0.001$ .



**Figure S3. Single-cell disease relevant score results for control traits.** (A) Visualization of the Space-Time Gut Cell Atlas using Uniform Manifold Approximation and Projection (UMAP) on the top 20 principal components from 1,997 variable genes from the single-cell RNA-seq expression matrix. Cells are colored based on the coarse cell type annotations from the Space-Time Gut Cell Atlas. (B) Barplots shows the cell type proportions within the whole Space-Time Gut Cell Atlas and within cells with significant disease relevant score (20% FDR) for AS (using IGAS GWAS), Alzheimer's disease (AD) and rheumatoid arthritis (RA). (C) Same UMAP visualization as in A, where cells with significant scDRS score (20% FDR) are colored in red and non-significant cells are colored in gray, for each control trait.



**Figure S4. Single-cell disease relevant score results at different FDR thresholds.** Bar graph showing the number of significant scDRS cells for each cell type using the fine-grained annotations from the Space-Time Gut Cell Atlas, at 10% FDR (**A**) and 5% FDR (**B**). (**C**) Bar graph showing enrichment of scDRS significant cells per cell type (cell-type percent within scDRS significant cells over cell-type percent in whole dataset) at different FDR thresholds.

## Supplemental tables

GENE_ID	GENE_NAME	beta	Std	x1_t	p_value	fdr
ENSG00000178562.17	CD28	-3.512	0.276	-12.724	1.19E-20	2.98E-18
ENSG00000106952.7	TNFSF8	-2.796	0.219	-12.751	3.26E-20	7.35E-18
ENSG00000122224.17	LY9	-0.903	0.090	-10.088	1.16E-15	9.98E-14
ENSG00000180871.7	CXCR2	2.997	0.297	10.079	1.70E-15	1.41E-13
ENSG00000148400.9	NOTCH1	1.435	0.145	9.915	4.27E-15	3.20E-13
ENSG00000143226.13	FCGR2A	1.987	0.246	8.065	7.93E-12	2.64E-10
ENSG00000122223.12	CD244	2.742	0.338	8.124	8.58E-12	2.83E-10
ENSG00000005844.17	ITGAL	1.064	0.134	7.916	2.07E-11	6.30E-10
ENSG00000163297.16	ANTXR2	-1.222	0.201	-6.066	3.88E-08	5.07E-07
ENSG00000185651.14	UBE2L3	0.553	0.093	5.967	7.65E-08	9.25E-07
ENSG00000197536.10	C5orf56	0.914	0.156	5.869	1.18E-07	1.36E-06
ENSG00000187118.12	CMC1	2.431	0.438	5.551	3.38E-07	3.42E-06
ENSG00000020633.18	RUNX3	1.367	0.246	5.556	3.51E-07	3.54E-06
ENSG00000108622.10	ICAM2	0.476	0.088	5.391	7.65E-07	6.99E-06
ENSG00000100376.11	FAM118A	-0.669	0.125	-5.362	8.62E-07	7.76E-06
ENSG00000067182.7	TNFRSF1A	0.845	0.170	4.965	4.14E-06	3.07E-05
ENSG00000175354.18	PTPN2	0.356	0.076	4.689	1.06E-05	7.07E-05
ENSG00000160791.13	CCR5	-2.094	0.449	-4.665	1.18E-05	7.75E-05
ENSG00000118503.14	TNFAIP3	-1.143	0.296	-3.867	2.30E-04	1.00E-03
ENSG00000141279.15	NPEPPS	0.378	0.099	3.827	2.62E-04	1.12E-03
ENSG00000140030.5	GPR65	1.179	0.311	3.788	2.82E-04	1.19E-03
ENSG00000164307.12	ERAP1	0.364	0.096	3.795	2.94E-04	1.24E-03
ENSG00000163599.14	CTLA4	-1.556	0.414	-3.760	3.49E-04	1.44E-03
ENSG00000105397.13	TYK2	0.490	0.137	3.583	5.63E-04	2.17E-03
ENSG00000111252.10	SH2B3	0.450	0.134	3.360	1.16E-03	4.00E-03
ENSG00000128604.18	IRF5	1.055	0.326	3.238	1.71E-03	5.48E-03
ENSG00000145996.11	CDKAL1	0.241	0.074	3.262	1.81E-03	5.72E-03
ENSG00000065675.14	PRKCQ	0.288	0.094	3.075	2.82E-03	8.31E-03
ENSG00000143365.16	RORC	-1.342	0.442	-3.037	3.15E-03	9.09E-03
ENSG00000119772.16	DNMT3A	-0.508	0.169	-3.009	3.46E-03	9.82E-03
ENSG00000138311.15	ZNF365	0.453	0.156	2.906	4.98E-03	1.32E-02
ENSG00000160712.12	IL6R	-0.846	0.301	-2.809	6.10E-03	1.56E-02

ENSG00000161847.13	RAVER1	0.448	0.176	2.550	1.26E-02	2.83E-02
ENSG00000164308.16	ERAP2	0.210	0.083	2.535	1.31E-02	2.93E-02
ENSG00000112182.14	BACH2	-0.723	0.292	-2.476	1.57E-02	3.37E-02

**Table S2. Differential expression analysis comparing NK cells with the six T cell subsets**

Gene	beta_NK vsTcells_bulkRNA-seq	Std_NKvsTcells_bulkRNA-seq	p_value_NKvsTcells_bulkRNA-seq	fdr_NKvsTcells_bulkRNA-seq	beta_NKvsImmuneGutCells_scRNA-seq	Std_NKvsImmuneGutCells_scRNA-seq	p_value_NKvsImmuneGutCells_scRNA-seq	fdr_NKvsImmuneGutCells_scRNA-seq
FCGR3A	5.5295	0.7807	7.14E-10	1.47E-08	3.7205	0.4759	4.49E-13	1.62E-12
SLAMF7	2.0193	0.5281	2.78E-04	1.18E-03	1.2402	0.3299	2.33E-04	4.02E-05
TBX21	1.9179	0.3242	9.77E-08	1.16E-06	3.3621	0.2877	9.41E-24	3.06E-22
APOBR	1.5098	0.1518	3.37E-15	2.61E-13	1.9559	0.3863	1.00E-06	2.83E-07
NOTCH1	1.4352	0.1448	4.27E-15	3.20E-13	1.4507	0.2324	2.99E-09	1.79E-09
RUNX3	1.3674	0.2461	3.51E-07	3.54E-06	1.9215	0.3934	2.26E-06	5.87E-07
IL18R1	1.3058	0.4360	3.56E-03	1.01E-02	2.3512	0.4063	3.46E-08	1.45E-08
GPR65	1.1787	0.3111	2.82E-04	1.19E-03	2.1500	0.3862	9.21E-08	3.40E-08

**Table S3. AS-associated genes that are upregulated in NK cells at 5% FDR in peripheral blood lymphocytes and immune cell types from the gut.**