**Fine-mapping and molecular characterisation of primary sclerosing cholangitis genetic risk loci**

**Short title:** Genetic characterisation of PSC

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**Supplementary Information**

**Supplementary Tables**

**Supplementary Table 1:** Characteristics of the PSC-specific eQTL map study cohort according to disease group.

| | PSC-UC (n=42) | UC (n=32) |
|---|---|---|
| **Gender (% Male)** | 81 | 69 |
| **Mean Age (Range)** | 50 (17-86) | 52 (38-75) |
| **UDCA use (%)** | 71 | 0 |
| **5-ASA use (%)** | 66 | 90 |
| **Azathioprine use (%)** | 10 | 21 |

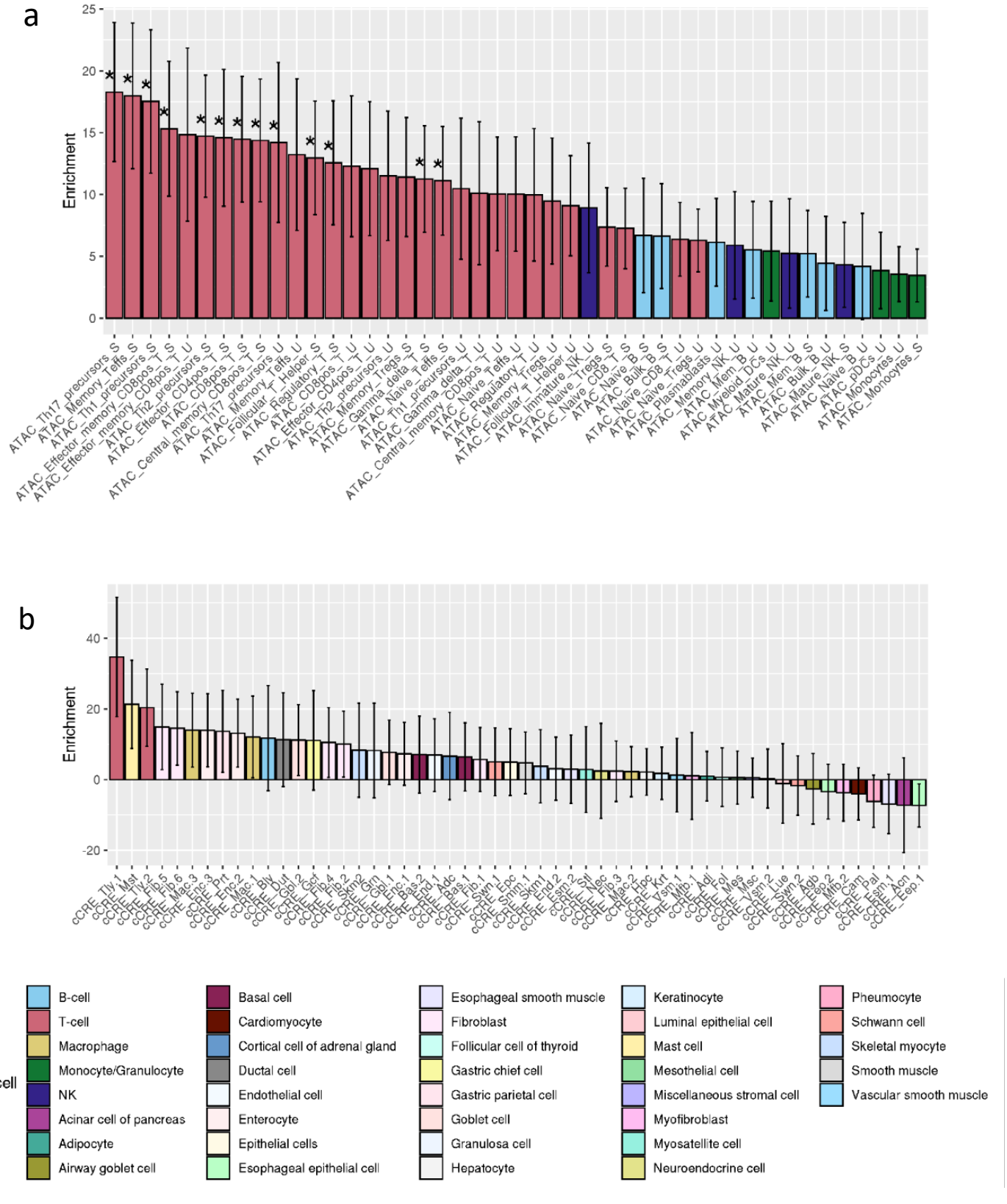
**Supplementary Table 2:** Results of colocalisation between T-cell eQTLs mapped in PSC-UC patients and GWAS risk loci for Ulcerative colitis (UC), Crohn's disease (CD), Rheumatoid arthritis (RhA) and Type 1 Diabetes (T1DM). Beta and two-sided test p-values were estimated through linear regression via QTLtools.

| Chr | GWAS SNP | Disease | eGene | Cell type | PP4 | eQTL Beta | eQTL p-val |
|---|---|---|---|---|---|---|---|
| 1 | rs3180018 | UC | *GBAP1* | T-regulatory | 0.91 | -0.74 | 3.88E-04 |
| | | | | T-memory | 0.98 | -1.01 | 1.30E-10 |
| | | | | CD4+CCR9- | 0.98 | -0.92 | 2.01E-07 |
| | | | | CD4+CCR9+ | 0.98 | -0.91 | 7.66E-07 |
| | | UC | *THBS3* | CD4+CCR9- | 0.98 | 0.88 | 5.59E-07 |
| 1 | rs2317230 | RhA | *FCRL3* | CD8+CCR9- | 0.93 | 0.82 | 3.29E-04 |
| 5 | rs7731626 | RhA | *IL6ST* | T-regulatory | 0.97 | -0.86 | 2.08E-04 |
| | | | | T-memory | 0.90 | -0.81 | 6.16E-04 |
| | | RhA | *ANKRD55* | T-memory | 1.00 | -1.00 | 5.94E-07 |
| | | | | CD4+CCR9- | 1.00 | -0.95 | 9.63E-06 |
| | | | | CD4+CCR9+ | 0.86 | -0.86 | 1.20E-03 |
| 7 | rs4728142 | UC | *IRF5* | T-memory | 0.86 | 0.77 | 4.71E-05 |
| 11 | rs663743 | PSC | *AP003774.1* | T-regulatory | 0.99 | 0.98 | 7.27E-06 |
| | | | | T-memory | 0.95 | 1.07 | 1.35E-07 |
| | | | | CD4+CCR9- | 0.95 | 0.96 | 1.83E-05 |
| 11 | rs968567 | RhA | *FADS1* | T-regulatory | 0.89 | 1.51 | 1.38E-07 |
| | | RhA | *FADS2* | T-regulatory | 0.98 | 1.60 | 2.01E-09 |
| | | | | T-memory | 1.00 | 1.58 | 2.23E-09 |
| | | | | CD4+CCR9- | 0.99 | 1.58 | 5.40E-09 |
| | | | | CD4+CCR9+ | 0.98 | 1.47 | 2.82E-07 |
| | | | | CD8+CCR9- | 0.96 | 1.56 | 9.58E-09 |
| | | | | CD8+CCR9+ | 0.95 | 1.46 | 4.22E-07 |
| 12 | rs4760341 | T1DM | *SUOX* | T-regulatory | 0.80 | -0.71 | 1.06E-03 |
| 14 | rs941576 | T1DM | *WARS* | T-regulatory | 0.85 | 1.07 | 3.90E-05 |
| | | | | T-memory | 0.93 | 1.19 | 1.46E-07 |
| | | | | CD4+CCR9- | 0.80 | 1.35 | 2.41E-08 |
| | | | | CD8+CCR9- | 0.97 | -1.03 | 1.37E-05 |
| 19 | rs4802307 | CD | *PPP5C* | T-memory | 0.85 | -0.92 | 1.63E-06 |
| | | | | CD4+CCR9- | 0.86 | -0.99 | 2.38E-08 |
| | | | | CD8+CCR9- | 0.83 | -0.82 | 1.48E-04 |
| 21 | rs1893592 | PSC | *UBASH3A* | T-mempry | 0.91 | 0.93 | 4.83E-04 |
| 22 | rs909685 | RhA | *SYNGR1* | CD8+CCR9+ | 0.98 | 1.14 | 7.15E-04 |

*UC; Ulcerative colitis, RhA; rheumatoid arthritis, T1DM; Type 1 diabetes mellitus, CD; Crohn's disease, PSC; Primary sclerosing cholangitis.*

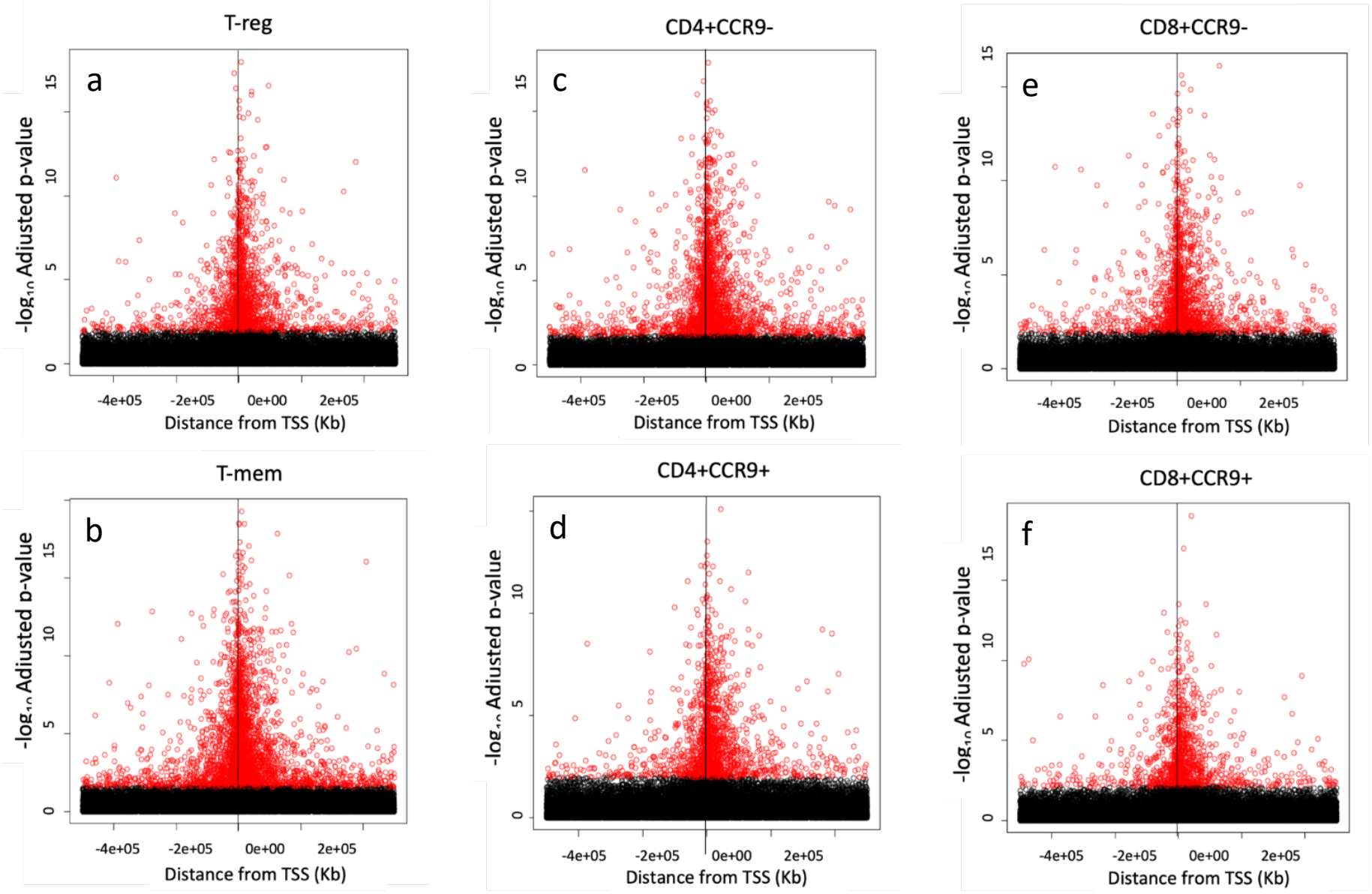
**Supplementary Figures**

**Supplementary Figure 1: Enrichment analyses results.**
The y axis shows the enrichment (Prop.h2/Prop.SNPs) per cell type, whereas the y axis indicates the cell types. Results have been coloured by cell type, grouping different cell types in a broader category (ie, Th17 precursors, Memory Teff etc into T-cell). Panel a): open chromatin regions (ATAC-seq) from immune cell types under resting (_U) and stimulated (_S) conditions[1]. Panel b): cis candidate regulatory elements (cCRE) inferred from single cell ATAC-seq from 30 adult tissues[2]. qvalues were estimated from the LDSC two sided test p-values to nominate significant results (qvalue < 0.05), labelled with an asterisk in the plot. Bars represent the enrichment standard error.

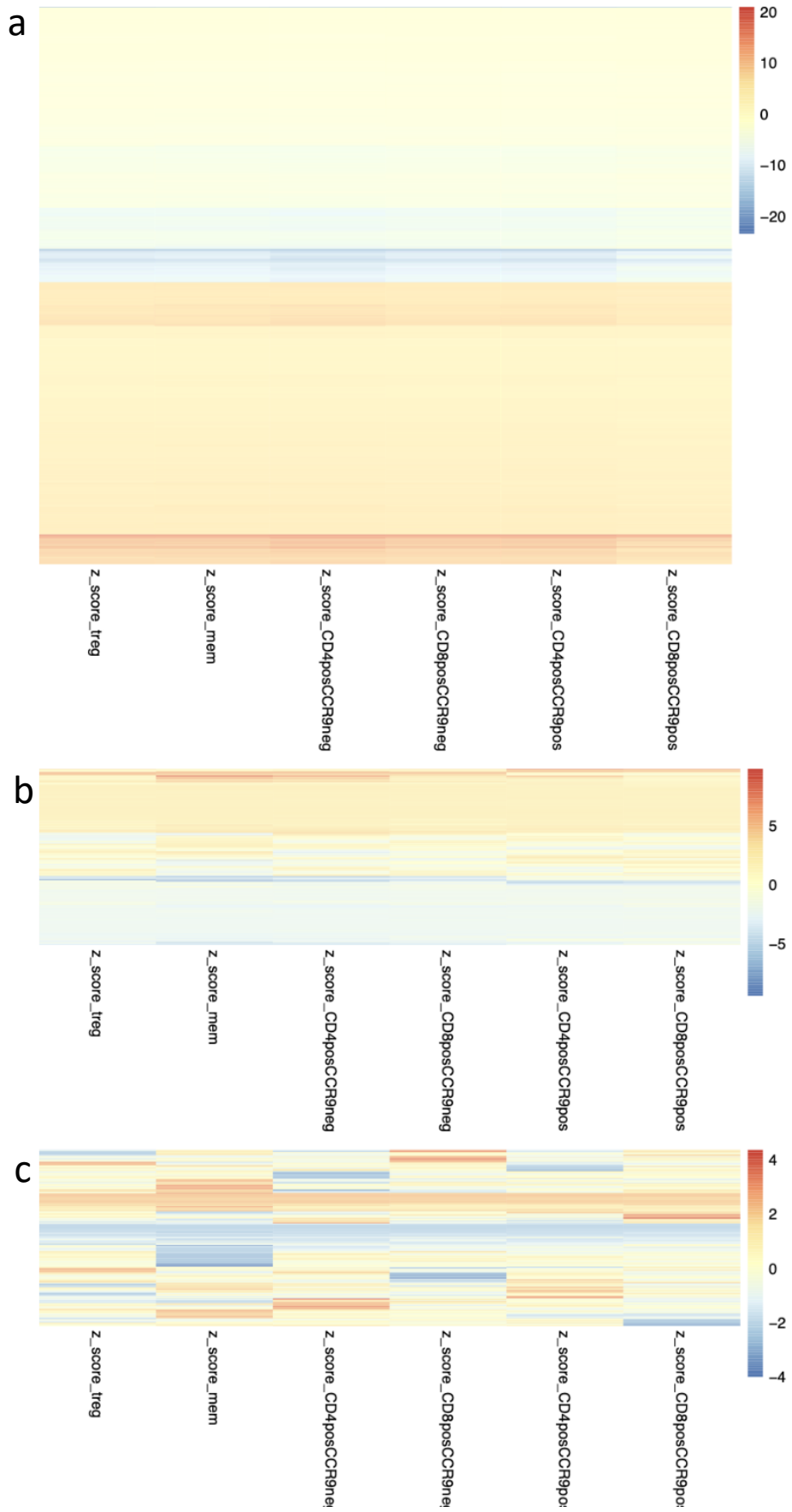


**Supplementary Figure 2: Distance to between eQTL and transcription start site**

Distance from transcription start site (TSS) for each significant eQTL (coloured red for those less than 5% FDR) per cell type. Panel a); T-regulatory cells, b); T-memory cells, c); CD4+CCR9- T-cells, d); CD4+CCR9+ T-cells, e); CD8+CCR9- T-cells, f); CD8+CCR9+T-cells.

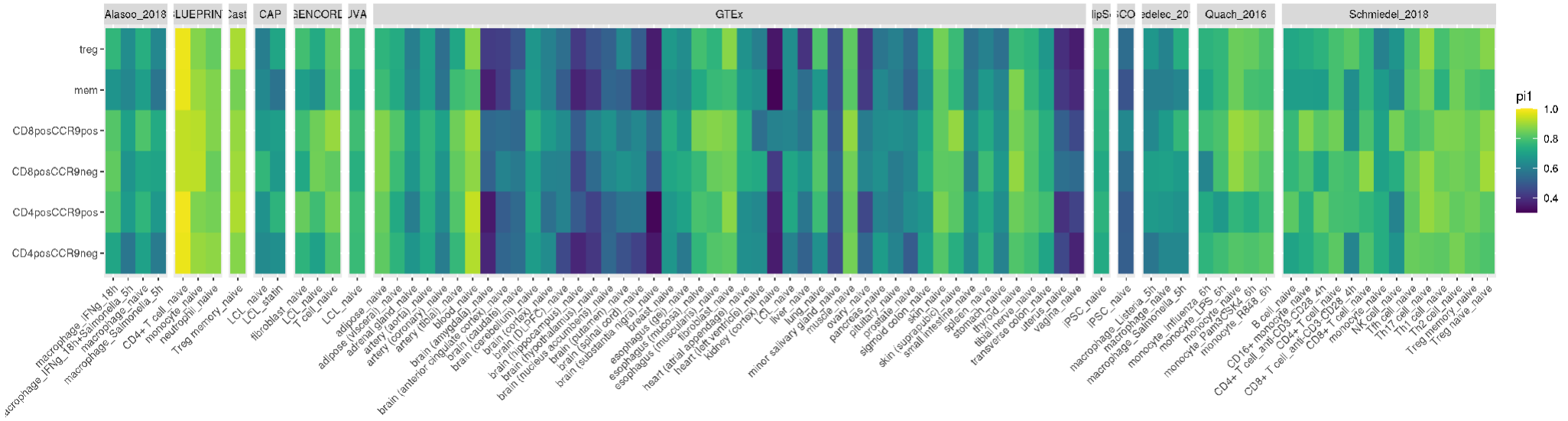


**Supplementary Figure 3: Posterior z-scores of significant eGenes as identified by mashR**
Posterior z-scores of significant eGenes as identified by mashR (lfdr <0.05 in at least one PSC T cell subtype; N = 10,459), grouped by (i) significant eGenes shared across all cell types (panel a), N = 9,176); (ii), significant eGenes in two or more cell types, but not in all cell types all (panel b), N = 794); and (iii) those condition specific eGenes, only significant in one cell type (panel c), N = 489).



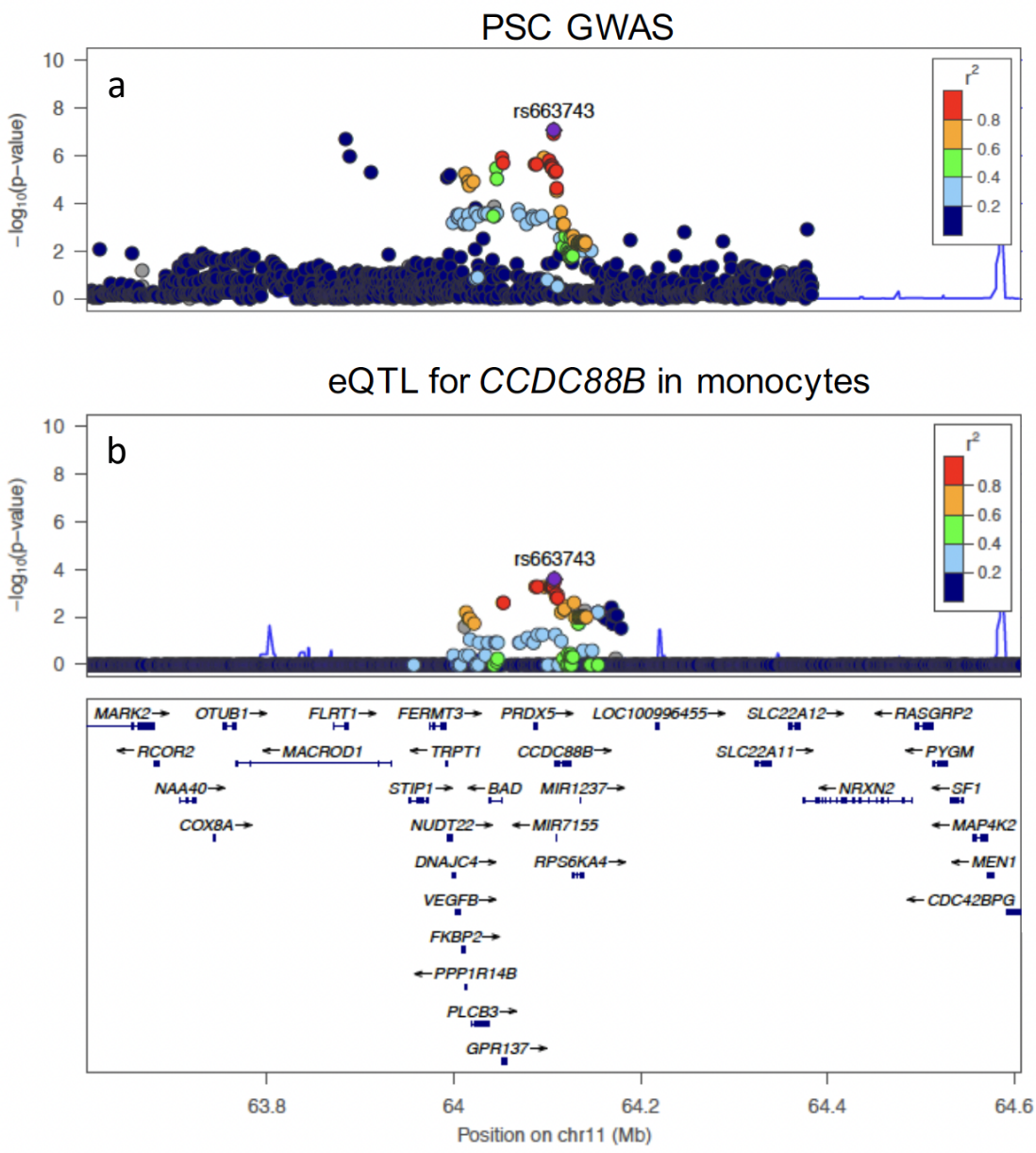
**Supplementary Figure 4: Replication of significant eGenes in each PSC T-cell subtype**

Proportion of significant eGenes in each PSC T cell subtypes (eQTL qvalue < 0.05; estimated from the two-sided p-values derived by QTLtools) replicated in external datasets (pi1)



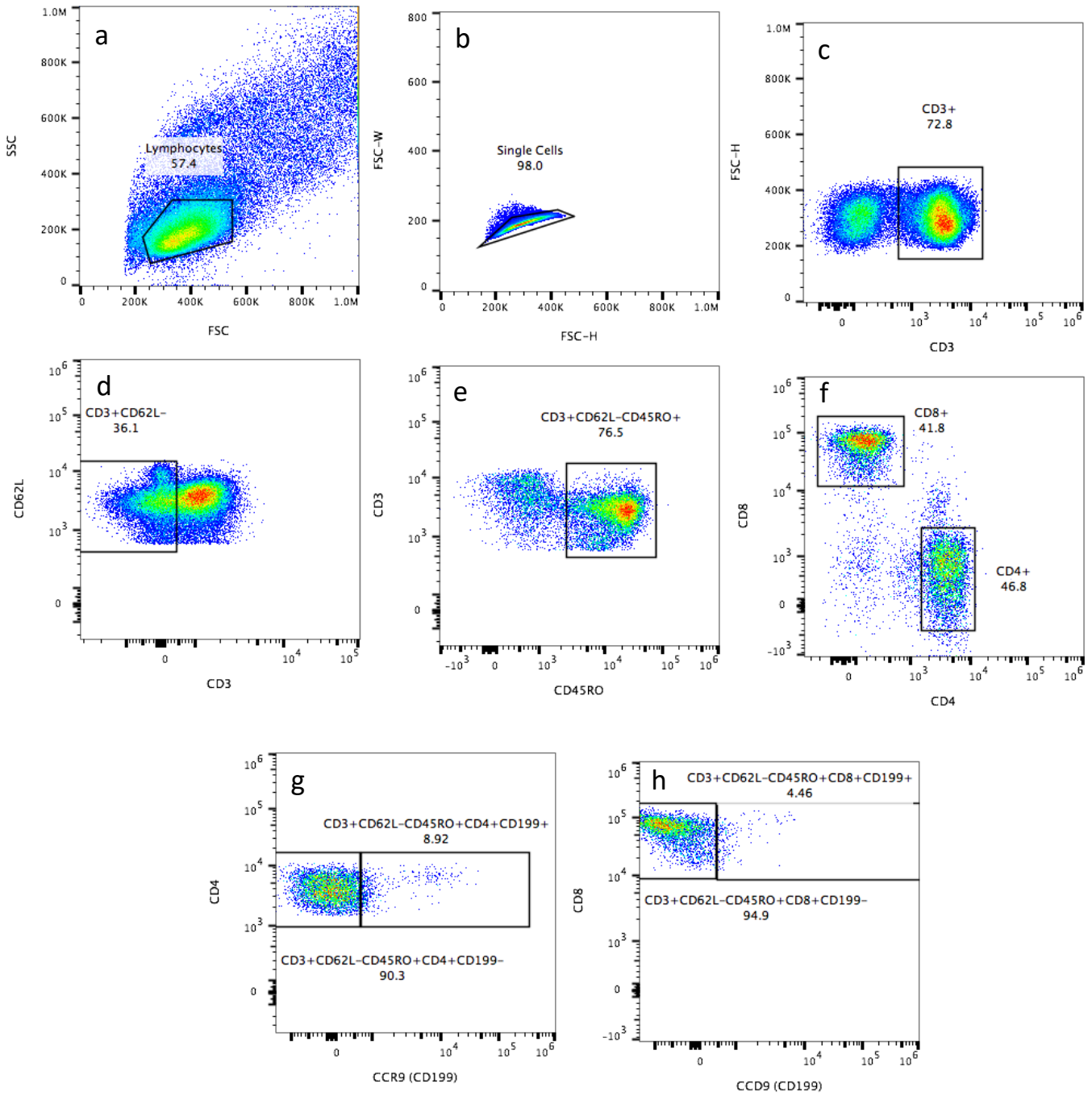
**Supplementary Figure 5: Colocalisation results for CCDC88B Chr11 region**

CCDC88B Chr11: regional association plot for a) PSC GWAS data (NCases= 4,796; NCtr= 19,955) and b) colocalising (PP4$\geq 0.8$) eQTL data for CCDC88B in monocytes (N = 194). The most-likely causal variant (rs663743 PP=0.85) is shown in purple. LD information is calculated from PSC GWAS data[3]

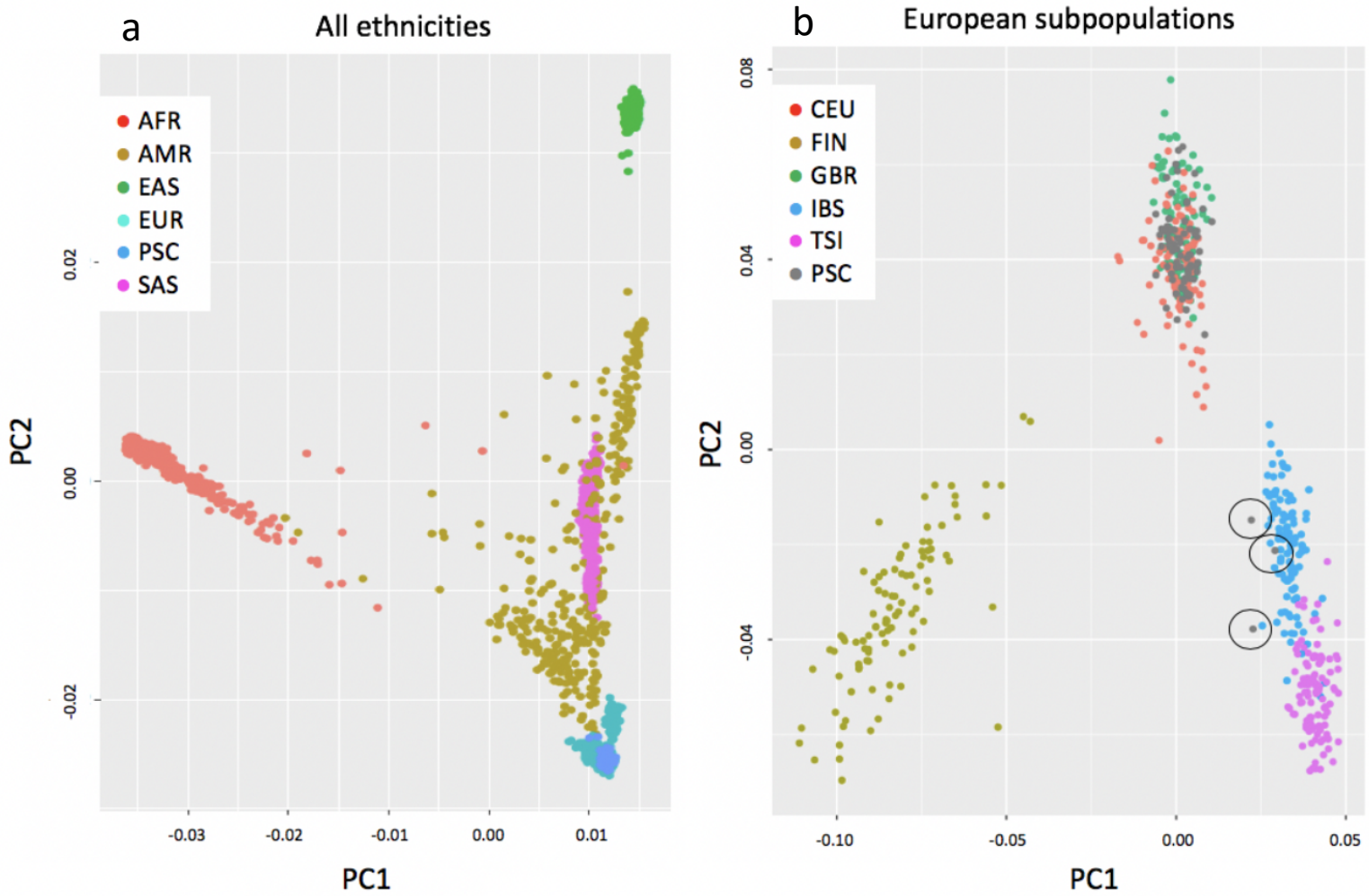


**Supplementary Figure 6: FACS gating strategy for PSC eQTL maps**

FACS gating strategy used for PSC specific T-cell separation with sequential sorting from left to right. Panel a); Forward versus side scatter, b); forward scatter height versus width, c); CD3+ versus forward scatter height, d); CD3 versus CD62L, e); CD45RO versus CD3+, f); CD4 versus CD8, g); CCR9 versus CD4.



**Supplementary Figure 7: Principal component analysis of study samples compared to 1000 Genomes.**
Principal component analysis of study samples compared to 1000 Genomes samples of known ethnicity using a pruned set of 62,805 independent variants with an r2<0.2 and MAF>0.01. Panel a) shows PSC samples compared to all ethnicities, and panel b) shows European subpopulations. Three individuals were of Southern European/Iberian ethnicity, highlighted on the Figure. All samples from individuals of Northern and Southern European ethnicity were retained for further analysis.



**Supplementary References**

1**.** Calderon D, Nguyen MLT, Mezger A, et al. Landscape of stimulation-responsive chromatin across diverse human immune cells. Nat Genet 2019;51:1494-1505.

2. Zhang K, Hocker JD, Miller M, et al. A single-cell atlas of chromatin accessibility in the human genome. Cell 2021;184:5985-6001 e19.

3. Maurano MT, Humbert R, Rynes E, et al. Systematic localization of common disease-associated variation in regulatory DNA. Science 2012;337:1190-5