

# Polygenic enrichment distinguishes disease associations of individual cells in single-cell RNA-seq data

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# 1 Polygenic enrichment distinguishes disease 2 associations of individual cells in single-cell 3 RNA-seq data

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## 38 ABSTRACT

Gene expression at the individual cell-level resolution, as quantified by single-cell RNA-sequencing (scRNA-seq), can provide unique insights into the pathology and cellular origin of diseases and complex traits. Here, we introduce single-cell Disease Relevance Score (*s*cDRS), an approach that links scRNA-seq with polygenic risk of disease at individual cell resolution; *s*cDRS identifies individual cells that show excess expression levels for genes in a disease-specific gene set constructed from GWAS data. We determined via simulations that *s*cDRS is well-calibrated and powerful in identifying individual cells associated to disease. We applied *s*cDRS to GWAS data from 74 diseases and complex traits (average  $N=341K$ ) in conjunction with 16 scRNA-seq data sets spanning 1.3 million cells from 31 tissues and organs. At the cell type level, *s*cDRS broadly recapitulated known links between classical cell types and disease, and also produced novel biologically plausible findings. At the individual cell level, *s*cDRS identified subpopulations of disease-associated cells that are not captured by existing cell type labels, including subpopulations of CD4<sup>+</sup> T cells associated with inflammatory bowel disease, partially characterized by their effector-like states; subpopulations of hippocampal CA1 pyramidal neurons associated with schizophrenia, partially characterized by their spatial location at the proximal part of the hippocampal CA1 region; and subpopulations of hepatocytes associated with triglyceride levels, partially characterized by their higher ploidy levels. At the gene level, we determined that genes whose expression across individual cells was correlated with the *s*cDRS score (thus reflecting co-expression with GWAS disease genes) were strongly enriched for gold-standard drug target and Mendelian disease genes.

## 40 Introduction

41 The mechanisms through which risk variants identified by genome-wide association studies (GWASs) impact critical tissues and  
42 cell types are largely unknown<sup>1,2</sup>; identifying these tissues and cell types is central to our understanding of disease etiologies  
43 and will inform efforts to develop therapeutic treatments<sup>3</sup>. Single-cell RNA sequencing (scRNA-seq) has emerged as the tool  
44 of choice for measuring gene abundances at single-cell resolution<sup>4,5</sup>, providing an increasingly clear picture of which genes are  
45 active in which cell types and also being able to identify novel cell populations within classically defined cell types. Integrating  
46 scRNA-seq with GWAS data offers the potential to identify critical tissues, cell types, and cell populations through which  
47 GWAS risk variants impact disease<sup>6-8</sup>, thus providing finer resolution than studies using bulk transcriptomic data<sup>9-12</sup>.

48 Previous studies integrating scRNA-seq with GWAS have largely focused on predefined cell type annotations (e.g., classical  
49 cell types defined using known marker genes), aggregating cells from the same cell type followed by evaluating overlap of the  
50 cell type-level information with GWAS<sup>6-8</sup>. However, this approach overlooks the considerable heterogeneity within cell types  
51 that has been reported in studies of scRNA-seq data alone<sup>13-18</sup>; the underlying methods (e.g., Seurat cell-scoring function<sup>15</sup>,  
52 Vision<sup>16</sup>, and VAM<sup>18</sup>) have sought to explain transcriptional heterogeneity in scRNA-seq data by scoring cells based on  
53 predefined gene sets such as pathway gene sets, but do not consider polygenic disease risk from GWAS and generally do not  
54 provide individual cell-level association p-values. Integrating information from scRNA-seq data at fine-grained resolution (e.g.,  
55 individual cells) with polygenic signals from disease GWAS has considerable potential to produce new biological insights.

56 Here, we introduce *single-cell Disease Relevance Score* (*s*cDRS), a method to evaluate polygenic disease enrichment of  
57 individual cells in scRNA-seq data. *s*cDRS assesses whether a given cell has excess expression levels across a set of putative  
58 disease genes derived from GWAS, using an appropriately matched empirical null distribution to estimate well-calibrated  
59 p-values. To our knowledge, *s*cDRS is the first method to associate individual cells in scRNA-seq data to disease GWAS. We  
60 performed extensive simulations to assess the calibration and power of *s*cDRS. We then applied *s*cDRS to 74 diseases and  
61 complex traits (average GWAS  $N=341K$ ) in conjunction with 16 scRNA-seq data sets (including the Tabula Muris Senis  
62 (TMS) mouse cell atlas<sup>19</sup>), assessing cell type-disease associations and within-cell type association heterogeneity, including  
63 heterogeneity of T cells in their association with inflammatory bowel disease (IBD) and other autoimmune diseases, neurons in  
64 their association with schizophrenia (SCZ) and other brain-related diseases/traits, and hepatocytes in their association with  
65 triglyceride levels (TG) and other metabolic traits; we analyzed a broader set of scRNA-seq data sets to provide validation  
66 across species (human vs. mouse) and across sequencing platforms, and to include scRNA-seq data sets with experimentally  
67 determined cell types and cell states.

## 68 Results

### 69 Overview of methods

70 *s*cDRS integrates gene expression profiles from scRNA-seq with polygenic disease information from GWAS to associate  
71 individual cells to disease, by assessing the excess expression of putative disease genes from GWAS. *s*cDRS consists of three  
72 steps (Fig. 1, Methods, and Supp. Note). First, *s*cDRS constructs a set of putative disease genes from GWAS summary statistics  
73 using MAGMA<sup>20</sup>, an existing gene scoring method (top 1,000 MAGMA genes; see Methods for other choices evaluated).  
74 Second, *s*cDRS quantifies the aggregate expression of the putative disease genes in each cell to generate cell-specific *raw*

75 *disease scores*; to maximize power, each putative disease gene is inversely weighted by its gene-specific technical noise level  
76 in the single-cell data, estimated via modeling the mean-variance relationship across genes<sup>18,21</sup> (alternative choices of cell  
77 scores are evaluated in Methods). To determine statistical significance, *sCDRS* also generates 1,000 sets of cell-specific *raw*  
78 *control scores* at Monte Carlo (MC) samples of matched control gene sets (matching the gene set size, mean expression, and  
79 expression variance of the putative disease genes); cell-specific MC p-values are defined as the proportion of the 1,000 raw  
80 control scores for a given cell exceeding the raw disease score for that cell<sup>22</sup>. Third, *sCDRS* approximates the ideal MC  
81 p-values (obtained using  $\gg 1,000$  MC samples) by pooling control scores across cells. Specifically, it normalizes the raw  
82 disease score and raw control scores for each cell (producing the *normalized disease score* and *normalized control scores*), and  
83 then computes cell-level p-values based on the empirical distribution of the pooled normalized control scores across all control  
84 gene sets and all cells; this approximation relies on the assumption that the raw control score distributions (across the 1,000  
85 control gene sets, for each cell) are from the same parametric distribution (e.g., normal distributions with different parameters,  
86 such that the normalization procedure can align these distributions across cells), a reasonable assumption when the disease gene  
87 set is neither too small nor too large (e.g.,  $>50$  genes and  $<20\%$  of all genes; Methods). Importantly, *sCDRS* does not use cell  
88 type or other cell-level annotations, although these annotations can be of value when interpreting its results.

89 *sCDRS* outputs individual cell-level p-values, normalized disease scores, and 1,000 sets of normalized control scores  
90 (referred to as “disease scores” and “control scores” in the rest of the paper) that can be used for a wide range of downstream  
91 applications (Methods). Here, we focus on three downstream analyses. First, we perform *cell type-level* analyses to associate  
92 predefined cell types to disease and assess heterogeneity in association to disease across cells within a predefined cell type.  
93 Second, we perform *individual cell-level* analyses to associate individual cells to disease and correlate individual cell-level  
94 variables to the *sCDRS* disease score. Third, we perform *gene-level* analyses to prioritize disease-relevant genes whose  
95 expression is correlated with the *sCDRS* disease score, reflecting co-expression with genes implicated by disease GWAS. In  
96 the cell type-level analyses, we compute a single MC p-value across the focal set of cells by comparing the diseases scores to  
97 the 1,000 sets of control scores (Methods), avoiding the assumption that the cells are independent—a strong assumption in  
98 scRNA-seq analyses, e.g., when analyzing cells in the same cluster that are dependent due to the clustering process.

99 We analyzed publicly available GWAS summary statistics of 74 diseases and complex traits (average  $N=341K$ ; Supp. Table  
100 1) in conjunction with 16 scRNA-seq or single-nucleus RNA-seq (snRNA-seq) data sets spanning 1.3 million cells from 31  
101 tissues and organs from mouse (*mus musculus*) and human (*homo sapiens*) (Supp. Table 2; 15 out of 16 data sets publicly  
102 available; Data Availability). The single-cell data sets include two mouse cell atlases from the Tabula Muris Senis (TMS)<sup>19</sup>  
103 collected using different technologies (fluorescence-activated cell sorting followed by Smart-seq2 amplification<sup>23</sup> for the TMS  
104 FACS data and 10x microfluidic droplet capture and amplification<sup>24</sup> for the TMS droplet data), the unpublished Tabula Sapiens  
105 (TS) human cell atlas<sup>25</sup>, and other data sets focusing on specific tissues containing well-annotated cell types and cell states. We  
106 focused on the TMS FACS data in our primary analyses due to its comprehensive coverage of 23 tissues and 120 cell types and  
107 more accurate quantification of gene expression levels (via Smart-seq2); we used the other 15 data sets to validate our results.  
108 We note the extensive use of mouse gene expression data to study human diseases and complex traits (see Bryois et al.<sup>8</sup>, other  
109 studies<sup>6,7,9,12,26</sup>, and Discussion).

## 110 Simulations assessing calibration and power

111 We performed null simulations and causal simulations to assess the calibration and power of *sCDRS*, comparing *sCDRS* to three  
112 state-of-art methods for scoring individual cells with respect to a specific gene set: Seurat (cell-scoring function)<sup>15</sup>, Vision<sup>16</sup>,  
113 and VAM<sup>18</sup>. To our knowledge, VAM is the only method for scoring individual cells that provides cell-level association  
114 p-values; Seurat and Vision provide quantitative cell-level scores that we transformed to p-values based on the standard normal  
115 distribution (Methods).

116 First, we evaluated each method in null simulations in which no cells have systematically higher expression across the  
117 putative disease genes analyzed. We subsampled 10,000 cells from the TMS FACS data and randomly selected 1,000 putative  
118 disease genes. *sCDRS* and Seurat produced well-calibrated p-values, Vision suffered slightly inflated type I error, and VAM  
119 suffered severely inflated type I error (Fig. 2A and Supp. Table 9). The slight miscalibration of Vision may be due to the  
120 mismatch between the normal distribution used for computing p-values and the actual null distribution of the cell-level scores.  
121 The poor calibration of VAM may be because it uses a permutation-based test that assumes independence between genes under  
122 the null, an assumption that is likely to be violated in scRNA-seq data. We performed 3 secondary analyses pertaining to null  
123 simulations. First, we considered other numbers of putative disease genes (100 or 500, instead of 1,000). We determined that  
124 *sCDRS* remained well-calibrated, VAM continued to suffer from severely inflated type I error, and Seurat and Vision suffered  
125 increased type I error at 500 genes and severely inflated type I error at 100 genes (Supp. Fig. 2A-C). Second, we considered  
126 biased sets of putative disease genes (randomly selected from genes with high mean expression, genes with high expression  
127 variance, or overdispersed genes (genes with high expression variance but normal levels of technical noise<sup>27</sup>)). We determined  
128 that *sCDRS* remained reasonably well-calibrated, VAM continued to suffer from severely inflated type I error, and Seurat and

129 Vision were conservative for high-expression genes and high-variance genes but suffered inflated type I error for overdispersed  
130 genes (Supp. Fig. 2D-L). Third, we assessed calibration of our MC test for *cell type*-disease association based on the output of  
131  $s_{\text{CDRS}}$ , using the same subsampled data (and 1,000 putative disease genes). We confirmed that this test was well-calibrated  
132 (Supp. Table 10).

133 Next, we evaluated  $s_{\text{CDRS}}$ , Seurat and Vision in causal simulations in which a subset of causal cells has systematically  
134 higher expression across putative disease genes (we did not include VAM, which was not well-calibrated in null simulations).  
135 We used the same 10,000 cells subsampled from the TMS FACS data, randomly selected 1,000 causal disease genes, randomly  
136 selected 500 of the 10,000 cells as causal cells and artificially perturbed their expression levels to be higher (1.05-1.50 times for  
137 different simulations) across the 1,000 causal disease genes, and randomly selected 1,000 putative disease genes (provided  
138 as input to each method) with 25% overlap with the 1,000 causal disease genes. We determined that  $s_{\text{CDRS}}$  attained higher  
139 power than Seurat and Vision to detect individual cell-disease associations at  $\text{FDR} < 0.1$  (Fig. 2B and Supp. Table 11); the  
140 improved power of  $s_{\text{CDRS}}$  may be due to its incorporation of gene-specific weights that down-weight genes with higher levels  
141 of technical noise. We performed 4 secondary analyses pertaining to causal simulations. First, we considered other levels of  
142 overlap between the 1,000 causal genes and 1,000 putative disease genes (from 5% to 50%, instead of 25%). We determined  
143 that  $s_{\text{CDRS}}$  continued to attain higher power than Seurat and Vision (Supp. Fig. 3B). Second, we considered causal simulations  
144 in which we selected all 528 B cells in the subsampled data as causal cells, instead of randomly selecting 500 causal cells.  
145 We observed a similar improvement in power of  $s_{\text{CDRS}}$  over Seurat and Vision (Supp. Fig. 3C). Third, we computed the  
146 actual FDR for each method in each of the above causal simulations. We determined that  $s_{\text{CDRS}}$  attained well-calibrated FDR  
147 across all parameter settings, whereas Seurat and Vision suffered from inflated type I error at smaller effect sizes ( $\leq 1.1$  times  
148 higher expression for causal cells) and lower levels of overlap ( $\leq 15\%$ ) (Supp. Fig. 3D-F). Fourth, since Seurat and Vision  
149 were not initially designed to produce calibrated p-values, we also evaluated each method's area under the receiver operating  
150 characteristic curve (AUC) in distinguishing causal from non-causal cells. We determined that  $s_{\text{CDRS}}$  attained more accurate  
151 classification than Seurat and Vision under this metric (Supp. Fig. 3G-I).

152 In summary,  $s_{\text{CDRS}}$  is well-calibrated in null simulations and attains higher power to detect causal cells than Seurat and  
153 Vision in causal simulations.

## 154 Results across 120 TMS cell types for 74 diseases and complex traits

155 We analyzed GWAS data from 74 diseases and complex traits (average  $N=341\text{K}$ ; Supp. Table 1) in conjunction with the  
156 TMS FACS data with 120 cell types (cells from different tissues were combined for a given cell type; Supp. Table 3). We  
157 first report  $s_{\text{CDRS}}$  results for individual cells aggregated at the cell type level; individual cell-level results are discussed in  
158 subsequent sections. Results for a subset of 20 representative cell types and 21 representative diseases/traits are reported in Fig.  
159 3 (complete results in Supp. Fig. 4 and Supp. Table 12). Within this subset,  $s_{\text{CDRS}}$  identified 70 associated cell type-disease  
160 pairs ( $\text{FDR} < 0.05$ ; squares in Fig. 3) and detected significant heterogeneity in association with disease across individual cells  
161 within cell type for 37 of these 70 associated cell type-disease pairs ( $\text{FDR} < 0.05$ ; cross symbols in Fig. 3; 247 of 577 associated  
162 cell type-disease pairs across all pairs of 120 cell types and 74 diseases/traits). We also report the proportion of significantly  
163 associated individual cells for each cell type-disease pair ( $\text{FDR} < 0.1$ , a less stringent threshold as false positive associations of  
164 individual cells are less problematic and we do not focus on the results for any one specific cell; heatmap colors in Fig. 3). We  
165 note these associated cell type-disease pairs (and individual cell-disease associations discussed in subsequent sections) may  
166 reflect indirect tagging of causal cell types rather than direct causal associations, analogous to previous work (see Discussion).

167 For cell type-disease associations, as expected,  $s_{\text{CDRS}}$  broadly associated blood/immune cell types with blood/immune-  
168 related diseases/traits, brain cell types with brain-related diseases/traits, and other cell types with other diseases/traits (block-  
169 diagonal pattern in Fig. 3). Interestingly, there were 3 exceptions to the block-diagonal pattern, involving 4 diseases/traits (Fig.  
170 3). First, hepatocytes (in addition to proerythroblasts) were associated with red blood cell distribution width (RDW), possibly  
171 because liver malfunction affects RDW. This association is consistent with the observation of increased RDW values in patients  
172 with liver disease<sup>28</sup>, but to our knowledge has not been reported in previous genetic studies. Second, ventricular myocytes (in  
173 addition to immune cell types) were associated with lymphocyte count. This association is consistent with the prognostic value  
174 of relative lymphocyte concentration in patients with symptomatic heart failure<sup>29</sup>, but to our knowledge has not been reported  
175 in previous genetic studies. Third, pancreatic beta cells (in addition to brain cell types) were associated with SCZ and body  
176 mass index (BMI); risk variants for SCZ and BMI are reported to be enriched in pancreatic islet-specific epigenomic regulatory  
177 elements<sup>30,31</sup>.

178 We discuss 3 main findings for the blood/immune-related diseases/traits (upper left block in Fig. 3). First, different  
179 blood/immune cell types were associated with the corresponding blood cell traits, including proerythroblasts with RDW,  
180 classical monocytes with monocyte count, and adaptive immune cells with lymphocyte count. We detected significant  
181 heterogeneity across cells for the proerythroblast-RDW association, which may correspond to erythrocytes at different  
182 differentiation stages<sup>32</sup> (see Supp. Fig. 5). Second, immune cell types were associated with immune diseases, including

183 dendritic cells, CD4<sup>+</sup>  $\alpha/\beta$  T cells, CD8<sup>+</sup>  $\alpha/\beta$  T cells, and/or regulatory T cells with rheumatoid arthritis (RA), multiple  
184 sclerosis (MS), and IBD, consistent with previous findings<sup>12,33</sup>. We detected significant heterogeneity across cells for many  
185 of these cell type-disease associations, consistent with the known diversity within the T cell population (see “Heterogeneous  
186 subpopulations of T cells associated with autoimmune disease” section). Third, granulocyte monocyte progenitors (GMP) were  
187 strongly associated with MS, highlighting the role of myeloid cells in MS<sup>34,35</sup>.

188 We discuss 2 main findings for brain-related diseases/traits (middle block in Fig. 3). First, neuronal cell types, including  
189 medium spiny neurons (MSNs), interneurons, and neurons (neuronal cells with undetermined subtypes), were associated  
190 with schizophrenia (SCZ), major depressive disorder (MDD), college education (ECOL), and several other brain-related  
191 traits; the role of MSN in SCZ, MDD and ECOL is supported by previous genetic studies<sup>8,26,36</sup>. We detected significant  
192 heterogeneity across neurons in their association with most brain-related diseases/traits (see “Heterogeneous subpopulations  
193 of neurons associated with brain-related diseases and traits” section). Second, oligodendrocytes, oligodendrocyte precursor  
194 cells (OPCs) were also associated with multiple brain-related diseases/traits. These associations are less clear in existing  
195 genetic studies<sup>6,8,26,37</sup>, but are biologically plausible, consistent with the increasingly discussed role of oligodendrocyte lineage  
196 cells in brain diseases/traits: the differentiation and myelination of oligodendrocyte lineage cells are important to maintain  
197 the functionality of neuronal cells<sup>38,39</sup>. We detected significant heterogeneity across OPCs in their association with many  
198 brain-related diseases/traits, consistent with recent evidence of functionally diverse states of OPCs<sup>40</sup>, traditionally considered to  
199 be a homogeneous population (see Supp. Fig. 6).

200 We discuss 3 main findings for other diseases/traits (lower right block in Fig. 3). First, hepatocytes were associated with  
201 several metabolic traits including TG and testosterone (TST) (and other lipid traits; Supp. Fig. 4); hepatocytes are known to  
202 play an important role in metabolism<sup>41</sup>. We detected significant heterogeneity across hepatocytes in their association with TG  
203 and TST (see “Heterogeneous subpopulations of hepatocytes associated with metabolic traits” section). Second, pancreatic beta  
204 cells were associated with glucose and type 2 diabetes (T2D). We detected significant heterogeneity across pancreatic beta  
205 cells in their association with glucose, which could be due to different insulin-producing beta cell states<sup>42,43</sup> (see Supp. Fig.  
206 7). Third, pancreatic PP cells (in addition to chondrocytes and bladder cells) were associated with bone mineral density heel  
207 T-score (BMD-HT), consistent with the fact that osteoblast and osteoclast cells (which form and reabsorb bones, respectively)  
208 are regulated by pancreatic polypeptide<sup>44</sup>, which are produced by pancreatic PP cells. To our knowledge, this finding has not  
209 been reported in previous genetic studies.

210 We performed 2 secondary analyses to assess robustness of these results. First, we performed the same analyses on a mouse  
211 cell atlas assayed with a different technology (TMS droplet) and a human cell atlas assayed using the same technology (TS  
212 FACS) to provide comparisons of the results across technologies and across species. Results are reported in Supp. Fig. 8.  
213 We determined that the associations are highly consistent across technologies ( $r=0.90$  for association  $-\log_{10}$  p-value across  
214 cell type-disease pairs;  $P=1.7 \times 10^{-26}$ , Fisher’s exact test) and reasonably consistent across species ( $r=0.65$  for association  
215  $-\log_{10}$  p-value;  $P=7.5 \times 10^{-7}$ , Fisher’s exact test). Second, we analyzed the same 120 TMS FACS cell types and 74 diseases  
216 using LDSC-SEG<sup>12</sup> for comparison purposes (Methods). Results are reported in Supp. Fig. 9. We determined that the  
217 cell type-disease associations identified by the two methods are highly consistent ( $r=0.65$  for association  $-\log_{10}$  p-value;  
218  $P=8.7 \times 10^{-295}$ , Fisher’s exact test). Interestingly,  $s_{\text{CDRS}}$  identified some biologically plausible associations that were missed  
219 by LDSC-SEG, including pancreatic PP cells and BMD-HT ( $s_{\text{CDRS}}$  FDR=0.046 vs. LDSC-SEG FDR=1.000; see ref.<sup>44</sup>),  
220 GMPs and MS (FDR 0.020 vs. 0.270; see ref.<sup>34,35</sup>), and OPCs and MDD (FDR 0.020 vs. 0.100; see ref.<sup>45</sup>).

221 We performed 3 secondary analyses to assess alternative versions of  $s_{\text{CDRS}}$ . First, we considered using an unweighted  
222 average for the cell-level score (without weighting genes by gene-specific technical noise). We determined that our default  
223 weighted score achieved moderately higher power than the unweighted score in detecting disease-associated cells (Supp.  
224 Fig. 10A). Second, we considered an overdispersion score capturing both overexpression and underexpression of putative  
225 disease genes in the relevant cell population (whereas the default weighted score only captures overexpression; Methods).  
226 We determined our default weighted score achieved substantially higher power than the overdispersion score, suggesting that  
227 most putative disease genes are overexpressed in the relevant cell population (Supp. Fig. 10B). Third, we investigated other  
228 choices of MAGMA gene window size for mapping SNPs to genes (0 kb or 50 kb, instead of 10 kb) and other numbers of  
229 putative disease genes (100, 500, or 2,000, instead of 1,000) and determined that results were not sensitive to the choices of  
230 these parameters (Supp. Fig. 11 and Supp. Table 16), although the optimal number of putative disease genes was significantly  
231 correlated with trait polygenicity<sup>46</sup> ( $r=0.54$ ,  $P=0.011$ , Supp. Fig. 12).

232 In summary, cell type-disease associations identified by  $s_{\text{CDRS}}$  recapitulate known biology but also produced novel,  
233 biologically plausible findings. Many cell type-disease associations were heterogeneous across individual cells, strongly  
234 motivating analysis at the level of individual cells instead of cell types; further investigation of three examples of heterogeneity  
235 is provided in the remaining sections.

## Heterogeneous subpopulations of T cells associated with autoimmune disease

We sought to further understand the heterogeneity across T cells in the TMS FACS data in their association with autoimmune diseases (Fig. 3). We jointly analyzed all T cells in the TMS FACS data (3,769 cells, spanning 15 tissues). Since the original study clustered cells from different tissues separately<sup>19</sup>, we reclustered these T cells, resulting in 11 clusters (Fig. 4A; Methods); we verified that cells from different tissues, age, or sex clustered together (Supp. Fig. 13). We considered 10 autoimmune diseases: IBD, Crohn's disease (CD), ulcerative colitis (UC), RA, MS, AIT, hypothyroidism (HT), eczema, asthma (ASM), and respiratory and ear-nose-throat diseases (RR-ENT) (Supp. Table 1); we also considered height as a negative control trait.

We focused on individual cells associated with IBD, a representative autoimmune disease (Fig. 4B; results for the other 9 autoimmune diseases and height are reported in Supp. Fig. 14). The 357 IBD-associated cells (FDR<0.1) formed subpopulations of 4 of the 11 T cell clusters; we characterized these subpopulations based on marker gene expression and overlap of specifically expressed genes in each subpopulation with T cell signature gene sets (Methods). First, the subpopulation of 120 IBD-associated cells in cluster 3 (labeled as "Treg") had high expression of regulatory T cell (Treg) marker genes (e.g., *FOXP3*<sup>+</sup>, *CTLA4*<sup>+</sup>, *LAG3*<sup>+</sup>; Supp. Fig. 15A), and their specifically expressed genes significantly overlapped with Treg signatures ( $P = 3.9 \times 10^{-7}$ , Fisher's exact test; Supp. Fig. 15B), suggesting these cells had Treg immunosuppressive functions. Interestingly, these 120 IBD-associated cells were non-randomly distributed in cluster 3 on the UMAP plot ( $P < 0.001$ , MC test; Methods). Genes specifically expressed in these IBD-associated cells are preferentially enriched (compared to the 509 non-IBD-associated cells in the same cluster) in pathways defined by response to lipopolysaccharide, T helper cell differentiation, and tumor necrosis factor-mediated signaling (Supp. Fig. 15D); these pathways are closely related to inflammation, a distinguishing feature of IBD<sup>47</sup>. Second, the 75 IBD-associated cells in cluster 4 (*IL1RL1*<sup>+</sup> *KLRG1*<sup>+</sup> *AREG*<sup>+</sup>; labeled as "Effector-like Treg") were characterized as effector-like Tregs, which have active functions in Treg differentiation, immunosuppression, and tissue repair<sup>48</sup>; to our knowledge, this subpopulation of effector-like Tregs has only been studied in the context of lung cancer<sup>48</sup>, but their role in IBD is not surprising given the strong connection between Treg functions and IBD<sup>49,50</sup>. Third, the 61 IBD-associated cells in cluster 5 (*IL23R*<sup>+</sup> *RORC*<sup>+</sup> *IL17A*<sup>+</sup>; labeled as "Th17-like") were characterized as having T helper 17 (Th17) proinflammatory functions. Interestingly, drugs targeting *IL17A* (secukinumab and ixekizumab) have been considered for treatment of IBD but their use was associated with the onset of paradoxical effects (disease exacerbation after treatment with a putatively curative drug); the mechanisms underlying these events are not well understood<sup>51</sup>. Fourth, the 38 IBD-associated cells in cluster 9 (*IFNG*<sup>+</sup> *GZMB*<sup>+</sup> *FASL*<sup>+</sup>; labeled as "Effector-like CD8<sup>+</sup>") were characterized as having effector CD8<sup>+</sup> (cytotoxic) T cell functions. Overall, these findings are consistent with previous studies associating subpopulations of effector T cells to IBD, particularly Tregs and Th17 cells<sup>47,49,50,52</sup>.

We investigated whether the heterogeneity of T cells in association with autoimmune diseases was correlated with T cell effectorness gradient, a continuous classification of T cells defined by naive T cells on one side (immunologically naive T cells matured from the thymus) and effector T cells on the other (differentiated from naive T cells upon activation and capable of mediating effector immune responses); we hypothesized that such a correlation might exist given the effector-like T cell subpopulations associated to IBD above. Following a recent study<sup>53</sup>, we separately computed the effectorness gradients for CD4<sup>+</sup> T cells (1,686 cells) and CD8<sup>+</sup> T cells (2,197 cells) using pseudotime analysis<sup>54</sup> (Supp. Fig. 16A,B; Methods), and confirmed that the inferred effectorness gradients were significantly negatively correlated with naive T cell signatures and positively correlated with memory and effector T cell signatures (Supp. Fig. 16C,D; Methods). We assessed whether the CD4 (resp., CD8) effectorness gradient was correlated with sCDRS disease scores for IBD or other autoimmune diseases, across CD4<sup>+</sup> T cells (resp., CD8<sup>+</sup> T cells). Results are reported in Fig. 4C and Supp. Table 17. We determined that the CD4 effectorness gradient was strongly associated with IBD, CD, UC, and AIT ( $P < 0.005$ , MC test; 18%-31% of variance in sCDRS disease score explained by CD4 effectorness gradient), weakly associated with HT, Eczema, ASM, and RR-ENT ( $P < 0.05$ , MC test; 6%-10% variance explained), but not significantly associated with RA or MS. This implies that these autoimmune diseases are associated with more effector-like CD4<sup>+</sup> T cells. We also determined that the CD8 effectorness gradient was weakly associated with IBD and CD ( $P < 0.05$ , MC test; 10%-11% variance explained), but not significantly associated with the other autoimmune diseases, suggesting that CD4<sup>+</sup> effector T cells may be more important than CD8<sup>+</sup> effector T cells for these diseases. Notably, after conditioning on the 11 cluster labels, the associations with CD4 effectorness gradient remained significant for IBD, CD, AIT ( $P < 0.005$ , MC test), and UC ( $P < 0.05$ , MC test), and the associations with CD8 effectorness gradient remained significant for IBD and CD ( $P < 0.05$ , MC test), indicating that sCDRS distinguishes effectorness gradients within clusters. In addition, as a negative control, height was not significantly associated in any of these analyses. The association of T cell effectorness gradients with autoimmune diseases has not previously been formally evaluated, but is consistent with previous studies linking T cell effector functions to autoimmune disease<sup>55,56</sup>; the results also suggest that different subpopulations of effector T cells share certain similarities in their association with autoimmune diseases, consistent with previous studies characterizing the similarities among different subtypes of effector T cells, such as an increase in the expression of cytokines and chemokines<sup>53,57,58</sup>.

Finally, we prioritized disease-relevant genes by computing the correlation (across all 110,096 TMS FACS cells) between

291 the expression of a given gene and the  $s_{\text{CDRS}}$  score for a given disease; this approach identifies genes that are co-expressed  
292 with genes implicated by disease GWAS. We compared the top 1,000 genes prioritized using this approach with gold-standard  
293 disease-relevant genes based on putative drug targets from Open Targets<sup>59</sup> (phase 1 or above; 8 gene sets with 27-250 genes;  
294 used for 8 autoimmune diseases except RR-ENT and HT; Supp. Table 18) or genes known to cause a Mendelian form of  
295 the disease<sup>60</sup> (550 genes corresponding to “immune dysregulation”, used for RR-ENT and HT; Supp. Table 18). Results are  
296 reported in Fig. 4D and Supp. Table 19. We determined that  $s_{\text{CDRS}}$  attained a more accurate prioritization of disease-relevant  
297 genes compared to the top 1,000 MAGMA genes (median ratio of (excess overlap - 1) was 2.02, median ratio of  $-\log_{10}$   
298 p-value was 2.76; see Methods), likely by capturing disease-relevant genes with weak GWAS signal<sup>46</sup>. For example, *ITGB7*  
299 was prioritized by  $s_{\text{CDRS}}$  for association with IBD (rank 9) but was missed by MAGMA (rank 10565, MAGMA  $P=0.54$ );  
300 *ITGB7* impacts IBD via controlling lymphocyte homing to the gut and is a drug target for IBD (using vedolizumab)<sup>61,62</sup>.  
301 In addition, *JAK1* was prioritized by  $s_{\text{CDRS}}$  for association with RA (rank 386) but was missed by MAGMA (rank 5228,  
302 MAGMA  $P=0.26$ ); *JAK1* plays a role in regulating immune cell activation and is a drug target for RA (using tofacitinib,  
303 baricitinib, or upadacitinib)<sup>63,64</sup>.

304 We performed 4 secondary analyses. First, we assessed cell type-disease associations using  $s_{\text{CDRS}}$  for two human scRNA-  
305 seq data sets (Cano-Gamez & Soskic et al.<sup>53</sup> and Nathan et al.<sup>65</sup>; Supp. Table 2) and each of the 10 autoimmune diseases (and  
306 height, a negative control trait); we focused on cell type-disease associations because these data sets contain well-annotated T  
307 cell subtypes and states. Results are reported in Supp. Table 20. In the Cano-Gamez & Soskic et al. data, cytokine-induced  
308 Tregs, cytokine-induced Th17 cells, and activated natural Tregs were significantly associated with IBD (FDR<0.05, MC  
309 test). In the Nathan et al. data, RORC<sup>+</sup> Tregs, Th17 cells, CD161<sup>+</sup> Th2 cells, Th2 cells, Th1 cells, and activated CD4<sup>+</sup> T  
310 cells were significantly associated with IBD (FDR<0.05, MC test). These findings are consistent with our discoveries in  
311 TMS FACS linking activated T cells, particularly Tregs and Th17 cells, to IBD. In addition, as a negative control, no cell  
312 type was significantly associated with height in these two data sets. Second, we compared  $s_{\text{CDRS}}$  to cluster-level analyses  
313 using LDSC-SEG at various clustering resolutions. Results are reported in Supp. Fig. 17. We determined that both methods  
314 produced similar results at the cluster level, but the cluster-level analyses failed to recapitulate the individual cell-disease  
315 associations detected in the  $s_{\text{CDRS}}$  individual cell-level analysis (even when clustering at a very high resolution). Third, we  
316 investigated alternative disease gene prioritization methods, including prioritizing genes based on specific expression in the  
317 disease-critical T cell population (differentially expressed genes for comparing T cells vs. other cells in the TMS FACS data)  
318 and based on correlating the expression level of a given gene with  $s_{\text{CDRS}}$  disease scores across T cells, CD4<sup>+</sup> T cells, or CD8<sup>+</sup>  
319 T cells (instead of all TMS FACS cells). We determined that our primary approach provided a more accurate prioritization of  
320 gold-standard disease-relevant genes (Supp. Fig. 18A-J). Fourth, we extended our prioritization of disease-relevant genes to all  
321 74 diseases/traits. We compared the prioritized genes with drug target genes for 27 diseases and Mendelian disease genes for 45  
322 diseases (Supp. Table 18). We determined that our approach attained a similar improvement over MAGMA across this broader  
323 set of diseases/traits (Supp. Fig. 18K-N).

324 We conclude that T cells exhibit strong heterogeneity in association with autoimmune diseases. This heterogeneity can be  
325 partially explained by T cell effectorness gradients (e.g., 31% variance explained by the CD4 effectorness gradient for IBD),  
326 with stronger associations for effector-like T cells. In addition, genes whose expression across individual cells is correlated  
327 with the  $s_{\text{CDRS}}$  disease score are strongly enriched for gold-standard drug target and Mendelian disease genes.

## 328 Heterogeneous subpopulations of neurons associated with brain-related diseases and traits

329 We sought to further understand the heterogeneity across neurons (in the non-myeloid brain tissue) in the TMS FACS data  
330 (484 cells labeled as “neuron”) in association with brain-related diseases and traits (Fig. 3). We considered 6 brain-related  
331 diseases and traits: SCZ, MDD, neuroticism (NRT), ECOL, BMI, Smoking (Supp. Table 1); we also considered height as  
332 a negative control trait. The TMS FACS data includes a partition of neurons into four brain subtissues (cerebellum, cortex,  
333 hippocampus, and striatum), but significant heterogeneity remained when we stratified our heterogeneity analyses by subtissue  
334 (Supp. Fig. 19). Since the TMS FACS data has limited coverage of neuronal subtypes, we focused our subsequent analyses on  
335 a separate mouse brain scRNA-seq data set<sup>66</sup> (Zeisel & Muñoz-Manchado et al.<sup>66</sup>; 3,005 cells), which has better coverage  
336 of neuronal subtypes and has been analyzed at cell type level in several previous genetic studies<sup>8,26,67</sup>. We first investigated  
337 cell type-trait associations using  $s_{\text{CDRS}}$ , which associated several neuronal subtypes (CA1 pyramidal neurons, SS pyramidal  
338 neurons, and interneurons) with the 6 brain-related traits (Supp. Fig. 20A, Supp. Table 21), consistent with previous genetic  
339 studies<sup>8,26,67</sup>. We focused on the CA1 pyramidal neurons from the hippocampus (827 cells), which exhibited the strongest  
340 within-cell type heterogeneity (FDR< 0.005 for all 6 brain traits, MC test; Supp. Table 21). Individual cell-trait associations for  
341 SCZ are reported in Fig. 5A, and individual cell-trait associations for all 6 brain-related traits are reported in Supp. Fig. 20B.  
342 We observed a continuous gradient of CA1 pyramidal neuron-SCZ associations, with similar results for other traits.

343 We investigated whether the heterogeneity observed in Fig. 5A was correlated with spatial location; we hypothesized that  
344 such a correlation might exist because of the known location-specific functions of hippocampal neurons<sup>17,68</sup>. We inferred

345 spatial coordinates of the CA1 pyramidal neurons along the natural CA1 spatial axes<sup>69</sup> (dorsal-ventral long axis, proximal-distal  
346 transverse axis, and superficial-deep radial axis) for each cell in terms of continuous individual cell-level scores for these 6  
347 spatial regions by applying *sCDRS* to published spatial signature gene sets (instead of MAGMA putative disease gene sets;  
348 Supp. Fig. 20C and Supp. Table 8; Methods). We verified that the inferred dorsal and ventral scores obtained by applying this  
349 procedure to independent mouse<sup>70</sup> and human<sup>71</sup> data sets with annotated spatial coordinates on the long axis were significantly  
350 correlated with the annotated spatial coordinates ( $r=0.54, 0.65$  for the mouse data,  $r=0.18, 0.20$  for the human data,  $P<0.01$   
351 each, MC test; Supp. Fig. 21); annotated spatial coordinates on the transverse and radial axes were not available in these data  
352 sets. The inferred spatial scores for the long (dorsal, ventral) and transverse (proximal, distal) axes varied along the top two  
353 UMAP axes, providing visual evidence of stronger neuron-SCZ associations in dorsal and proximal regions (Fig. 5A, Supp.  
354 Fig. 20).

355 We used the results of *sCDRS* for individual cells to assess whether the inferred spatial scores for each of the 6 spatial  
356 regions (dorsal/ventral/proximal/distal/superficial/deep) were correlated to the *sCDRS* disease scores for each of the 6 brain-  
357 related traits (and height, a negative control trait) across CA1 pyramidal neurons (Methods). Results are reported in Fig. 5B (for  
358 the proximal region, which had the strongest associations), Supp. Fig. 22 and Supp. Table 22. We determined that proximal  
359 score was strongly associated with all 6 brain-related traits (all  $P<0.001$  except  $P=0.002$  for MDD;  $P=0.008$  for height,  
360 non-significant after Bonferroni correction; MC test; 15%-29% of variance in *sCDRS* disease score explained by proximal  
361 scores across 6 brain-related traits), suggesting proximal CA1 pyramidal neurons may be more relevant to these brain-related  
362 traits (instead of distal CA1 pyramidal neurons). The association between the proximal region and brain-related traits is  
363 consistent with the fact that the proximal region of the hippocampus receives synaptic inputs in the perforant pathway, which is  
364 the main input source of the hippocampus<sup>72,73</sup>.

365 We reapplied *sCDRS* to three additional mouse single-cell data sets<sup>70,74,75</sup> and three human single-cell data sets<sup>71,76,77</sup>  
366 (Supp. Table 2), computing both spatial scores and disease scores for each cell as above. Results are reported in Supp. Fig. 22.  
367 We determined that the proximal score was consistently associated with the 6 brain-related traits across these 7 data sets (while  
368 the distal score was consistently non-associated). For the long (dorsal-ventral) and radial (superficial-deep) axes, while the  
369 dorsal and deep scores were consistently associated with the 6 brain-related traits across the 7 data sets, the corresponding  
370 ventral and superficial scores were consistently associated across the 3 human data sets but consistently non-associated across  
371 the 4 mouse data sets, possibly due to differences in brain biology between human and mouse<sup>68,78</sup>.

372 We conclude that CA1 pyramidal neurons exhibit strong heterogeneity in association with brain-related diseases and  
373 traits. This heterogeneity can be partially explained by inferred spatial coordinates and may reflect the underlying functional  
374 organization of CA1 pyramidal neurons.

### 375 **Heterogeneous subpopulations of hepatocytes associated with metabolic traits**

376 Finally, we sought to further understand the heterogeneity across hepatocytes (in the liver) in the TMS FACS data in their  
377 association with metabolic traits (Fig. 3). Since the original study clustered all cells from the liver together<sup>19</sup> (limiting the  
378 resolution for distinguishing cell states within hepatocytes), we reclustered the hepatocytes alone, resulting in 6 clusters (1,102  
379 cells, Fig. 5C; Methods). We considered 9 metabolic traits: TG, high-density lipoprotein (HDL), low-density lipoprotein  
380 (LDL), total cholesterol (TC), TST, alanine aminotransferase (ALT), alkaline phosphatase (ALP), sex hormone-binding globulin  
381 (SHBG), and total bilirubin (TBIL) (Supp. Table 1); we also considered height as a negative control trait.

382 We focused on individual cells associated with TG, a representative metabolic trait (Fig. 5C; results for the other 8 metabolic  
383 traits and height are reported in Supp. Fig. 23). The 530 TG-associated cells ( $FDR<0.1$ ) formed subpopulations of 5 of the 6  
384 hepatocyte clusters; we characterized these subpopulations based on ploidy level (number of sets of chromosomes in a cell)  
385 and zonation (pericentral/mid-lobule/periportal spatial location in the liver lobule), which have been extensively investigated  
386 in previous studies of hepatocyte heterogeneity<sup>79-81</sup>. We inferred the ploidy level and zonation for each individual cell in  
387 terms of a polyploidy score, a pericentral score, and a periportal score by applying *sCDRS* to published polyploidy/zonation  
388 signature gene sets<sup>82-84</sup> (instead of MAGMA putative disease gene sets; Supp. Fig. 24; Methods); we verified that the  
389 inferred high-ploidy hepatocytes had higher expression levels of the *Xist* (X-inactive specific transcript) non-coding RNA gene  
390 (for hepatocytes in female mice) and higher numbers of expressed genes (Supp. Fig. 24H,I), two distinguishing features of  
391 high-ploidy hepatocytes<sup>83,85</sup>. We further verified that the inferred polyploidy score obtained by applying this procedure to  
392 independent data<sup>83</sup> with experimentally determined ploidy level annotation were significantly correlated with the experimentally  
393 determined annotation ( $r=0.28, P<0.001$ , MC test), and that the inferred zonation scores obtained by applying this procedure  
394 to independent data<sup>84</sup> with experimentally determined zonation annotations were significantly correlated with the experimentally  
395 determined annotations ( $r=0.42, P<0.001$  for pericentral score,  $r=0.45, P<0.001$  for periportal score, MC test). The inferred  
396 ploidy level and zonation varied across clusters, providing visual evidence of stronger cell-TG associations in high-ploidy  
397 clusters (cluster 1,2), particularly the periportal high-ploidy cluster (cluster 2; Fig. 5C).

398 We used the results of *sCDRS* for individual cells to assess whether the inferred polyploidy, pericentral and periportal

399 scores were correlated to the *sCDRS* disease score for each of the 9 metabolic traits (and height, a negative control trait)  
400 across hepatocytes; we jointly regressed the *sCDRS* disease score for each trait on the polyploidy score, pericentral score,  
401 and periportal score (because the polyploidy score was positively correlated with the other 2 scores; Methods). Results are  
402 reported in Fig. 5D (for the polyploidy score which had the strongest associations), Supp. Fig. 25 and Supp. Table 23. The  
403 polyploidy, pericentral, and periportal scores jointly explained 42%-63% of variance of the *sCDRS* disease scores across the 9  
404 metabolic traits. We determined that the polyploidy score was strongly associated with all 9 metabolic traits (all  $P < 0.005$   
405 except  $P = 0.01$  for LDL;  $P = 0.62$  for height; MC test), suggesting that high-ploidy hepatocytes may be more relevant to these  
406 metabolic traits. The association between ploidy level and metabolic traits is consistent with previous findings that ploidy  
407 levels are associated with changes in the expression level of genes for metabolic processes such as de novo lipid biosynthesis  
408 and glycolysis<sup>81,82</sup>, and supports the hypothesis that liver functions are enhanced in polyploid hepatocytes<sup>81</sup>. In addition, the  
409 periportal score was associated with the 9 metabolic traits ( $P < 0.005$  for ALT and ALP, all  $P < 0.05$  except  $P = 0.19$  for TBIL;  
410  $P = 0.24$  for height; MC test). While the pericentral score was not significantly associated with these traits in the TMS FACS  
411 data, we detected significant associations across multiple other data sets (see below). These results suggest that these metabolic  
412 traits are impacted by complex processes involving both pericentral and periportal hepatocytes.

413 We performed 3 secondary analyses. First, we reapplied *sCDRS* to 4 additional mouse single-cell data sets<sup>83,84,86</sup> and  
414 1 human single-cell data set<sup>87</sup> (Supp. Table 2). Results are reported in Supp. Fig. 25A,B. The results suggest consistent  
415 association of the polyploidy score and both the pericentral and periportal scores with the 9 metabolic traits. Second, given  
416 that *sCDRS* associated both pericentral and periportal hepatocytes to metabolic traits, we assessed whether *sCDRS* is able to  
417 detect pericentral-specific and periportal-specific effects. We analyzed all 6 hepatocyte scRNA-seq data sets using 8 metabolic  
418 pathway gene sets<sup>88,89</sup> (instead of MAGMA genes from GWAS; Methods) whose zonation patterns are well-understood (4  
419 pericentral-specific pathways and 4 periportal-specific pathways<sup>80</sup>). Results are reported in Supp. Fig. 25C,D. We determined  
420 that pericentral-specific pathways generally exhibited pericentral-specific effects, and periportal-specific pathways generally  
421 exhibited periportal-specific effects. Third, we assessed the robustness of our polyploidy score by inferring the ploidy level  
422 of hepatocytes using 3 additional sets of polyploidy signatures and 3 additional sets of diploidy signatures<sup>82</sup> (expected to be  
423 negatively correlated with the polyploidy score; Methods) for each of the 6 data sets. Results are reported in Supp. Table 24.  
424 We determined that the polyploidy score is strongly positively correlated with scores obtained using the additional polyploidy  
425 signatures ( $P < 0.005$  for 17/18 correlations, MC test) and strongly negatively correlated with scores obtained using the  
426 additional diploidy signatures ( $P < 0.005$  for 10/18 correlations, MC test).

427 We conclude that hepatocytes exhibit strong heterogeneity in association with metabolic traits. This heterogeneity can be  
428 partially explained by inferred ploidy levels and zonation patterns, with stronger associations for hepatocytes with higher ploidy  
429 level and hepatocytes located both in pericentral or periportal regions (instead of the mid-lobule region).

## 430 Discussion

431 We have introduced *sCDRS*, a method that leverages polygenic GWAS signals to associate individual cells in scRNA-seq data  
432 with diseases and complex traits; we showed via extensive simulations that *sCDRS* is well-calibrated and powerful. We applied  
433 *sCDRS* to 74 diseases and complex traits in conjunction with 16 scRNA-seq data sets and detected extensive heterogeneity in  
434 disease associations of individual cells within classical cell types, including subpopulations of T cells associated with IBD  
435 partially characterized by their effector-like states, subpopulations of neurons associated with SCZ partially characterized by  
436 their spatial location, and subpopulations of hepatocytes associated with TG partially characterized by their higher ploidy levels.  
437 These findings have improved our understanding of these diseases/traits, and may prove useful for targeting the relevant cell  
438 populations for in vitro experiments to elucidate the molecular mechanisms through which GWAS risk variants impact disease.

439 *sCDRS* does not rely on annotations of classical cell types based on known marker genes, a standard approach for integrating  
440 GWAS with scRNA-seq data<sup>6-8</sup> (and bulk gene expression data<sup>9-12</sup>; see Supp. Note). Thus, *sCDRS* is particularly well-suited  
441 for analyzing data sets that are less well-annotated (e.g., large-scale cell atlases<sup>19,25</sup>) or contain less well-studied cell populations.  
442 In addition, *sCDRS* characterizes heterogeneity across individual cells in their associations to common diseases and complex  
443 traits, providing a unique perspective relative to studies of single-cell transcriptional heterogeneity focusing on scRNA-seq  
444 data alone<sup>13-16,18,90,91</sup>; it also improves upon recent methods for scoring individual cells with respect to a given gene set (e.g.,  
445 Seurat<sup>15</sup>, Vision<sup>16</sup>, and VAM<sup>18</sup>) by providing robust individual cell-level association p-values and higher detection power (see  
446 Supp. Note).

447 We have demonstrated the value of *sCDRS* in associating individual cells to disease; assessing the heterogeneity across  
448 individual cells within predefined cell types in their association to disease; identifying cell-level variables partially characterizing  
449 the individual cells that are associated to disease; and broadly associating predefined cell types to disease. We anticipate that  
450 application of *sCDRS* to future scRNA-seq/snRNA-seq and GWAS data sets will continue to further these goals.

451 We note several limitations and future directions of our work. First, identifying a statistical correlation between individual  
452 cells (or cell types) and disease does not imply causality, but may instead reflect indirect tagging of causal cells/cell types,

453 analogous to previous work<sup>6,7,12,20</sup>. However, even in such cases, the implicated cells/cell types are likely to be closely  
454 biologically related to the causal cells/cell types, based on their similar expression patterns. Second, the relevant cell-level  
455 variables that we identified (e.g., T cell effectorness gradients for autoimmune diseases) only partially explain the heterogeneity  
456 across individual cells in their association to disease; there are likely more cell-level variables driving this heterogeneity that  
457 remain to be identified. Third, we primarily used mouse RNA-seq data (TMS FACS) to study human diseases and complex  
458 traits, but there are biological differences between human and mouse. Arguments in favor of using mouse RNA-seq data to  
459 study human diseases and complex traits include (1) it is easier to obtain high-quality atlas-level scRNA-seq data from mice, (2)  
460 our key findings were replicated in human data, (3) we evaluated only protein-coding genes with 1:1 orthologs between mice  
461 and humans, which are highly conserved, (4) we used a large number of genes to associate cells to diseases (1,000 MAGMA  
462 putative disease genes), minimizing potential bias due to individual genes differentially expressed across species (see Bryois  
463 et al.<sup>8</sup> and other studies<sup>6,7,12,26</sup> for additional discussion). However, it is possible that some cell types are less conserved  
464 across species<sup>8,92</sup> (e.g., our results for CA1 pyramidal neurons along the long and radial axes (Supp. Fig. 22) seem to indicate  
465 different disease association patterns between human and mouse), motivating follow-up analyses involving human scRNA-seq  
466 data (including those that we have performed here). Fourth, we identified putative disease genes using MAGMA, a widely  
467 used method<sup>20</sup>. However, it may be possible to construct more accurate sets of disease genes by incorporating other types  
468 of data, such as protein-protein interaction data<sup>93</sup> or functionally informed SNP-to-gene linking strategies<sup>94</sup>; we caution that  
469 such efforts must strive to avoid biases towards well-studied tissues. Fifth, *scDRS* detects overexpression of putative disease  
470 genes (analogous to previous works<sup>7,8,12</sup>), but is not designed to detect underexpression. Our initial implementation of an  
471 overdispersion score was less well-powered than *scDRS* in analyses of real disease/traits (Supp. Fig. 10), but further efforts to  
472 combine directional and overdispersion scores may be warranted<sup>95</sup>. Sixth, *scDRS* results for a given cell depends on the other  
473 cells in the data set through both the estimation of technical noise levels and the selection of matched control genes; however,  
474 both steps depend only on gene-specific quantities averaged across all cells (gene-specific expression mean and expression  
475 variance) and are thus robust to inclusion or exclusion of a small set of cells (or a large random subset of cells). Seventh, the  
476 fact that *scDRS* assesses the statistical significance of an individual cell's association to disease by implicitly comparing it to  
477 other cells via matched control genes may reduce power if most cells in the data are truly causal. For example, association with  
478 IBD in a data set containing only Tregs (one of the causal cell types for IBD) will likely yield largely non-significant results.  
479 This limitation did not impact our main analyses, because the TMS data includes a broad set of cell types; in more specialized  
480 data sets (which may be preferred in some settings due to the more comprehensive profiling of the focal cell population), this  
481 limitation can potentially be addressed by selecting matched control genes based on a broad cell atlas (e.g., the TMS or TS data).  
482 Eighth, we have only analyzed scRNA-seq data from control samples. Extending *scDRS* to analyze scRNA-seq data from  
483 case-control samples or experimentally perturbed samples<sup>96</sup>, perhaps by applying *scDRS* and comparing disease scores of  
484 cells from different conditions, may provide further insights about disease. Despite all these limitations, *scDRS* is a powerful  
485 method for distinguishing disease associations of individual cells in single-cell RNA-seq data.

## 486 Methods

### 487 scDRS method

488 We consider a scRNA-seq data set with  $n_{\text{cell}}$  cells and  $n_{\text{gene}}$  genes. We denote the cell-gene matrix as  $\mathbf{X} \in \mathbb{R}^{n_{\text{cell}} \times n_{\text{gene}}}$ , where  
489  $X_{cg}$  represents the expression level of cell  $c$  and gene  $g$ . We assume that  $\mathbf{X}$  is size-factor-normalized (e.g., 10,000 counts per  
490 cell) and log-transformed ( $\log(x + 1)$ ) from the original raw count matrix<sup>21</sup>. We regress the covariates out from the normalized  
491 data<sup>21</sup> (with a constant term in the regressors to center the data), before adding the original log mean expression of each gene  
492 back to the residual data. Such a procedure preserves the mean-variance relationship in the covariate-corrected data, which is  
493 needed for estimating the gene-specific technical noise levels (see Supp. Note).

494 The *scDRS* algorithm is described in Box 1. Given a disease GWAS and a scRNA-seq data set, *scDRS* computes a p-value  
495 for each individual cell for association with the disease. *scDRS* also outputs cell-level normalized disease scores and  $B$  sets of  
496 normalized control scores (default  $B = 1,000$ ) that can be used for data visualization and Monte Carlo-based statistical inference  
497 (see Downstream applications and MC test). *scDRS* consists of three steps. First, *scDRS* constructs a set of putative disease  
498 genes from the GWAS summary statistics. Second, *scDRS* computes a raw disease score and  $B$  MC samples of raw control  
499 scores for each cell. Third, after gene set-wise and cell-wise normalization, *scDRS* computes an association p-value for each  
500 cell by comparing its normalized disease score to the empirical distribution of the pooled normalized control scores across all  
501 control gene sets and all cells. These steps are detailed below.

502 **Step 1: Constructing disease gene set.** We use MAGMA<sup>20</sup> to compute gene-level association p-values from disease  
503 GWAS summary statistics (Box 1, step 1). We use a reference panel based on individuals of European ancestry in the 1000  
504 Genomes Project<sup>97</sup>. We use a 10-kb window around the gene body to map SNPs to genes. We select the top 1,000 genes based  
505 on MAGMA p-values as putative disease genes. We denote the disease gene set as  $G \subset \{1, 2, \dots, n_{\text{gene}}\}$ . Alternative parameter

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**Box 1** Single-cell disease relevance score ( $s_{\text{cDRS}}$ )

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**Input:** Disease GWAS summary statistics (or putative disease gene set  $G$ ), scRNA-seq data  $\mathbf{X} \in \mathbb{R}^{n_{\text{cell}} \times n_{\text{gene}}}$ .

**Parameters:** Number of MC samples of control gene sets  $B$  (default 1,000).

1: **Construct putative disease gene set**

a: Construct putative disease gene set  $G \subset \{1, 2, \dots, n_{\text{gene}}\}$  from GWAS summary statistics using MAGMA.

2: **Compute disease scores and control scores**

a: Sample  $B$  sets of control genes  $G_1^{\text{ctrl}}, \dots, G_B^{\text{ctrl}}$  matching mean expression and expression variance of disease genes.

b: Estimate gene-specific technical noise level  $\sigma_{\text{tech},g}^2, \forall g \in \{1, \dots, n_{\text{gene}}\}$ .

c: Compute raw disease score and  $B$  raw control scores for each cell  $c = 1, \dots, n_{\text{cell}}$ ,

$$\text{raw disease score: } s_c = \frac{\sum_{g \in G} \sigma_{\text{tech},g}^{-1} X_{cg}}{\sum_{g \in G} \sigma_{\text{tech},g}^{-1}}, \quad B \text{ raw control scores: } s_{cb}^{\text{ctrl}} = \frac{\sum_{g \in G_b^{\text{ctrl}}} \sigma_{\text{tech},g}^{-1} X_{cg}}{\sum_{g \in G_b^{\text{ctrl}}} \sigma_{\text{tech},g}^{-1}}, \quad \forall b \in \{1, \dots, B\} \quad (1)$$

3: **Compute disease association p-values**

a: First gene set alignment by mean and variance. Let  $\sigma_g^2$  be the expression variance of gene  $g$ . For each cell  $c$ ,

$$s_c \leftarrow s_c - \frac{1}{n_{\text{cell}}} \sum_{c'=1}^{n_{\text{cell}}} s_{c'}, \quad s_{cb}^{\text{ctrl}} \leftarrow \left( s_{cb}^{\text{ctrl}} - \frac{1}{n_{\text{cell}}} \sum_{c'=1}^{n_{\text{cell}}} s_{c'b}^{\text{ctrl}} \right) \frac{\sum_{g \in G_b^{\text{ctrl}}} \sigma_{\text{tech},g}^{-1}}{\sum_{g \in G} \sigma_{\text{tech},g}^{-1}} \sqrt{\frac{\sum_{g \in G} \sigma_{\text{tech},g}^{-2} \sigma_g^2}{\sum_{g \in G_b^{\text{ctrl}}} \sigma_{\text{tech},g}^{-2} \sigma_g^2}}, \quad \forall b \in \{1, \dots, B\} \quad (2)$$

b: Cell-wise standardization for each cell  $c$  by the mean  $\hat{\mu}_c^{\text{ctrl}}$  and variance  $\hat{\sigma}_c^{\text{ctrl}}$  of control scores  $s_{c1}^{\text{ctrl}}, \dots, s_{cB}^{\text{ctrl}}$  of that cell,

$$s_c \leftarrow (s_c - \hat{\mu}_c^{\text{ctrl}}) / \hat{\sigma}_c^{\text{ctrl}}, \quad s_{cb}^{\text{ctrl}} \leftarrow (s_{cb}^{\text{ctrl}} - \hat{\mu}_c^{\text{ctrl}}) / \hat{\sigma}_c^{\text{ctrl}}, \quad \forall b \in \{1, \dots, B\} \quad (3)$$

c: Second gene set alignment by mean. For each cell  $c$ ,

$$s_c \leftarrow s_c - \frac{1}{n_{\text{cell}}} \sum_{c'=1}^{n_{\text{cell}}} s_{c'}, \quad s_{cb}^{\text{ctrl}} \leftarrow s_{cb}^{\text{ctrl}} - \frac{1}{n_{\text{cell}}} \sum_{c'=1}^{n_{\text{cell}}} s_{c'b}^{\text{ctrl}}, \quad \forall b \in \{1, \dots, B\} \quad (4)$$

d: Compute cell-level p-values based on the empirical distribution of the pooled normalized control scores for each cell  $c$ ,

$$p_c = \left[ 1 + \sum_{c'=1}^{n_{\text{cell}}} \sum_{b=1}^B \mathbb{I}(s_c \leq s_{c'b}^{\text{ctrl}}) \right] / (1 + n_{\text{cell}} B) \quad (5)$$

**Output:** cell-level p-values  $p_c$ , normalized disease scores  $s_c$ , and normalized control scores  $s_{c1}^{\text{ctrl}}, \dots, s_{cB}^{\text{ctrl}}$ .

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506 choices and methods for constructing putative disease gene sets are considered below (see Alternative versions of  $s_{\text{cDRS}}$   
507 method).

508 **Step 2: Computing disease scores and control scores.** We construct  $B$  sets of control genes  $G_1^{\text{ctrl}}, \dots, G_B^{\text{ctrl}}$  by randomly  
509 selecting genes matching the mean expression and expression variance of the disease genes (Box 1, step 2a). Specifically,  
510 each control gene set  $G_b^{\text{ctrl}}$  has the same size as the disease gene set  $G$  and is constructed by first dividing all genes into  $20 \times 20$   
511 equal-sized mean-variance bins and then for each gene in the disease gene set, randomly sampling a control gene from the same  
512 bin (containing the disease genes) without replacement. Next, we estimate the technical noise level for each gene  $\sigma_{\text{tech},g}^2$  in the  
513 scRNA-seq data using a procedure similar to previous works<sup>18,21</sup>, and compute the raw disease score and raw control scores for  
514 each cell as weighted average expression of genes in the corresponding gene set (Box 1, steps 2b-2c, Supp. Note). The weight  
515 for gene  $g$  is proportional to  $\sigma_{\text{tech},g}^{-1}$ , which down-weights genes with higher levels of technical noise to increase detection power.  
516 The weighting strategy was adapted from VAM<sup>18</sup>, where the cell-specific score is proportional to  $\sum_{g \in G} \sigma_{\text{tech},g}^{-2} X_{cg}^2$  and was  
517 shown to have a superior classification accuracy. Alternative cell scores (instead of the weighted average score) are evaluated  
518 below (see Alternative versions of  $s_{\text{cDRS}}$  method).

519 **Step 3: Computing disease-association p-values.** We first describe the alternative distribution that  $s_{\text{cDRS}}$  aims to detect.  
520 Since the control genes match the mean expression and expression variance of the disease genes, it can be shown that the  
521 raw disease score has the same mean but a higher variance compared to each set of raw control scores; the higher variance is

522 because the disease genes are more positively correlated with each other due to co-expression in the associated cell population  
 523 (Supp. Fig. 1A-C). As a result, the disease-relevant cells, with high expression of the disease genes, are expected to have larger  
 524 raw disease scores than raw control scores. Please see Supp. Note for more details.

The first gene set alignment (Box 1, step 3a) corrects for the potential mismatch of control gene sets by first centering the scores and then aligning the variance level for each gene set. The variance of the raw disease score is estimated as  $\sum_{g \in G} w_g^2 \sigma_g^2$  and similarly for the raw control scores, with  $\sigma_g^2$  being the expression variance of gene  $g$  and  $w_g = \sigma_{\text{tech},g}^{-1} / \sum_{g \in G} \sigma_{\text{tech},g}^{-1}$  the corresponding weight; this heuristic assumes independence of the genes (or different gene sets have similar levels of gene-gene correlation), and consequently avoids down-weighting the raw disease score due to the higher correlation between disease genes (Supp. Fig. 1D, Supp. Note). After adjusting the control gene sets, the gold standard MC p-values, based on comparison to  $B$  MC samples of raw control scores of the same cell, can be written as<sup>22</sup>

$$p_c^{\text{MC}} = \frac{1 + \sum_{b=1}^B \mathbb{I}(s_c \leq s_{cb}^{\text{ctrl}})}{1 + B}, \forall c \in \{1, \dots, n_{\text{cell}}\}. \quad (6)$$

525 This finite-sample MC p-value is a conservative estimate of the ideal MC p-value obtained via an infinite number of MC  
 526 samples<sup>22</sup>. However, as Eq. (6) suggests, an MC test with  $B$  MC samples can only produce an MC p-value no smaller than  
 527  $1/(1+B)$ . Instead of using a large number of MC samples which is computationally intensive, we approximate the ideal MC  
 528 p-value by pooling the control scores across cells. Specifically, we first align the control score distributions (across the  $B$   
 529 control gene sets, for each cell) by matching their means and variances, followed by re-centering the mean scores of different  
 530 gene sets (Box 1, steps 3b-3c, Supp. Fig. 1E,F, Supp. Note). This procedure produces a normalized disease score and  $B$   
 531 normalized control scores for each cell. Finally, we compute the  $s_{\text{cDRS}}$  p-values based on the empirical distribution of the  
 532 pooled normalized control scores across all control gene sets and all cells (Box 1, step 3d). The pooling procedure assumes  
 533 that the raw control score distributions (across the  $B$  control gene sets, for each cell) are from the same location-scale family  
 534 (e.g., the family of all normal distributions or that of all student's  $t$ -distributions) such that they can be aligned by matching  
 535 the first two moments; it is a reasonable assumption when the number of disease genes is neither too small nor too large (e.g.,  
 536  $50 < |G| < 20\%n_{\text{gene}}$ ), where the control score distributions are close to normal distributions by the central limit theorem (Supp.  
 537 Note). As shown in Supp. Fig. 1G-I, the  $s_{\text{cDRS}}$  p-values with  $B = 1,000$  is indeed able to well approximate the MC p-values  
 538 obtained using a much larger number of MC samples ( $B = 20,000$ ).

### 539 Downstream applications and MC test

$s_{\text{cDRS}}$  outputs individual cell-level p-values, (normalized) disease scores, and (normalized) control scores that can be used for a wide range of downstream applications: assessing association between a given cell type and a given disease; assessing heterogeneity in association with a given disease across a given set of cells; and assessing association between a cell-level variable and a given disease across a given set of cells. We use a unified MC test for these 3 analyses based on the disease score and control scores. Specifically, let  $t$  be the test statistic computed from the disease score of the given set of cells (the 3 analyses differ by the test statistics they use) and let  $t_1^{\text{ctrl}}, \dots, t_B^{\text{ctrl}}$  be the same test statistics computed from the  $B$  sets of control scores of the same set of cells. The MC p-value can be written as

$$p^{\text{MC}} = \frac{1 + \sum_{b=1}^B \mathbb{I}(t \leq t_b^{\text{ctrl}})}{1 + B}. \quad (7)$$

540 The MC test avoids the assumption that the cells are independent—a strong assumption in scRNA-seq analyses, e.g., when  
 541 analyzing cells in the same cluster that are dependent due to the clustering process. We can also compute an MC z-score  
 542 as  $z^{\text{MC}} = [t - \text{Mean}(\{t_b^{\text{ctrl}}\}_{b=1}^B)] / \text{SD}(\{t_b^{\text{ctrl}}\}_{b=1}^B)$ ; this MC z-score is not restricted by the MC limit of  $1/(1+B)$  but relies  
 543 the assumption that the control test statistics  $\{t_b^{\text{ctrl}}\}_{b=1}^B$  approximately follow a normal distribution. Below, we describe the  
 544 test statistics used by the 3 analyses listed above. We note that the MC test can in principle be extended to any analysis that  
 545 computes a test statistic from the disease scores of a set of cells.

546 **Assessing association between a given cell type and a given disease.** We use the top 5% quantile of the disease scores  
 547 of cells from the given cell type as the test statistic. This test statistic is robust to annotation outliers, e.g., a few misannotated  
 548 but highly significant cells. One can also use other test statistics such as the top 1% quantile or the maximum.

**Assessing heterogeneity in association with a given disease across a given set of cells.** We use Geary's  $C^{16,98}$  as the test statistic. Geary's  $C$  measures the spatial autocorrelation of the disease score across a set of cells (e.g., cells from the same cell type or cell cluster) with respect to a cell-cell similarity matrix. Given a set of  $n$  cells, the corresponding disease scores  $s_1, \dots, s_n$ , and the cell-cell similarity matrix  $W \in \mathbb{R}^{n \times n}$ , Geary's  $C$  is calculated as

$$C = \frac{(n-1) \sum_{i,j} W_{ij} (s_i - s_j)^2}{2(\sum_{i,j} W_{ij}) \sum_i (s_i - \bar{s})^2}, \quad (8)$$

549 where  $\bar{s} = \frac{1}{n} \sum_{i=1}^n s_i$ . We use the cell-cell connectivity matrix for the similarity matrix like previous works<sup>16</sup>, which corresponds  
 550 to the “connectivities” output from the scanpy function “scanpy.pp.neighbors”<sup>99</sup>. A value significantly lower than 1 indicates  
 551 positive spatial autocorrelation, suggesting cells close to each other on the similarity matrix have similar disease scores, forming  
 552 subclusters of cells with similar levels of disease association. This indicates a high level of disease association heterogeneity  
 553 across the given set of cells. We use this test to assess within-cell type disease association heterogeneity and within-cluster  
 554 association disease heterogeneity.

555 **Assessing association between a cell-level variable and a given disease across a given set of cells.** For associating a  
 556 single cell-level variable with disease, we use the Pearson’s correlation between the cell-level variable and the disease score  
 557 across the given set of cells as the test statistic. For jointly associating multiple cell-level variables with disease, we use the  
 558 regression  $t$ -statistic as the test statistic, obtained from jointly regressing the disease score against the cell-level variables.

### 559 Alternative versions of sCDRS method

560 We consider 3 alternative versions of sCDRS, involving (1) other choices of MAGMA gene window size and number of putative  
 561 disease genes, (2) other choices of cell-level raw scores, (3) other strategies of constructing putative disease genes.

562 **Other choices of MAGMA gene window size and number of putative disease genes.** We evaluated other choices of the  
 563 MAGMA gene window size for mapping SNPs to genes (0 kb or 50 kb, instead of 10 kb) and other numbers of the putative  
 564 disease genes (100, 500, or 2,000, instead of 1,000). We considered 6 configurations (varying gene window size while fixing the  
 565 putative disease gene set size as 1,000 or varying disease gene set size while fixing the gene window to be 10 kb) and evaluated  
 566 the performance of each configuration using 5 traits each with a positive control and a negative control cell type (Supp. Table  
 567 15). Results are reported in Supp. Table 16. We determined that the default setting (10 kb window size and 1,000 disease genes)  
 568 attained a reasonable overall performance relative to other parameter choices. As a secondary analysis, we investigated if the  
 569 optimal number of putative disease genes is trait-specific and specifically if it depends on the trait heritability (Supp. Table 1) or  
 570 polygenicity<sup>46</sup> ( $M_e$  for common SNPs; Supp. Table 1). We obtained the optimal number of disease genes (from 500, 1,000, or  
 571 2,000 while using 10-kb MAGMA gene window) for each trait that yields most significantly associated cells (FDR<0.1). We  
 572 then correlated the optimal gene set size with heritability and polygenicity across traits. Results are reported in Supp. Fig. 12.  
 573 We determined that the optimal disease gene set size is significantly correlated with trait polygenicity but non-significantly  
 574 correlated with trait heritability.

**Other choices of cell-level raw scores.** We evaluated two alternative cell-level raw scores, namely

$$\text{unweighted average: } s_c = \frac{1}{|G|} \sum_{g \in G} X_{cg}, \quad \text{overdispersion score: } s_c = \frac{\sum_{g \in G} [(X_{cg} - \mu_g)^2 - \sigma_{\text{tech},g}^2] / \sigma_{\text{tech},g}^2}{\sum_{g \in G} 1 / \sigma_{\text{tech},g}^2}, \quad (9)$$

575 where  $\mu_g$  and  $\sigma_{\text{tech},g}^2$  are the average expression and technical noise level of gene  $g$  respectively. The overdispersion score tests  
 576 for both overexpression and underexpression of the putative disease genes in the relevant cell population (unlike the weighted  
 577 average score which only tests for overexpression of the disease genes). We applied the two alternative scores to the TMS  
 578 FACS data and the 74 diseases and complex traits. Results are reported in Supp. Fig. 10. We determined that the weighted  
 579 average score (used by sCDRS) attained high power than the two alternative scores. It further suggests that the GWAS putative  
 580 disease genes are mostly overexpressed in the relevant cell population.

581 **Other strategies of constructing putative disease genes.** While we constructed putative disease genes using GWAS data  
 582 and mapped SNPs to genes based on genomic locations, it is potentially possible to obtain a more accurate disease gene set by  
 583 either incorporating data from other sources like protein-protein interaction data<sup>93</sup> or using a more sophisticated SNP-to-gene  
 584 linking strategy<sup>94</sup>; we did not use these approaches which may be biased towards well-studied tissues.

### 585 Simulations

586 We performed simulations on a data set with 10,000 cells subsampled from the TMS FACS data. In null simulations, we  
 587 randomly selected putative disease genes from a set of non-informative genes. We considered three numbers of putative disease  
 588 genes (100, 500, or 1,000) and four types of genes to sample from: (1) the set of all genes, (2) the set of top 25% genes with  
 589 high mean expression, (3) the set of top 25% genes with high expression variance, (4) the set of top 25% overdispersed genes,  
 590 where the level of overdispersion is calculated as the difference between the actual variance and the estimated technical variance  
 591 in the log scale data. For the MC test for cell type-disease association, we used the top 5% quantile as the test statistic and  
 592 computed the MC p-values for each cell type and each set of random putative disease genes by comparing the test statistic  
 593 from the disease scores to those computed from the 1,000 sets of control scores (see Monte-Carlo-based downstream analyses  
 594 above). In causal simulations, we randomly selected 1,000 causal disease genes, randomly selected 500 of the 10,000 cells as

causal cells and artificially perturbed their expression levels to be higher (at various effect sizes) across the 1,000 causal disease genes, and randomly selected 1,000 putative disease genes (provided as input to `sCDRS` and other methods) with various levels of overlap with the 1,000 causal disease genes. Here, the effect size corresponds to the fold change of expression of the causal genes in the causal cells (multiplicative in the original count space and additive in the log space). We performed three sets of causal simulations: (1) varying effect size from 5% to 50% while fixing 25% overlap, (2) varying level of overlap from 5% to 50% while fixing 25% effect size, (3) assigning the 528 B cells in the subsampled data to be causal (instead of the 500 randomly selected cells; varying effect size while fixing 25% overlap). The FDR and power reported in Fig. 2B and Supp. Fig. 3 are based on applying the B-H procedure<sup>100</sup> to all cells at nominal FDR=0.1. All experiments were repeated 100 times and confidence intervals were computed based on the normal distribution. We considered three methods for comparison, namely Seurat<sup>15</sup> (“score\_genes” as implemented in scanpy<sup>99</sup>), Vision<sup>16</sup>, and VAM<sup>18</sup>. To our knowledge, VAM is the only published cell-scoring method that provides cell-level association p-values. We chose to include Seurat due to its wide use and standardized its output cell-level scores (mean 0 and SD 1) before computing the cell-level p-values based on the standard normal distribution. We chose to include Vision because its outputs are nominal cell-level z-scores and can be easily converted to p-values; we again added the standardization step because otherwise the results of Vision were highly unstable. We did not include other methods like PAGODA<sup>14</sup> or AUCCell<sup>14</sup> because it is not straightforward to convert their outputs to cell-level association p-values and also because the z-scoring methods (e.g., Vision) outperformed other methods in a comprehensive evaluation in Frost et al.<sup>18</sup>

### 612 GWAS summary statistic data sets

613 We analyzed GWAS summary statistics of 74 diseases and complex traits from the UK Biobank<sup>101</sup> (47 of the 74 diseases/traits  
614 with average  $N=415K$ ) and other publicly available sources<sup>102-124</sup> (27 of the 74 diseases/traits with average  $N=212K$ ); average  
615  $N=341K$  for all 74 diseases/traits; Supp. Table 1). All diseases and traits were well-powered (heritability  $z$ -score $>6$ ), except  
616 celiac disease (Celiac), systemic lupus erythematosus (SLE), multiple sclerosis (MS), primary biliary cirrhosis (PBC), subject  
617 well being (SWB), fasting glucose (FG), and type 1 diabetes (T1D), which were included due to their clinical importance.  
618 The major histocompatibility complex (MHC) region was removed from all analyses because of its unusual LD and genetic  
619 architecture<sup>125</sup>.

### 620 scRNA-seq data sets

621 We analyzed 16 scRNA-seq or snRNA-seq data sets (Supp. Table 2). We included 3 atlas-level data sets (TMS FACS, TMS  
622 droplet, and TS FACS) to broadly associate diverse cell types and cell populations to disease; these 3 data sets cover different  
623 species (mouse and human) and different technologies (FACS and droplet), which allows us to assess the robustness of our  
624 results across different species and technologies. We included another 13 data sets that focus on a single tissue and contain  
625 finer-grained annotations of cell types and cell states. Notably, several of these data sets contain experimentally determined  
626 annotations which allow us to better validate our results, including Cano-Gamez & Soskic et al. data<sup>53</sup> containing experimentally  
627 perturbed CD4<sup>+</sup> T cell states, Nathan et al. data<sup>65</sup> containing T cells states determined by profiling surface markers using  
628 CITE-seq, Habib & Li et al. data<sup>70</sup> containing experimentally determined spatial locations for CA1 pyramidal neurons based on  
629 ISH of spatial landmark genes, Ayhan et al. data<sup>71</sup> containing experimentally determined spatial locations for CA1 pyramidal  
630 neurons (dorsal and ventral) based on surgical resection, and Richter & Deligiannis et al. data<sup>83</sup> containing experimentally  
631 determined hepatocyte ploidy levels based on Hoechst staining.

### 632 Analysis of T cells and autoimmune diseases

633 We collectively analyzed all T cells from the TMS FACS data (4,125 cells labeled as CD4<sup>+</sup>  $\alpha$ - $\beta$  T cell, CD8<sup>+</sup>  $\alpha$ - $\beta$  T cell,  
634 regulatory T cell, mature NK T cell, mature  $\alpha$ - $\beta$  T cell, or T cell in the TMS data; Supp. Table 3); the more general terms  
635 like “T cell” and “mature  $\alpha$ - $\beta$  T cell” were used for cells whose more specific identities were not clear. We processed the T  
636 cells following the standard procedure using scanpy<sup>99</sup>. First, we performed size factor normalization (10,000 counts per cell)  
637 and log transformation. Second, we selected highly variable genes and computed the batch-corrected PCA embedding using  
638 Harmony<sup>126</sup>, treating each mouse as a batch. Finally, we constructed KNN graphs and clustered the cells using the Leiden  
639 algorithm<sup>127</sup> (resolution=0.7), followed by computing the UMAP embedding. We removed 376 cells either from small clusters  
640 (less than 100 cells) or whose identities are ambiguous, resulting in 3,769 cells. We annotated the clusters based on the major  
641 TMS cell types in the cluster; the label “mature  $\alpha$ - $\beta$  T cell” was omitted because a more specific TMS cell type label (e.g.,  
642 “CD8<sup>+</sup>  $\alpha$ - $\beta$  T”) was available in the corresponding cluster. We considered cells from clusters 1-4 as clear CD4<sup>+</sup> T cells (1,686  
643 cells) and cells from clusters 1, 2, 7-9 as clear CD8<sup>+</sup> T cells (2,197 cells; the shared clusters 1 and 2 contain a mix of naive  
644 CD4<sup>+</sup> and CD8<sup>+</sup> T cells). We used diffusion pseudotime (DPT)<sup>54</sup> to assign effectorness gradient for CD4<sup>+</sup> and CD8<sup>+</sup> T cells  
645 separately, where we used the leftmost cell in cluster 2 on the UMAP as the root cell (clearly naive T cell).

646 We used MSigDB<sup>88,89</sup> (v7.1) to curate T cell signature gene sets, including naive CD4, memory CD4, effector CD4, naive  
647 CD8, memory CD8, effector CD8, Treg, Th1 (T helper 1), Th2 (T helper 2), and Th17 (T helper 17) signatures. For each T cell

signature gene set, we identified a set of relevant MSigDB gene sets (22-34, Supp. Table 7), followed by selecting the top 100 most frequent genes in these MSigDB gene sets as the T cell signature genes; a gene was required to appear at least twice and genes appearing the same number of times were all included, resulting in 62 to 513 genes for the 10 T cell signature gene sets (Supp. Table 8). For gold-standard gene sets used in the analysis of disease gene prioritization, we curated 27 putative drug target gene sets from Open Targets<sup>59</sup> (mapped to 27 of the 74 diseases/traits considered in the paper; Supp. Table 18); for a given disease, we selected all genes with drug score >0 (clinical trial phase 1 and above) and only considered diseases with at least 10 putative drug target genes. We curated 16 Mendelian diseases gene sets from Freund et al.<sup>60</sup> (mapped to 45 of the 74 diseases/traits considered in the paper; Supp. Table 18). For comparison of two gene sets, the p-value is based on Fisher's exact test and excess overlap is defined as the ratio between the observed overlap of the two gene sets and the expected overlap (by chance). Of note, for a given query gene set with a fixed size and a fixed level of excess overlap with the reference gene set, the  $-\log_{10}$  p-value increases with the size of the reference gene set; we report both excess overlap and  $-\log_{10}$  p-value while using the former as our primary metric, which is more interpretable.

For the analysis of individual cells associated with IBD, we considered 4 major clusters of T cells with >25 IBD-associated cells (FDR<0.1) and inferred the identities of the subpopulations of IBD-associated cells in these 4 clusters based on the expression of marker genes and overlap of the specifically expressed genes in each of these subpopulations with T cell signatures. First, the subpopulation of 120 IBD-associated cells in cluster 3 (which consisted of 629 cells with TMS cell type labels "CD4<sup>+</sup>  $\alpha$ - $\beta$  T" or "regulatory T") were labeled as "Treg" as described in the main paper. Second, the 75 IBD-associated cells in cluster 4 (which consisted of 165 cells with TMS cell type label "CD4<sup>+</sup>  $\alpha$ - $\beta$  T") had specifically expressed genes overlapping with a *KLRG1*<sup>+</sup> *AREG*<sup>+</sup> effector-like Treg program<sup>48</sup> characterized by high expression levels of *IL1RL1* (*ST2*), *KLRG1*, and *AREG* ( $P=1.3 \times 10^{-50}$ , Fisher's exact test; Supp. Fig. 15A,C), suggesting these cells had active functions for Treg differentiation, immunosuppression, and tissue repair<sup>48</sup> (labeled as "Effector-like Treg" in Fig. 4B). Third, the 61 IBD-associated cells in cluster 5 (which consisted of 370 cells with TMS cell type label "T cell") had high expression of Th17 marker genes (e.g., *IL23R*, *RORC*, *IL17A*; Supp. Fig. 15A) and their specifically expressed genes significantly overlapped with Th17 signatures ( $P=2.0 \times 10^{-6}$ , Fisher's exact test; Supp. Fig. 15B) and a Th17-like Treg program<sup>48</sup> ( $P=1.9 \times 10^{-24}$ , Fisher's exact test; Supp. Fig. 15C), suggesting Th17 proinflammatory functions (labeled as "Th17-like" in Fig. 4B). Finally, the 38 IBD-associated cells in cluster 9 (consisting of 499 cells with TMS cell type label "CD8<sup>+</sup>  $\alpha$ - $\beta$  T") had high expression of genes related to cytotoxicity (e.g., *IFNG*, *GZMB*, *FASL*; Supp. Fig. 15A,B), and their specifically expressed genes significantly overlapped with effector CD8<sup>+</sup> T cell signatures ( $P=1.4 \times 10^{-7}$ , Fisher's exact test; Supp. Fig. 15B), suggesting cytotoxic T cell functions (labeled as "Effector-like CD8<sup>+</sup>" in Fig. 4B).

### 677 Analysis of neurons and brain-related diseases/traits

678 For the TMS FACS data, we focused on the 484 neurons (TMS label "neuron", excluding cells with TMS label "medium  
679 spiny neuron" or "interneuron"). For the Zeisel & Muñoz-Manchado et al. data, we applied *sCDRS* to all 3,005 cells and  
680 then focused on the 827 CA1 pyramidal neurons ("level1class" label "pyramidal CA1"). For inferring spatial coordinates, we  
681 curated differentially expressed genes for each of the 6 spatial regions (dorsal vs. ventral, ventral vs. dorsal, proximal vs. distal,  
682 distal vs. proximal, deep vs. superficial, and superficial vs. deep) using the gene expression data from Cembrowski et al.<sup>69</sup>  
683 (GEO GSE67403; gene sets in Supp. Table 8). For each differential gene expression analysis, we selected genes based on  
684 FPKM>10 for the average expression in the enriched region (e.g., dorsal for the dorsal vs. ventral comparison),  $q$ -value<0.05,  
685 and  $\log_2$ (fold change) >2. We used *sCDRS* and these signature gene sets to assign 6 spatial scores for each cell. For the  
686 regression analysis, we separately regressed the *sCDRS* disease scores for each of the 6 brain-related diseases/traits (and height,  
687 a negative control trait) on each of the 6 spatial scores. We performed marginal regression instead of joint regression for these  
688 spatial scores because the inferred spatial scores for opposite regions on the same axis (e.g., dorsal vs. ventral) were highly  
689 collinear (strongly negatively correlated), and the inferred spatial scores for dorsal, proximal, and deep regions (which had  
690 strong marginal associations to diseases) had very low pairwise correlations (average  $|r|=0.10$ ; Supp. Fig. 20D), suggesting  
691 these associations were independent. We reported correlation p-values (MC test) and variance explained for each of the 6  
692 spatial scores.

### 693 Analysis of hepatocytes and metabolic traits

694 We considered all hepatocytes in the TMS FACS data (1,162 cells) and reprocessed them following the same procedure as we  
695 did for the T cells. We further filtered out low-quality cells (mitochondrial proportion $\geq$ 0.3; likely to be apoptotic or lysing  
696 cells), resulting in 1,102 hepatocytes (Fig. 5C). We curated signature gene sets for ploidy level, zonation, and putative zoned  
697 pathways. We curated 4 sets of polyploidy signatures, including differentially expressed genes (DEGs) for partial hepatectomy  
698 (PH) vs. pre-PH<sup>82</sup> (used for the polyploidy score), Cdk1 knockout (case) vs. control<sup>82</sup>, 4n vs. 2n hepatocytes<sup>83</sup>, large vs. small  
699 hepatocytes<sup>82</sup>. We curated 3 sets of diploidy signatures, including DEGs for pre-PH vs. PH<sup>82</sup>, control vs. Cdk1 knockout<sup>82</sup>, and  
700 2n vs. 4n hepatocytes<sup>83</sup>. We curated signature gene sets for pericentral (CV) and periportal (PN) hepatocytes from Halpern et  
701 al.<sup>84</sup>. We curated gene sets for putative zoned pathways from MSigDB<sup>88,89</sup> (v7.1), including glycolysis (pericentral), bile acid

702 production (pericentral), lipogenesis (pericentral), xenobiotic metabolism (pericentral), beta-oxidation (periportal), cholesterol  
703 biosynthesis (periportal), protein secretion (periportal), and gluconeogenesis (periportal). All signature gene sets are reported  
704 in Supp. Table 8. For the joint regression analysis of scDRS disease score on ploidy and zonation scores, we regressed the  
705 polyploidy score out of both the pericentral and periportal score before the joint regression because the ploidy level confounded  
706 both zonation scores. We performed joint regression instead of marginal regression here (unlike the regression analysis in the  
707 neuron section) because the polyploidy score was positively correlated with the pericentral and periportal scores (unlike the  
708 analysis in the neuron section where the 3 sets of scores had low correlations).

## 709 Data availability

710 We release our data at [https://figshare.com/projects/Single-cell\\_Disease\\_Relevance\\_Score\\_scDRS\\_](https://figshare.com/projects/Single-cell_Disease_Relevance_Score_scDRS_/118902)  
711 [/118902](https://figshare.com/projects/Single-cell_Disease_Relevance_Score_scDRS_/118902) (instructions at <https://github.com/martinjzhang/scDRS>), including GWAS summary statistics of  
712 the 74 diseases/traits, TMS FACS scRNA-seq data, reprocessed TMS FACS data (for T cells and hepatocytes), MAGMA  
713 and gold standard gene sets, and scDRS results for TMS FACS (disease scores and control scores for the 74 diseases/traits).  
714 The 16 scRNA-seq data sets were obtained as follows. The TMS FACS data and TMS droplet data<sup>19</sup> was downloaded  
715 from the official release [https://figshare.com/articles/dataset/Processed\\_files\\_to\\_use\\_with\\_](https://figshare.com/articles/dataset/Processed_files_to_use_with_scanpy_/8273102)  
716 [scanpy\\_/8273102](https://figshare.com/articles/dataset/Processed_files_to_use_with_scanpy_/8273102). The TS FACS data<sup>25</sup> was downloaded from the official release [https://figshare.com/](https://figshare.com/articles/dataset/Tabula_Sapiens_release_1_0/14267219)  
717 [articles/dataset/Tabula\\_Sapiens\\_release\\_1\\_0/14267219](https://figshare.com/articles/dataset/Tabula_Sapiens_release_1_0/14267219). The Cano-Gamez & Soskic et al. data<sup>53</sup>  
718 was downloaded from <https://www.opentargets.org/projects/effectorness>. The Nathan et al. data<sup>65</sup>  
719 was downloaded from <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE158769>. The Zeisel  
720 & Muñoz-Manchado et al. data<sup>66</sup> was downloaded from <http://linnarssonlab.org/cortex/>. The Zeisel et  
721 al. data<sup>74</sup> was downloaded from <http://mousebrain.org/downloads.html>. The Habib & Li et al. data<sup>70</sup> and  
722 Habib, Avraham-Davidi, & Basu et al. data<sup>76</sup> were downloaded from [https://singlecell.broadinstitute.org/](https://singlecell.broadinstitute.org/single_cell)  
723 [single\\_cell](https://singlecell.broadinstitute.org/single_cell). The Ayhan et al. data<sup>71</sup> was downloaded from <https://cells.ucsc.edu/human-hippo-axis/>.  
724 The Yao et al. data<sup>75</sup> was downloaded from <https://assets.nemoarchive.org/dat-jb2f34y>. The Zhong et  
725 al. data<sup>77</sup> was downloaded from <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE119212>.  
726 The Aizarani et al. data<sup>87</sup> was downloaded from [https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=](https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE124395)  
727 [GSE124395](https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE124395). Halpern & Shenhav et al. data<sup>84</sup> was downloaded from [https://www.ncbi.nlm.nih.gov/geo/](https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE84498)  
728 [query/acc.cgi?acc=GSE84498](https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE84498). The Richter & Deligiannis et al. data<sup>83</sup> (annotated count matrix) was obtained via  
729 communication with the authors (raw data publicly available via links in the paper). The Taychameekiatchai et al. data<sup>86</sup> is not  
730 publicly available, but was obtained via communication with the authors.

## 731 Code availability

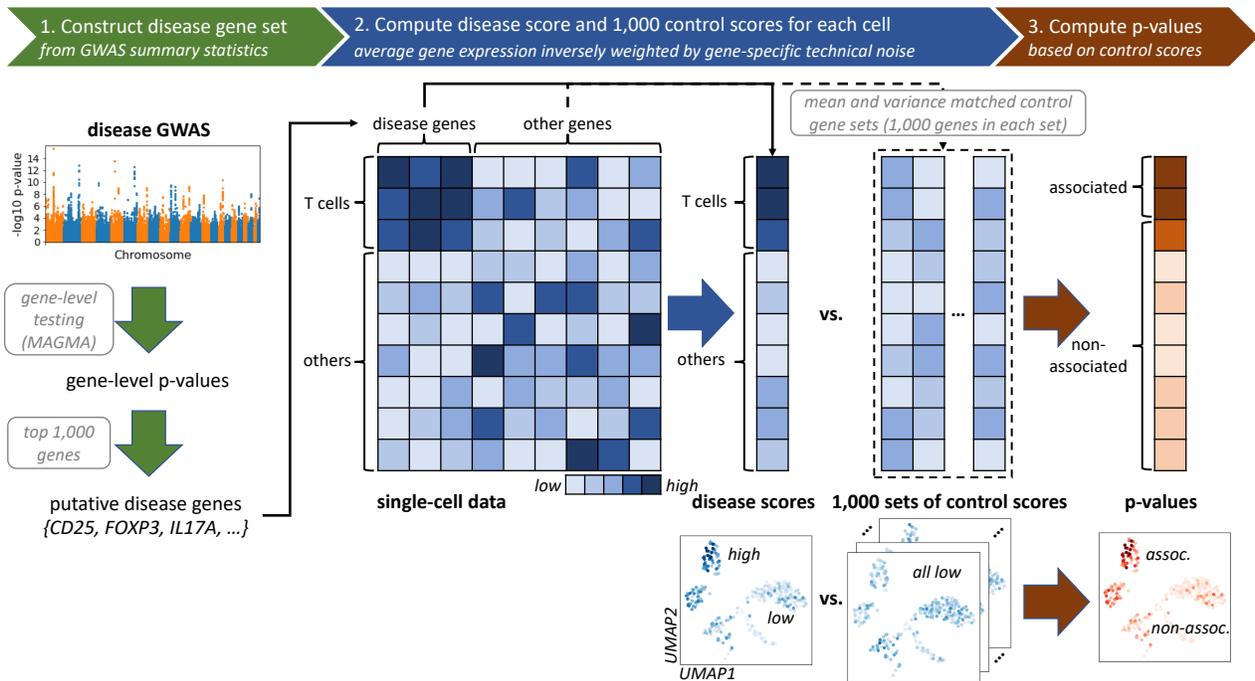
732 Software implementing scDRS and its downstream applications and a web interface for interactively exploring results of  
733 scDRS are available at <https://github.com/martinjzhang/scDRS>.

## 734 Acknowledgements

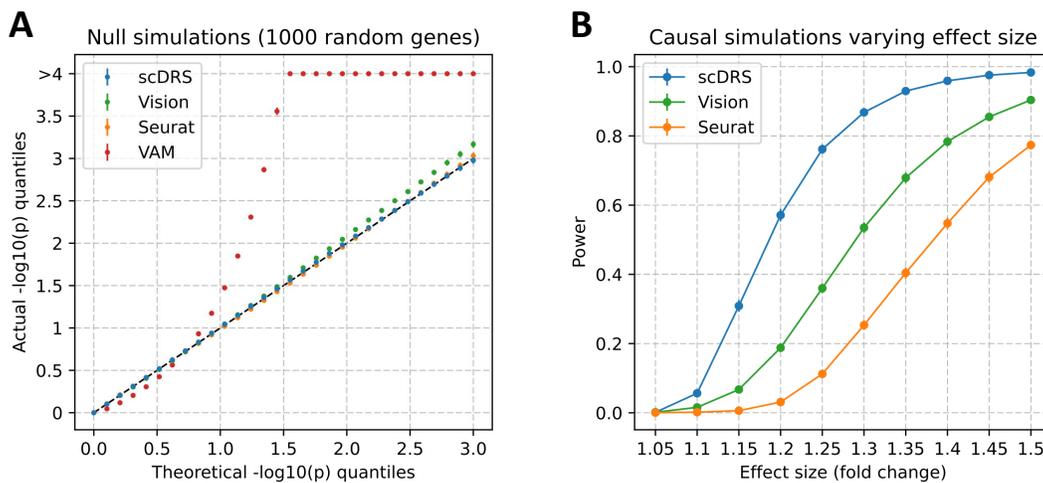
735 We thank Huwenbo Shi, Katherine Siewert-Rocks, Tiffany Amariuta, and Xiaoyu Xu for helpful suggestions. This research  
736 was funded by NIH grants U01 HG009379, R01 MH101244, R37 MH107649, and R01 MH115676.

## 737 Competing interests

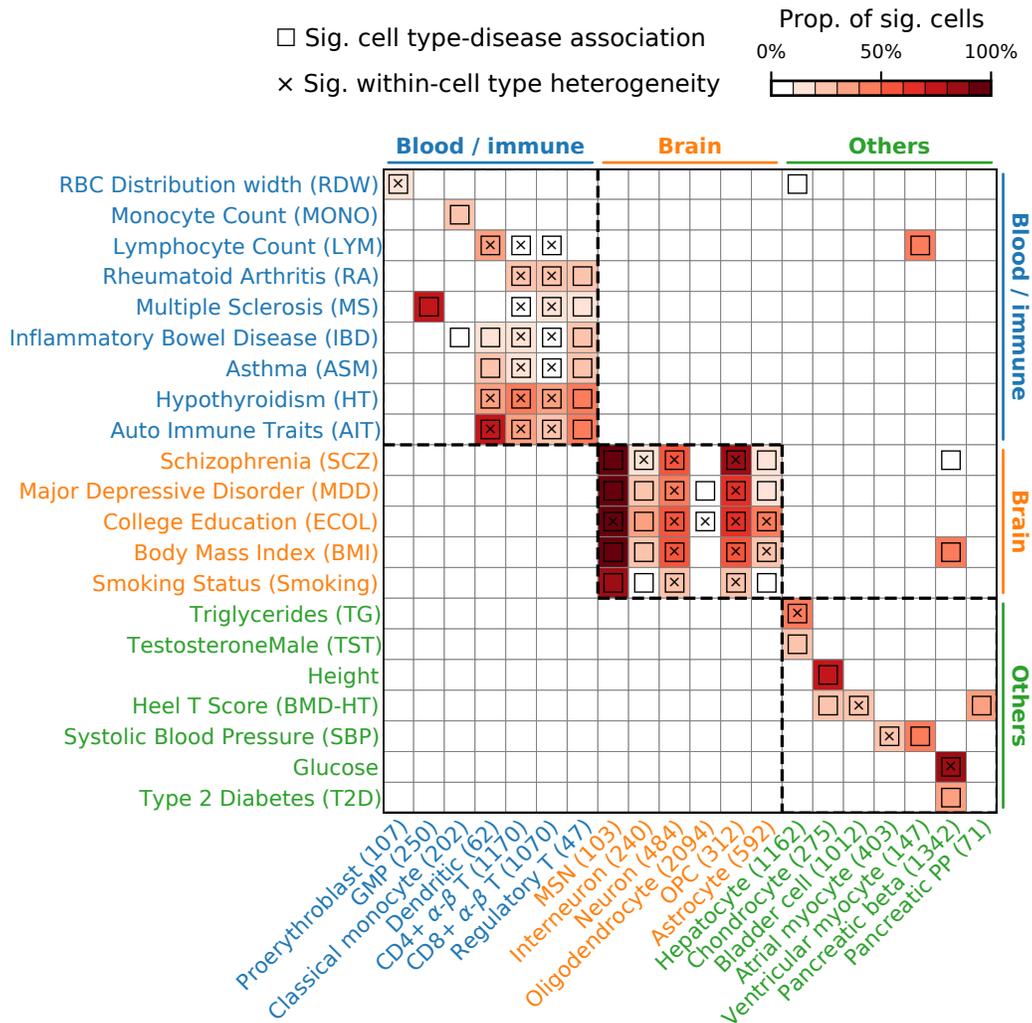
738 The authors declare no competing interests.



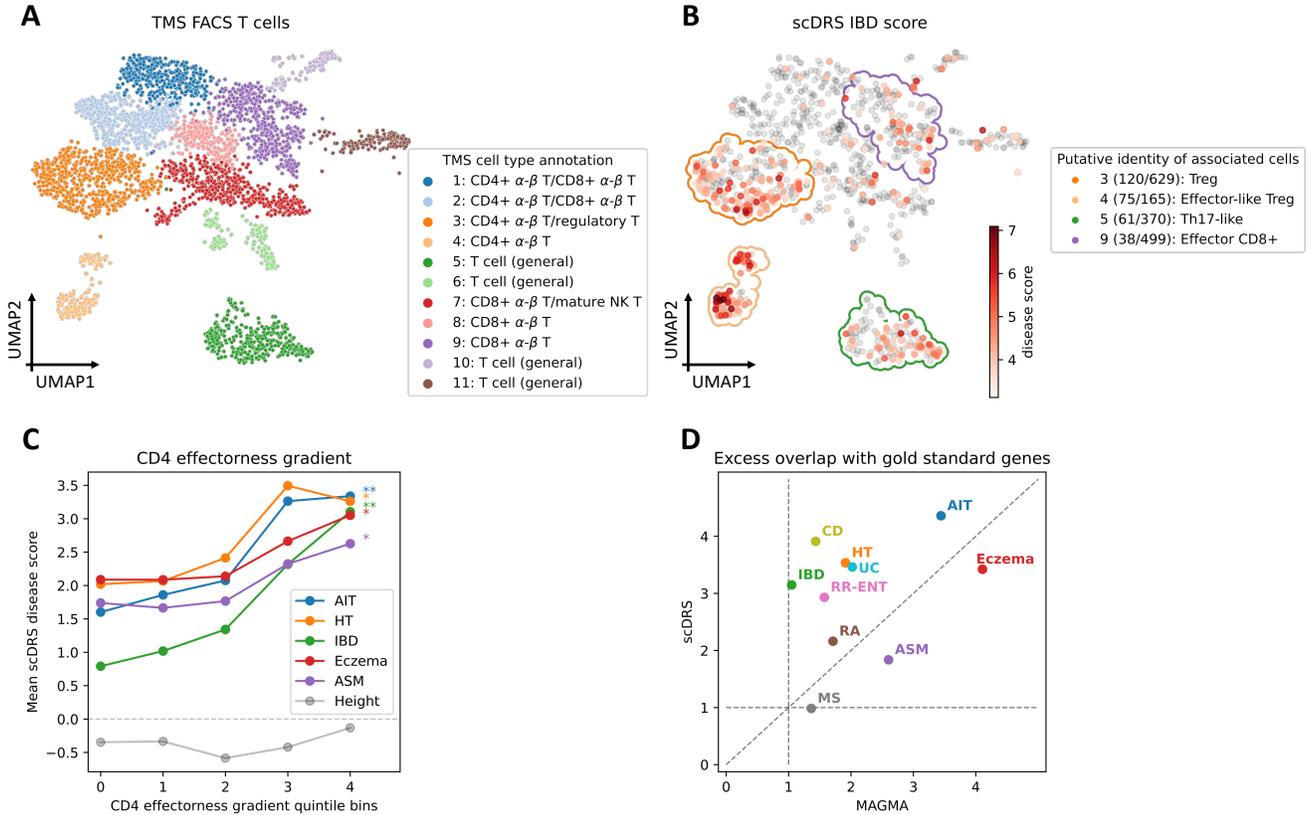
**Figure 1. Overview of sCDRS method.** sCDRS takes disease GWAS and scRNA-seq data sets as input and outputs individual cell-level p-values for association with the disease. **(1)** sCDRS constructs a set of putative disease genes from GWAS summary statistics by selecting the top 1,000 MAGMA genes; these putative disease genes are expected to have higher expression levels in the relevant cell population. **(2)** sCDRS computes a raw disease score for each cell, quantifying the aggregate expression of the putative disease genes in that cell; to maximize power, each putative disease gene is inversely weighted by its gene-specific technical noise level in the scRNA-seq data. sCDRS also computes a set of 1,000 Monte Carlo raw control scores for each cell, in each case using a random set of control genes matching the gene set size, mean expression, and expression variance of the putative disease genes. **(3)** sCDRS normalizes the raw disease score and raw control scores across gene sets and across cells, and then computes a p-value for each cell based on the empirical distribution of the pooled normalized control scores across all control gene sets and all cells. The choice of 1,000 for the number of putative disease genes and the choice of 1,000 for the number of control scores are independent.



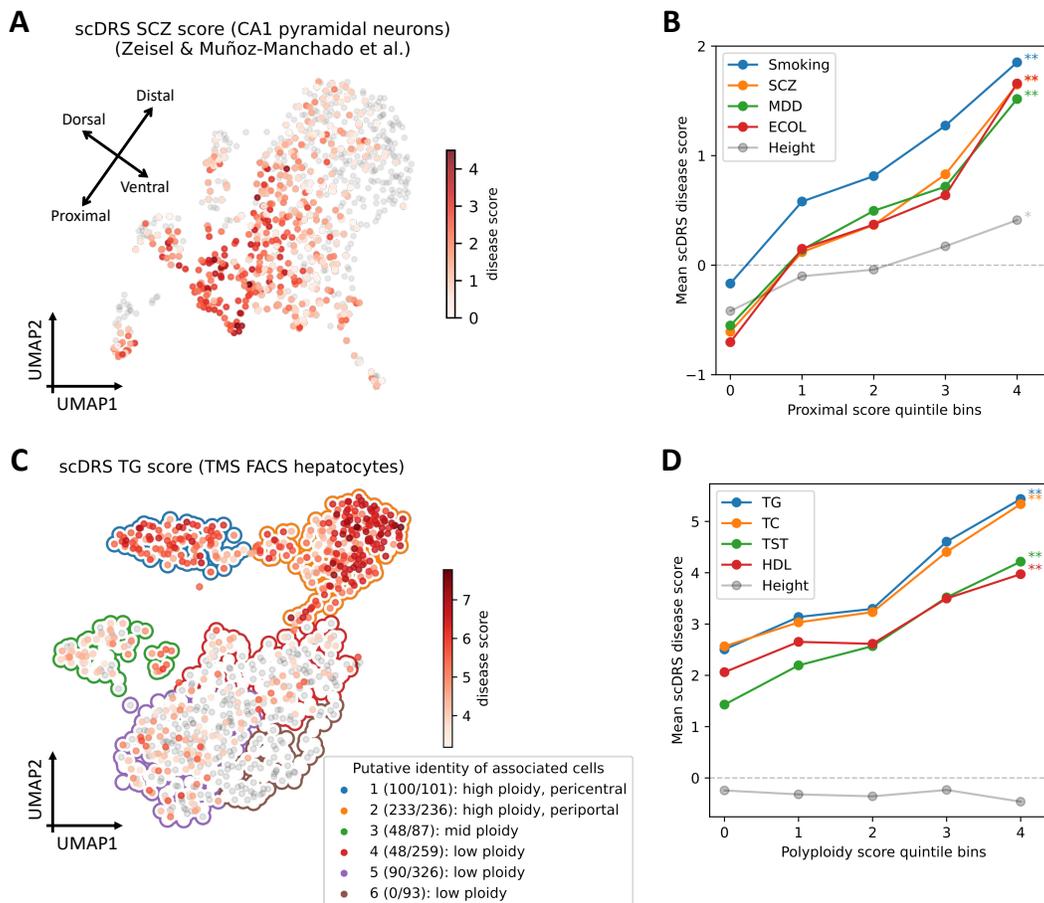
**Figure 2. Results for null and causal simulations. (A)** Q-Q plot for null simulations using 1,000 randomly selected genes as the putative disease genes. The x-axis denotes theoretical  $-\log_{10}$  p-value quantiles and the y-axis denotes actual  $-\log_{10}$  p-value quantiles for different methods. Each point is based on 100 simulation replicates (with 10,000 cells per simulation replicate); error bars denote 95% confidence intervals (all error bars are  $<0.05$  from the point estimate). Numerical results are reported in Supp. Table 9 and additional results are reported in Supp. Fig. 2. **(B)** Power for causal simulations with perturbed expression of causal genes in causal cells. We report the power at FDR=0.1 for different methods and different effect sizes. Each point is based on 100 simulation replicates (with 10,000 cells per simulation replicate); error bars denote 95% confidence intervals (all error bars are  $<0.02$  from the point estimate). Numerical results are reported in Supp. Table 11 and additional results are reported in Supp. Fig. 3.



**Figure 3. Disease associations at the cell type-level.** We report  $s_{cDRS}$  results for individual cells aggregated at the cell type-level for a subset of 20 cell types and 21 diseases/traits in the TMS FACS data. Each row represents a disease/trait and each column represents a cell type (with number of cells indicated in parentheses). Heatmap colors for each cell type-disease pair denote the proportion of significantly associated cells (FDR<0.1 across all cells for a given disease). Squares denote significant cell type-disease associations (FDR<0.05 across all pairs of the 120 cell types and 74 diseases/traits; p-values via MC test; Methods). Cross symbols denote significant heterogeneity in association with disease across individual cells within a given cell type (FDR<0.05 across all pairs; p-values via MC test; Methods). Heatmap colors (>10% of cells associated) and cross symbols are omitted for cell type-disease pairs with non-significant cell type-disease associations via MC test (heatmap colors omitted for 2 pairs (GMP-MONO and Dendritic-MS) and cross symbols omitted for 6 pairs (CD4<sup>+</sup>  $\alpha$ - $\beta$  T-MONO, CD8<sup>+</sup>  $\alpha$ - $\beta$  T-MONO, oligodendrocyte-MONO, bladder cell-ASM, hepatocyte-ECOL, and dendritic-BMD-HT)). Auto Immune Traits (AIT) represents a collection of diseases in the UK Biobank that characterize autoimmune physiopathogenic etiology<sup>128,129</sup>. Abbreviated cell type names include red blood cell (RBC), granulocyte monocyte progenitor (GMP), medium spiny neuron (MSN), and oligodendrocyte precursor cell (OPC). Neuron refers to neuronal cells with undetermined subtypes (whereas MSN and interneuron (non-overlapping with neuron) refer to neuronal cells with those inferred subtypes). Complete results for 120 cell types and 74 diseases/traits are reported in Supp. Fig. 4 and Supp. Table 12.



**Figure 4. Associations of T cells with autoimmune diseases.** (A) UMAP visualization of T cells in the TMS FACS data. In the legend, cluster labels are based on annotated TMS cell types in the cluster. Composition of tissue, sex, and age of cells in each cluster are reported in Supp. Fig. 13. (B) Subpopulations of T cells associated with IBD. Significantly associated cells (FDR<0.1) are denoted in red, with shades of red denoting  $s_{\text{CDRS}}$  disease scores; non-significant cells are denoted in grey. Cluster boundaries indicate the corresponding T cell clusters from panel A. In the legend, numbers in parentheses denote the number of IBD-associated cells vs. the total number of cells and cluster labels are based on the putative identity of the IBD-associated subpopulations, for the 4 of 11 clusters with IBD-associated cells. Results for the other 9 autoimmune diseases and height are reported in Supp. Fig. 14. (C) Association between  $s_{\text{CDRS}}$  disease score and CD4 effectorness gradient across CD4<sup>+</sup> T cells for 5 representative autoimmune diseases and height, a negative control trait. The x-axis denotes CD4 effectorness gradient quintile bins and the y-axis denotes average  $s_{\text{CDRS}}$  disease score in each bin for each disease. \* denotes  $P < 0.05$  and \*\* denotes  $P < 0.005$  (MC test). Numerical results for all 10 autoimmune diseases are reported in Supp. Table 17. (D) Excess overlap of genes prioritized by  $s_{\text{CDRS}}$  with gold standard gene sets. The x-axis denotes the excess overlap of genes prioritized by MAGMA and the y-axis denotes the excess overlap of genes prioritize by  $s_{\text{CDRS}}$ , for each of 10 autoimmune diseases. The median ratio of (excess overlap – 1) for  $s_{\text{CDRS}}$  vs. MAGMA was 2.02. Numerical results are reported in Supp. Table 19.



**Figure 5. Associations of neurons with brain-related disease/traits and hepatocytes with metabolic traits. (A)** Subpopulations of CA1 pyramidal neurons associated with SCZ in the Zeisel & Muñoz-Manchado et al. data. Colors of cells denote  $sCDRS$  disease scores (negative disease scores are denoted in grey). We include a visualization of putative dorsal-ventral and proximal-distal axes (see text). Results for all 6 brain-related diseases/traits and height are reported in Supp. Fig. 20B. **(B)** Association between  $sCDRS$  disease score and proximal score across CA1 pyramidal neurons for 4 representative brain-related disease/traits and height, a negative control trait. The x-axis denotes proximal score quintile bins and the y-axis denotes average  $sCDRS$  disease score in each bin for each disease. \* denotes  $P < 0.05$  and \*\* denotes  $P < 0.005$  (MC test). Results for all 6 spatial scores and all 6 brain-related diseases/traits are reported in Supp. Fig. 22 and Supp. Table 22. **(C)** Subpopulations of hepatocytes associated with TG in the TMS FACS data. Significantly associated cells ( $FDR < 0.1$ ) are denoted in red, with shades of red denoting  $sCDRS$  disease scores; non-significant cells are denoted in grey. Cluster boundaries indicate the corresponding hepatocyte clusters. In the legend, numbers in parentheses denote the number of TG-associated cells vs. the total number of cells and cluster labels are based on the putative identity of cells in the cluster. Results for the other 8 metabolic traits and height are reported in Supp. Fig. 23. **(D)** Association between  $sCDRS$  disease score and polyploidy score for 4 representative metabolic traits and height, a negative control trait. The x-axis denotes polyploidy score quintile bins and the y-axis denotes average  $sCDRS$  disease score in each bin for each disease. \* denotes  $P < 0.05$  and \*\* denotes  $P < 0.005$  (MC test). Results for all 3 scores (polyploidy score, pericentral score, periportal score) and all 9 metabolic traits (and height) are reported in Supp. Fig. 25 and Supp. Table 23.

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