Stratified Linkage Disequilibrium Score Regression reveals enrichment of eQTL effects on complex traits is not tissue specific

Authors

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Abstract

Both gene expression levels and eQTLs (expression quantitative trait loci) are partially tissue-specific, complicating the detection of eQTLs in tissues with limited sample availability, such as the brain. However, eQTL overlap between tissues might be non-trivial, allowing for inference of eQTL functioning in the brain via eQTLs measured in readily accessible tissues, e.g. whole blood. Using Stratified Linkage Disequilibrium Score Regression (SLDSR), we quantify the enrichment in GWAS signal of blood and brain eQTLs in genome-wide association study (GWAS) on 11 complex traits (schizophrenia, BMI, educational attainment, Crohn's disease, rheumatoid arthritis, ulcerative colitis, age at menarche, coronary artery disease, height, LDL levels, and smoking behavior). Our analyses established significant enrichment of blood and brain eQTLs in their effects across all traits. As we do not know the true number of causal eQTLs, it is difficult to determine the precise magnitude of enrichment. We found no evidence for tissue-specific enrichment in GWAS signal for either eQTLs uniquely seen in the brain or whole blood. To follow up on our findings, we tested tissue-specific enrichment of eQTLs discovered in 44 tissues by the Genotype-Tissue Expression (GTEx) consortium, and, again, found no tissue-specific eQTL effects. We further integrated the GTEx eQTLs with SNPs associated with tissue-specific histone modifiers, and interrogate its effect on rheumatoid arthritis and schizophrenia. We observed substantially enriched effects on schizophrenia, though again not tissue-specific. Finally, we extracted eQTLs in tissue-specific differentially expressed genes, and determined their effects on rheumatoid arthritis and schizophrenia. We conclude that, while eQTLs are strongly enriched in GWAS signal, the enrichment is not specific to the tissue used in eQTL discovery. Therefore, working with relatively accessible tissues, such as whole blood, as proxy for eQTL discovery is sensible; and restricting lookups for GWAS hits to a specific tissue might not be advisable.

Key words

eQTL; gene expression; tissue-specificity; complex traits; enrichment; genome-wide; brain; whole blood; stratified linkage disequilibrium score regression; SLDSR; eQTL discovery

Introduction

The aim of genome-wide association studies (GWASs) is to detect statistically significant associations between genetic variants, such as single nucleotide polymorphisms (SNPs), and a trait of interest (Hirschhorn and Daly 2005). GWASs have identified many genetic variants and thereby provided insights into the genetic architecture of complex traits (Hirschhorn and Daly 2005; Visscher et al. 2012). However, as a large number of variants identified through GWASs are located outside of coding regions and specific knowledge of regulatory elements is limited, uncovering a relationship between GWAS hits and biological function has proven to be complicated (Lowe and Reddy 2015). Expression quantitative trait loci (eQTLs) contain SNPs that influence gene expression, and are not necessarily located in coding regions. eQTLs may aid functional annotation of SNPs that have been identified in a GWAS and are located outside of coding regions (Morley et al. 2004; Lowe and Reddy 2015). Previous work has found substantial enrichment of eQTLs among GWAS hits (Manolio et al. 2009; Nicolae et al. 2010; Torres et al. 2014) and an enrichment in their genome-wide effect on complex traits (Davis et al. 2013). Therefore, eQTLs are viewed as an important tool in moving from genome-wide association to biological interpretation.

As a result of difference in gene expression between cells originating from different tissues, eQTLs are potentially tissue-specific (Hernandez et al. 2012; GTEx Consortium 2015). Tissue-specificity poses no problem if the tissue of interest is readily available for research, such as whole blood. However, discovery of eQTLs gets complicated when measurement of expression levels in a tissue is limited by ethical and practical considerations, for example in brain tissue. Several studies have shown that the overlap between eQTLs from different tissues might actually be larger than initially assumed (Ding et al. 2010; Nica et al. 2011). The Genotype-Tissue Expression (GTEx)

74 consortium identified eQTLs in a wide range of human tissues and showed that 54-90% of the eQTLs
75 identified in one tissue are also designated as an eQTL in at least one other tissue (GTEx Consortium
76 2015; Aguet et al. 2016). In another study, Liu *et al* (2016) found a high average pairwise genetic
77 correlation (r_g=0.738) of local gene expression between tissues. Nevertheless, small differences in
78 terms of eQTL effect may be of considerable importance in terms of the effect an eQTL might have
79 on complex traits related to specific tissues. It is, therefore, worthwhile to investigate the specific
80 utility of tissue-specific eQTLs in their effect on complex traits, as studied in GWAS, as the discovery
81 of eQTLs for tissues such as the brain might be advanced by eQTLs discovered in more accessible
82 tissues, such as whole blood. The use of accessible tissues, though, depends on a substantial degree
83 of similarity of eQTL effect across tissue, and to what extend eQTL differences between tissues are
84 important in complex trait etiology.

85 Stratified Linkage Disequilibrium Score Regression (SLDSR) is a technique that estimates the
86 SNP-heritability (h^2_{SNP}) of a trait based on GWAS summary statistics (Bulik-Sullivan et al. 2015;
87 Finucane et al. 2015). By simultaneously analyzing multiple categories of SNPs (annotations), SLDSR
88 can partition h^2_{SNP} by annotation (h^2_{annot}) and thereby provides a way to jointly quantify the
89 enrichment in GWAS signal of several annotations. Here, we extend SLDSR by including annotations
90 containing *cis*-eQTLs, i.e. eQTLs located closely to the gene with which they associate (Brem et al.
91 2002; Ramasamy et al. 2014), discovered in multiple tissues. To this end, we perform analyses based
92 on representative eQTL resources, and consider a variety of traits as outcomes.

93 Firstly, we selected all eQTLs per gene discovered in large samples of RNA expression levels
94 assessed in whole blood (N=4896)(Wright et al. 2014; Jansen et al. 2017) and in brain tissues (N=134)
95 (Ramasamy et al. 2014), and quantified the contribution of these blood and brain eQTLs to the
96 genetic variance in complex traits captured in GWAS. We then estimated tissue-specific eQTL effects
97 on complex traits by quantifying the enrichments of eQTLs uniquely found in whole blood or
98 uniquely found in brain, conditional on the enrichment of the complete blood eQTL annotation or
99 complete brain eQTL annotation, respectively. We considered the effect of eQTLs on 11 complex

100 traits: schizophrenia, BMI, educational attainment, Crohn's disease, rheumatoid arthritis, ulcerative
101 colitis, age at menarche, coronary artery disease, height, LDL levels, and smoking behavior.
102 Secondly, we retrieved all eQTLs identified in any of the 44 tissues from the GTEx consortium
103 (N=70-361, median=126.5)(GTEx Consortium 2015; Aguet et al. 2016). We considered the
104 enrichment in GWAS signal of the union of all GTEx eQTLs, and, additionally, the enrichment of
105 tissue-specific eQTL effects on top of the union of all GTEx eQTLs. We expected to observe tissue-
106 specific enrichment of eQTLs in their effects on complex traits related to the tissue in question, e.g.
107 eQTLs discovered in immune-related tissues are expected to show higher enrichments in their effect
108 on immune-related traits compared to eQTLs found in skin tissue. We considered tissue-specific
109 enrichment of *cis*-eQTLs in their effect on schizophrenia (a disorder where there is strong prior
110 evidence for the involvement of processes in the brain) and rheumatoid arthritis (a disease with
111 strong prior evidence for the involvement of processes in immune tissue) as GWAS for these traits
112 are well powered for extended LD-score-based analyses. We further considered the enrichment of
113 the intersection of *cis*-eQTLs discovered in any tissue, and histone modification in a specific tissue
114 (i.e. tissue-specific epigenetically changed chromatin states in regulatory regions). Finally, we
115 explored the enrichment in GWAS signal of eQTLs for tissue-specific differentially expressed genes.
116 Our analyses were designed to elucidate the relation between eQTLs and complex traits, and
117 to quantify the extent to which this relation is dependent on the tissue used in eQTL discovery. Our
118 analysis further considered the enrichment of genomic regions related to gene expression and
119 epigenetically modified in specific tissues.
120

121 ## Material and Methods

122 ### SLDSR method

123 A measure of linkage disequilibrium (LD) for each SNP, called an "LD score", can be computed by
124 taking the sum of correlations between that SNP and all neighboring SNPs (Bulik-Sullivan et al. 2015;
125 Finucane et al. 2015). Under a polygenic model, LD scores are expected to show a linear relationship

126 with GWAS test statistics of corresponding SNPs, where the slope is proportional to h^2_{SNP}. For SLDSR,
127 LD scores are based on only (functional) parts of the genome and used as predictors in a multiple
128 linear regression (Finucane et al. 2015). In this manner, SLDSR is able to partition h^2_{SNP} into parts that
129 are explained by these parts of the genome (i.e. h^2_{annot}), while accounting for influences of the
130 remaining annotations in the model. The enrichment of an annotation is then obtained by taking the
131 ratio of h^2_{annot} over the proportion of SNPs that fall within that annotation. For eQTLs, the
132 denominator, i.e. the number of SNPs in the annotation, is a complicated quantity: not all significant
133 eQTLs are likely causal; whereas including only lead, or putative causal, eQTLs may result in very
134 small annotations located near genes and other regulatory elements, which presents a risk of
135 inflated estimates of the enrichment in GWAS signal. What constitutes an eQTL is sufficiently vague
136 and open for interpretation for us to consider the effect of multiple inclusion rules for inclusion of a
137 SNP into the eQTL annotation. Since eQTLs are essentially discovered in what amounts to a local
138 GWAS, we expect the average LD score of eQTLs to be higher than that of an average SNP, which
139 may influence the results of downstream SLDSR analysis. In order to break the relation between LD
140 score and probability of inclusion, we consider eQTL annotations which are based on a sample of
141 from all significant eQTLs for a given probe. First, we included the most strongly associated SNP, a
142 SNP with a high expected LD score. Second, we included one SNP per probe with a median *p*-value.
143 Third, we included one SNP per probe with a mean *p*-value. Fourth, we included the 10 most
144 strongly associated SNPs per probe. Finally, we included all SNPs significantly associated with gene
145 expression after FDR correction at α=0.05. We add each annotation separately to the baseline
146 categories in an SLDSR model, and determined how the various *p*-value thresholds influence the
147 SLDSR coefficient and its test statistic. For each annotation, we looked up the SNPs in the baseline
148 category, and extracted their baseline LD scores and minor allele frequencies (MAF). We then
149 compared the mean LD score, median LD score and mean MAF between the annotations and the
150 entire baseline category. Based on the results (S1 Figure – S2 Figure, S3 Table), we consider all

151 significant *cis*-eQTLs as an annotation, and retain additional gene-centric and regulatory annotations
152 ins the model.
153
154 **Target traits**
155 As outcome for SLDSR, we used summary statistics of GWASs on Crohn's disease (Jostins et al. 2012),
156 rheumatoid arthritis (Okada et al. 2014), ulcerative colitis (Jostins et al. 2012), BMI (EK et al. 2010),
157 educational attainment (Rietveld et al. 2013), schizophrenia (Ripke et al. 2014), age at menarche
158 (Perry et al. 2014), coronary artery disease (Schunkert et al. 2011), height (Allen et al. 2010), LDL
159 levels (Teslovich et al. 2010), and smoking behavior (Furberg et al. 2010). The first three traits were
160 chosen because they are related to the immune system and are therefore expected to reveal
161 considerable enrichment of blood eQTL signal (Jostins et al. 2012; Okada et al. 2014). Similarly, brain
162 eQTLs are expected to show substantial enriched effects due to previous reports on the involvement
163 of the central nervous system (CNS) in schizophrenia (Ripke et al. 2014), educational attainment
164 (Rietveld et al. 2013), and BMI (Vimaleswaran et al. 2012). Of course, these traits do not perfectly
165 align with either tissue, e.g. the immune system has been implicated in the etiology of schizophrenia
166 (Andreassen et al. 2015) and BMI (Karalis et al. 2009), and might therefore also be enriched in their
167 effects for the other eQTL set. Enrichment of blood and brain eQTL effects on the remaining traits
168 was calculated to contrast the results with traits for which we do not have a strong *a priori*
169 expectation of the relationship between trait and tissue.
170 The discovery sample for detection of blood eQTLs (Wright et al. 2014; Jansen et al. 2017)
171 included participants from the Netherlands Twin Register (NTR)(Boomsma et al. 2008) and
172 participants from the Netherlands Study of Depression and Anxiety (NESDA)(Penninx et al. 2008).
173 These two cohorts did not participate in the GWAS for schizophrenia, Crohn's disease, rheumatoid
174 arthritis, ulcerative colitis, or coronary artery disease. However, participants from these two cohorts,
175 not necessarily the same ones, did participate in the GWAS for height, BMI, LDL levels, smoking
176 behavior, educational attainment, and age at menarche. For educational attainment and smoking

177 behavior, we were able to obtain summary statistics omitting subjects from NTR/NESDA. For both
178 these traits, we looked at trait-specific enrichment of blood and brain eQTL effect in GWAS signal,
179 comparing results from using publicly available datasets with using summary statistics based on the
180 same sample without subjects from the NTR or NESDA. The results did not reveal appreciable
181 differences between the respective datasets for educational attainment, but did show substantial
182 differences for smoking behavior (S4 Figure). This latter finding could conceivably be a function of
183 relatively strong effects of smoking behavior on gene-expression levels (Vink et al. 2015). Therefore,
184 the remaining analyses for smoking behavior were performed using the summary statistics omitting
185 the NTR and NESDA, whereas analyses for the remaining traits (height, BMI, LDL levels, and
186 educational attainment) were run using publicly available summary statistics. This caveat only
187 applies to eQTL annotations based on NTR/NESDA data (i.e. whole blood). We note that the issue of
188 overlap also applies to other techniques where the error covariance is assumed to be zero (e.g.
189 TWAS, mendelian randomization analysis, SMR, etc.).
190

191 **Blood and brain eQTL enrichment**

192 A catalog of whole blood *cis*-eQTLs was obtained from Jansen *et al* (2017; Wright et al. 2014), where
193 all eQTLs significantly associated with gene expression in whole blood for each probe set were
194 selected for inclusion in our whole blood eQTL annotation. A list of brain eQTLs was obtained from
195 the UK brain expression consortium (UKBEC), for which the analyses are described in Ramasamy *et al*
196 (2014). We based the brain eQTL annotation on SNPs that were significantly associated with the
197 average gene expression across 12 brain regions. SLDSR annotations were constructed as per the
198 instructions in Bulik-Sullivan et al. and Finucane et al. (2015). To guard against upward bias in the
199 eQTL enrichment signal, two extra annotations containing SNPs within a 500 base pair (bp) and
200 100bp window around any eQTL were constructed for each eQTL set (Finucane et al. 2015). To
201 ensure that the enrichment of eQTL effects in GWAS signal was not in fact caused by their proximity
202 to the genes they influence, an additional gene centric annotation was computed, which contained

203 all genes for which eQTLs were included. Finally, we performed an inverse-variance weighted meta-
204 analysis across the traits to determine the average effect of blood and brain eQTLs on complex traits
205 in general.
206

207 **Tissue-specific eQTL enrichment**

208 To distinguish between the effects of blood- and brain-specific eQTLs, we split each annotation into
209 two sets based on the overlap in genes that were tagged by eQTLs from both tissue. That is, the
210 brain eQTL annotation was split into an annotation of brain eQTLs which regulate genes for which
211 also at least one blood eQTL was found, and a second annotation of eQTLs that tagged genes for
212 which only brain eQTLs were found. Likewise, the blood eQTL annotation was split into an
213 annotation containing only eQTLs that tagged genes for which eQTLs from both tissue was found,
214 and an annotation consisting of blood eQTLs that tagged genes for which only eQTLs have been
215 found in blood. In doing so, we are saying that the effect of an eQTL is mediated via the gene it is
216 associated with. Then, if two different SNPs are associated with the expression of the same gene,
217 but in different tissues, this gene is likely the mechanism by which the SNP influences a trait.
218 Contrary, when the same SNP affects different genes in different tissues, this SNP can be seen to
219 have a tissue-specific mediation of its effect. We thus define eQTLs shared across tissue as eQTLs
220 that influence a common gene in separate tissues.
221

222 **Enrichment of eQTLs from 44 tissues**

223 There are several limitations to above mentioned analyses of tissue-specific enrichments of eQTL
224 effects in GWAS signal. The eQTLs are obtained from two different projects, which vary in terms of
225 sample size and their definition of an eQTL. To mitigate the heterogeneity between studies, and to
226 extend to additional tissues. We performed additional analyses using eQTLs obtained by a common
227 pipeline from 44 tissues (see S5 Table) and based on a broader eQTL locus definition (GTEx
228 Consortium 2015; Aguet et al. 2016). For each of the 44 tissues, we created annotations for analysis

229 in SLDSR following the previously described procedure. Analogous to the procedure of Finucane *et al*
230 (2015) for cell-type-specific analysis using SLDSR, we did not specify windows for the individual GTEx
231 annotations, but included an additional annotation that contained the union of all GTEx eQTLs, i.e.
232 all SNPs that are designated as part of at least one of the 44 individual GTEx annotations, and added
233 a 100bp and 500bp window around this union of GTEx eQTLs. SLDSR is essentially a multiple
234 regression and, due to the high number of models and high number of predictors (i.e. annotations)
235 in each model, has a high multiple testing burden. As such, it requires well-powered GWAS in order
236 to accurately partition the heritability the various annotations (Bulik-Sullivan et al. 2015; Finucane et
237 al. 2015). Based on the Z-score of the SNP-heritability and previous reports of substantial influence
238 of either tissue in the etiology of the traits (Okada et al. 2014; Ripke et al. 2014; Finucane et al. 2015;
239 Finucane et al. 2017), we obtained two well-powered traits, one for which we assume there to be
240 significant enrichment in signal for blood eQTLs (rheumatoid arthritis) and one for brain eQTLs
241 (schizophrenia). For each of these two traits, we ran one SLDSR model containing only the baseline
242 categories and the union of GTEx eQTLs, and 44 additional models with the two previous
243 annotations and one of the individual GTEx annotations at a time.

244 GTEx has relative small sample sizes for the brain eQTL discovery (mean=89 sample size,
245 range=72-103) compared to other tissues (mean=160 sample size, range=70-361) (GTEx Consortium
246 2015; Aguet et al. 2016). To investigate the effect of differences in sample size on estimates of
247 enrichments in GWAS signal, we collapsed the union of individual brain eQTL annotations into a
248 shared brain eQTL annotation (i.e. an eQTL found in at least one of the GTEx brain annotations was
249 included in the shared brain eQTL annotation). This annotation was then analyzed as an additional
250 GTEx eQTL annotation. We further tested the relationship between tissue sample size and tissue
251 eQTL enrichment.

252

253 **Enrichment of the intersection between eQTLs and histone marks**

254 The availability of annotations based on tissue-specific histone marks made it possible to create an
255 annotation that represents the intersection between eQTLs and this type of epigenetic modification
256 related to enhancers and promoters of actively transcribed genes. We obtained LD score
257 annotations of SNPs in regions that bear histone marks in cells from the CNS or immune system from
258 Finucane *et al* (2015). Out of the 220 cell-type-specific histone mark that were available, 101 were
259 found in the CNS or immune tissues. For each of the 101 annotations of SNPs in cell-type-specific
260 histone marks, we extracted its intersection with the union of GTEx eQTLs and made a new
261 annotation of eQTLs which intersected with histone marks (i.e. SNPs found in both annotations). We
262 then analyzed each of the intersection annotations individually in a model together with the baseline
263 categories, the union of GTEx eQTLs, and the corresponding cell-type-specific histone marks.
264 Enrichments in GWAS signal of the intersection should be interpreted as enrichment of genome-
265 wide SNP effects on a complex trait beyond the additive effects which work on all SNPs that are a
266 *cis*-eQTL and histone mark in question. In fact, we test whether the interaction between tissue-
267 specific chromatin state and eQTLs are enriched in their genome-wide effect on complex traits.
268

269 **Intersection of GTEx eQTLs and tissue-specific differentially expressed genes**

270 Finucane *et al* (2017) looked at tissue-specific gene expression and determined that the top 10% of
271 these differentially expressed genes are substantially enriched in their effects in GWAS signals for a
272 wide range of traits. Here, we build on these findings by taking the top 10% most highly differentially
273 expressed genes in the 44 GTEx tissues; obtaining the eQTLs for these specific genes, regardless of
274 the discovery tissue; and added these separately as an annotation to an SLDSR model together with
275 the baseline categories and union of all GTEx eQTLs. A significant increase in enrichment in GWAS
276 signal in the eQTLs compared to the genes themselves, would indicate that eQTLs explain part of the
277 enrichment seen by Finucane *et al*.
278

279 **Results**

280 **Effect of eQTL selection on regression parameter and test statistics**

281 We compare five annotations that included various SNPs based on the *p*-value of their associations
282 with gene-expression levels (lead eQTL, median eQTL, mean eQTL, top 10 lead eQTLs, and all eQTLs).
283 Supplementary table S3 shows various metrics of these annotations. Surprisingly, lead eQTLs had the
284 lowest mean and median LD score amongst the annotations, indicating that the annotation contains
285 less signal (S3 Table). However, it was still higher compared to the mean or median of all SNPs in the
286 baseline annotation. Including all significant eQTLs in the annotation resulted in the highest mean
287 and median LD score. All annotations had a mean MAF 0.27-0.28, whereas the mean MAF of the
288 entire baseline category was 0.24. Smaller annotations had a higher enrichment in GWAS signal (S1
289 Figure). However, the enrichment in GWAS signal did not differ between taking the lead eQTL, eQTLs
290 with a mean *p*-value, or eQTLs with a median *p*-value. Finally, coefficient test statistics did not differ
291 much between the annotations (S2 Figure). Based on the explorative analysis, we selected the
292 annotation based on all significant eQTLs for further analysis.

293

294 **Blood and brain eQTL enrichment**

295 We fitted an SLDSR model containing the baseline categories; the complete annotation for both
296 brain and blood eQTL tissues, their 100 and 500bp windows, and gene-centric annotations to all
297 traits (Crohn's disease, rheumatoid arthritis, ulcerative colitis, BMI, educational attainment,
298 schizophrenia, age at menarche, coronary artery disease, height, LDL levels, and smoking behavior).
299 We found significant effects of brain eQTLs on educational attainment, rheumatoid arthritis,
300 smoking behavior, and schizophrenia, and significant effect of blood eQTLs on height and smoking
301 behavior (see S6 Table). We then meta-analyzed the results for all annotations, both in the baseline
302 model, and those associated with eQTLs across the 11 traits. Our analyses revealed significant effect
303 of both blood ($p < 0.001$) and brain ($p < 0.001$) eQTL effects on all traits (Figure 1, S7 Table),
304 exceeding, in terms of significance, all the baseline categories considered by Finucane *et al* (2015)

305 but conserved genomic regions. The gene-centric annotation for both blood and brain eQTLs showed
306 no effect on any trait.

307 We then separated the list of blood eQTLs into a list of unique and shared blood eQTLs
308 based on the overlap in target genes with brain eQTLs, and modelled the baseline categories
309 together with all blood eQTLs and the unique blood eQTLs. We did the same for brain eQTLs. We
310 observed no evidence for depletion of blood-specific eQTLs (relative to all blood eQTLs) on brain-
311 related traits, nor do we find significant depletion of effect on immune-related traits of eQTLs
312 associated with genes for which eQTLs were solely identified in brain tissue (Table I and Table II).

313

314 **Enrichment of eQTLs from 44 tissues in GTEx**

315 We interrogated the enrichment of the union of GTEx eQTLs and 44 individual GTEx annotations in
316 their effect on schizophrenia and rheumatoid arthritis. Figure 2 shows the coefficient of the 45 GTEx
317 annotations, sorted on their Z-scores for rheumatoid arthritis. In both cases, the union of GTEx
318 eQTLs contributed significantly to explaining the polygenic signal(S8 Table), indicating that eQTLs
319 were significantly enriched in their effects on complex traits. The individual annotations, however,
320 performed notably worse and in some cases even suggested depletion of genome-wide effects of
321 tissue-specific eQTLs on schizophrenia and rheumatoid arthritis. For rheumatoid arthritis, the
322 coefficient Z-scores of the whole blood annotation reached nominal significance (Z=2.251), but failed
323 correction for multiple testing. None of the other annotations reached nominal significance. The
324 union of all GTEx brain annotations did not contribute significantly to explaining h^2_{SNP} (Z=0.147,
325 p=0.441). Sample size in the eQTL discovery phase appears to be a strong determinant of tissue-
326 specific enrichment in GWAS signal. The correlation coefficients between the coefficient Z-scores
327 and sample sizes were 0.6453 ($p=2.253*10^{-6}$) and 0.4247 (p=0.004) for schizophrenia and
328 rheumatoid arthritis, respectively.

329

330 **Enrichment of the intersection between eQTLs and histone marks**

331 We interrogated the intersection of eQTLs and histone marks found in specific CNS and immune cells,
332 and estimated the enrichment of the intersection in its effect on rheumatoid arthritis and
333 schizophrenia. We found significant enrichment in GWAS signal for eQTLs that intersect with
334 histones that bear modification H3K4me1, a modification thought to be present in the enhancer of
335 actively transcribed genes (Zhou et al. 2011; Allis and Jenuwein 2016), in CNS cells for schizophrenia
336 (see Figure 3). There was some evidence for significant enrichment of eQTLs that intersected with
337 genomic regions in immune cells baring the H3K4me1 mark in their effect on schizophrenia, but not
338 on rheumatoid arthritis. Specifically, none of the intersecting annotations showed evidence of
339 enrichment for rheumatoid arthritis. For the separate annotations, we found significant enrichment
340 in GWAS signal across all histone marks found in CNS cells and three significant immune cell-types
341 that bear the H3K4me3 modification, a modification associated with transcriptional start sites and
342 promoters of actively transcribed genes (Zhou et al. 2011; Allis and Jenuwein 2016), for
343 schizophrenia (S9 Figure). The opposite picture was seen for rheumatoid arthritis: a wide variety of
344 immune-cell specific histone marks showed significant enrichments in GWAS signal, while all marks
345 found in CNS cells were below zero. The union of GTEx eQTLs reached statistical significance for all
346 models.
347

348 **Intersection of GTEx eQTLs and tissue-specific differentially expressed genes**

349 We extracted all eQTLs within the top 10% of tissue-specific differentially expressed genes in all 44
350 GTEx tissues. We then compare the enrichment in GWAS signal for these eQTLs with the genes
351 themselves. The correlation between the coefficients was 0.58 and 0.24 for schizophrenia and
352 rheumatoid arthritis, respectively. For schizophrenia, we see that the eQTL annotation most brain
353 tissues have the highest regression coefficient and Z-score, although none reached the significance
354 threshold (S10 Table). Furthermore, the eQTLs showed larger coefficients compared to the whole
355 genes, although the large standard errors made the difference non-significant. Interestingly, the top
356 10% differentially expressed genes within the nucleus accumbens showed a significant coefficient

357 comparable to the other brain regions, although the eQTLs for these genes showed a non-significant
358 depletion. For rheumatoid arthritis, whole blood showed the most significant coefficient, however,
359 again failed correction for multiple testing (S11 Figure). Furthermore both the whole genes as the
360 eQTLs for these genes showed a similar regression coefficient.
361

362 ## Discussion

363 Stratified Linkage Disequilibrium Score Regression provides a way to partition h^2_{SNP} into parts
364 explained by (functional) parts of the genome (Finucane et al. 2015). A "full baseline model"
365 containing 24 non-cell-type-specific annotations of SNPs, such as SNPs located in promoters or
366 coding regions, was developed previously for analysis using SLDSR. Here, we added annotations
367 containing eQTLs derived from whole blood and brain tissue into the model, and showed that eQTLs
368 were substantially stronger enriched in their effect on complex traits compared to all categories
369 considered by Finucane *et al* (2015). The complete brain eQTL annotation was significantly enriched
370 in GWAS signal for educational attainment, rheumatoid arthritis, smoking behavior, and
371 schizophrenia. This finding is consistent with previous estimates of eQTL effect enrichment (Davis et
372 al. 2013). Considerable enrichment for eQTLs, even for traits not apparently linked to the brain or
373 immune system (e.g. smoking behavior), suggested that non-trivial eQTL overlap across tissues
374 might be present.

375 Inclusion of both brain and blood eQTLs into the SLDSR model did not separate the signal
376 into tissue-specific effects. In general, we are not able to clearly identify tissue-specific eQTL signals
377 using these datasets and SLDSR. Our second analysis of eQTL enrichment based on 44 tissue-specific
378 *cis*-eQTL sets, obtained from the GTEx consortium (2015; Aguet et al. 2016), confirms the lack of
379 tissue-specific eQTL enrichment. While an annotation containing all eQTLs identified in GTEx is
380 significantly enriched in its effect on schizophrenia and rheumatoid arthritis ($Z=5.501$ and $Z=3.802$,
381 respectively, both $p<0.001$), none of the analyzed brain tissues are enriched beyond all eQTLs in
382 their effect on schizophrenia. Similarly, whole blood eQTLs are not significantly enriched beyond all

383 GTEx eQTLs taken together in their effect on rheumatoid arthritis. Again, these findings are not
384 consistent with the hypothesis of abundant tissue-specific *cis*-eQTLs with effects on complex traits
385 related to the specific tissue in question. Our findings are consistent with a lack of power to detect
386 any tissue-specific eQTL effects. Especially, when contrasted with tissue-specific gene expression
387 levels and tissue-specific histone modifications (Liu et al. 2016; Finucane et al. 2017), tissue-specific
388 eQTLs are of limited value in relating complex traits to a tissue. In fact, considering eQTLs associated
389 with genes expressed in a specific tissue improves our detection of tissue-specific effects. But, while
390 the regression parameter subsets eQTLs for specifically expressed genes have larger effects than the
391 rest of these genes, the significance of the enrichment is weak compared to the significance of the
392 tissue-specific enrichment of the whole gene body plus a 100kb window.

393 One of the limitations of the study presented here involves the substantial differences in
394 discovery sample size between the tissues, which influences the power to detect eQTLs (Lonsdale et
395 al. 2013). Even within the GTEx tissues, where differences in sample sizes are relatively small
396 compared to eQTLs obtained from Jansen *et al* and Ramasamy *et al*, we still see a significant
397 correlation between the discovery sample size and enrichment of eQTLs in GWAS signal. Several
398 methods have been developed to capitalize on cross-tissue overlap in eQTLs to improve power to
399 detect SNP effects on gene expression within tissue (Flutre et al. 2013; Li et al. 2013). The aim of this
400 paper was to explore the possibilities of assessing the effects of eQTLs expressed in whole blood on
401 presumably brain-related traits, and vice versa. In the analyses with eQTLs for differentially
402 expressed genes, we show that enrichment in GWAS signal is stronger in these eQTLs compared to
403 taking the all SNPs in the same genes. This indicates that eQTLs, irrespective of the tissue in which
404 they were discovered, play an important role in the etiology of complex traits, and do so via the
405 gene they are associated with. This, however, does not take away the need to increase sample sizes
406 when performing tissue-specific discovery of (*cis*-)eQTLs. Tissue specificity, in the end, is a relative
407 judgement best reached based on weighing multiple lines of evidence, among which are differential
408 expression, epigenetic regulation, and eQTLs. For eQTLs to play a large role in determining the

409 tissue-specific effects on complex traits, a continued investment in resources like GTEx is required in
410 order to increase sample sizes for detection, especially in rare tissues.

411 Our conclusions are limited to *cis*-eQTLs and it is not unlikely that trans-eQTLs behave
412 differently in terms of tissue-specificity. We do find evidence for possible enrichment for eQTLs that
413 intersect with tissue-specific H3K4me1 histone marks in the brain, but also immune cells, in their
414 effect on schizophrenia but not rheumatoid arthritis. This means that eQTLs in H3k4me1 marks are
415 enriched in their effect on schizophrenia above the expected enrichment based on the fact that
416 these SNPs are both eQTLs and located in H3K4me1 histone marks. What is of substantial interest is
417 that the e

418 nrichment in GWAS signal appears specific to H3K4me1 marks, and no other Histone marks,
419 suggesting that these marks specifically can aid in prioritizing genomic regions in which tissue-
420 specific eQTLs may reside. Though, again, the totality of evidence is inconclusive on the relevance of
421 tissue-specific eQTLs to variation in complex traits.

422 Our results are consistent with, and complimentary to, a study investigating the genetic
423 correlation between gene expression levels across 15 tissues (Liu et al. 2016). This study revealed
424 substantial correlations between *cis*-genetic effects on gene expression across 15 tissues (Liu et al.
425 2016). Our analyses confirmed the value of using whole blood as discovery tissue for detection of
426 *cis*-eQTLs and further demonstrated the usefulness of techniques that use *cis*-eQTLs discovered in
427 whole blood to study the etiology of complex traits related to different tissues (Gamazon et al. 2015;
428 Gusev et al. 2016). The results presented here highlight the overlap of *cis*-eQTL effects across tissues
429 on a genome-wide level. However, the effect of a *cis*-eQTL might vary substantially across tissues for
430 individual genes (Grundberg et al. 2012). Our conclusions are based on genome-wide enrichments
431 and therefore should not be interpreted as limited evidence for tissue-specific eQTL effects for
432 individual genes. Therefore, eQTL discovery in the tissue most relevant to a specific trait or disorder
433 remains important to further our understanding of the genetic regulation of tissue-specific gene
434 expression. What is also clear is that to discover those tissue-specific eQTLs that are of relevance to

435 the interpretation of GWASs of complex traits, tissue-specific eQTL discovery needs to be refined.
436 The practice of, as a post-hoc analysis to GWAS, performing eQTL lookup in a specific tissue linked to
437 a trait, when larger dataset for other accessible tissues are available, may be suboptimal. In fact, one
438 may prefer to perform a lookup in the overlap between histone modifications in a relevant tissue
439 and eQTLs regardless of tissue. One can further consider utilizing eQTLs to link GWAS findings to a
440 gene, and subsequently consider the differential expression of a gene to identify the tissue in which
441 the gene is most likely to act in effecting the trait. Tissue-specific differential gene expression vastly
442 outperforms eQTLs in tagging regions of the genome enriched in their effect on complex traits
443 (Finucane et al. 2017).

444 It is also evident that a limited dichotomous definition of eQTL/no-eQTL may be insufficient
445 to identify tissue-specific eQTL effects. An evident improvement would be to compute the *difference*
446 in eQTL effect on expression of the gene between tissues, and perform inference based on this
447 difference in effect. eQTLs are strongly enriched SNPs, with clear biological function and utility for
448 the translation of GWAS findings, though tissue-specific eQTL mechanisms remain elusive. The
449 discovery of tissue-specific eQTL effects, which can aid in linking complex trait to tissue, may require
450 novel research strategies.

451

452 ## Supplemental Data

453 Supplemental Data includes 4 figures and 7 tables

454

455 ## Compliance with Ethical Standards

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Conflict of Interest

The authors declare that they have no conflict of interest

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Web Resources

Age at menarche summary statistics, www.reprogen.org/data_download.html

Blood eQTLs, https://eqtl.onderzoek.io/

Brain eQTLs, http://www.braineac.org/

Coronary artery disease summary statistics, www.cardiogramplusc4d.org/data-downloads/

Crohn's disease and ulcerative colitis summary statistics, www.ibdgenetics.org/downloads.html

Educational attainment summary statistics, http://www.thessgac.org/data

Full baseline model LD scores, http://data.broadinstitute.org/alkesgroup/LDSCORE/

GTEx dataset, http://www.gtexportal.org/home/datasets

Height and BMI summary statistics,

www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files

LDL levels summary statistics, www.broadinstitute.org/mpg/pubs/lipids2010/

Rheumatoid arthritis summary statistics, http://plaza.umin.ac.jp/yokada/datasource/software.htm

Schizophrenia and smoking behavior summary statistics, www.med.unc.edu/pgc/results-and-downloads

SLDSR software, https://github.com/bulik/ldsc/

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594

Figure Titles and Legends

Figure 1. Average enrichment in GWAS signal of the 24 baseline annotations, 4 brain eQTL annotations and 4 blood eQTL annotations.

Bar plot of the average enrichment in GWAS signal across all traits for the 24 main baseline annotations and 8 main eQTL annotations. Grey beans represent the baseline categories. Blue beans represent eQTLs. Black bars indicate average enrichment. Boxes show upper- and lower-bounds of the 95% confidence interval of the mean. Red dots show enrichments for immune-related traits. Horizontal red line indicates enrichment of 1, i.e. no enrichment.

Figure 2. Coefficient Z-scores of the 45 GTEx annotations

Barplot of coefficient z-scores for all GTEx annotations for schizophrenia (grey) and rheumatoid arthritis (red). Bars are sorted from highest to lowest based on the results from schizophrenia. Horizontal dotted line indicates Bonferroni threshold for 45 tests. Two asterisks indicate bars passing Bonferroni correction for multiple testing.

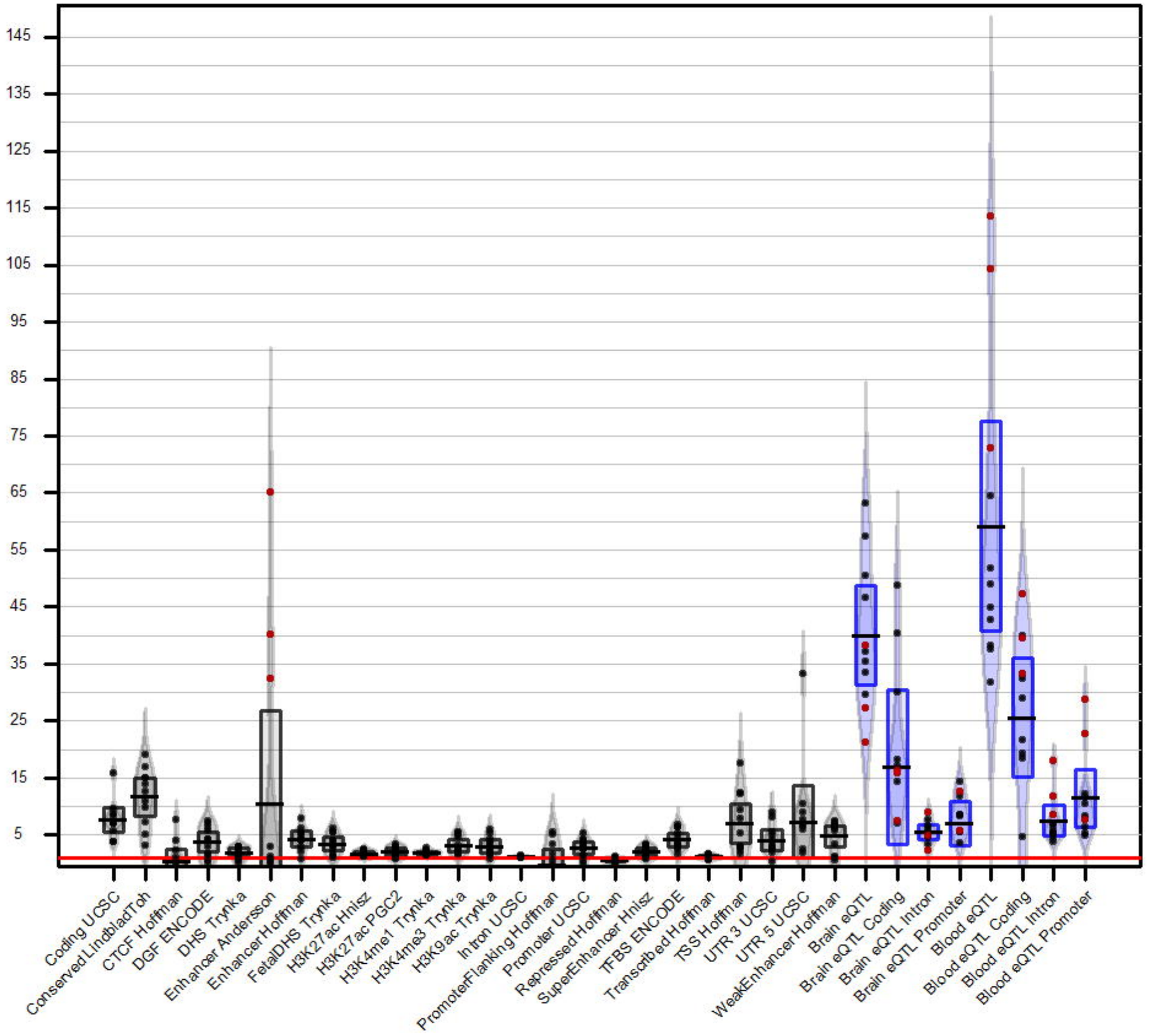
Figure 3. Coefficient Z-score of intersection between union of GTEx eQTLs and cell-type-specific histone marks

Top two graphs show coefficient Z-scores for schizophrenia. Bottom two graphs show the same for rheumatoid arthritis. Grey bars indicate histone marks found in cells from the central nervous system. Red bars represent histone marks found in cells from the immune system. From dark to light, shades of the bars indicate histone marks H3K27ac, H3K4me1, H3K4me3, and H3K9ac. Vertical dotted lines indicate separation between histone marks. One asterisk above the bars indicate annotations passing FDR correction for multiple testing. Two asterisks indicate bars passing Bonferroni correction for multiple testing. Horizontal dotted line indicates Bonferroni threshold for 101 tests.

Tables

Table I. (see attachments)

Table II. (see attachments)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CTCF Hoffman
DGF ENCODE
DHS Trynka
Enhancer Andersson
Enhancer Hoffman
FetalDHS Trynka
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H3K27ac PGC2
H3K4me1 Trynka
H3K4me3 Trynka
H3K9ac Trynka
Intron UCSC
PromoterFlanking Hoffman
Promoter UCSC
Repressed Hoffman
SuperEnhancer Hnisz
TFBS ENCODE
Transcribed Hoffman
TSS Hoffman
UTR 3 UCSC
UTR 5 UCSC
WeakEnhancer Hoffman
Brain eQTL
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Blood eQTL
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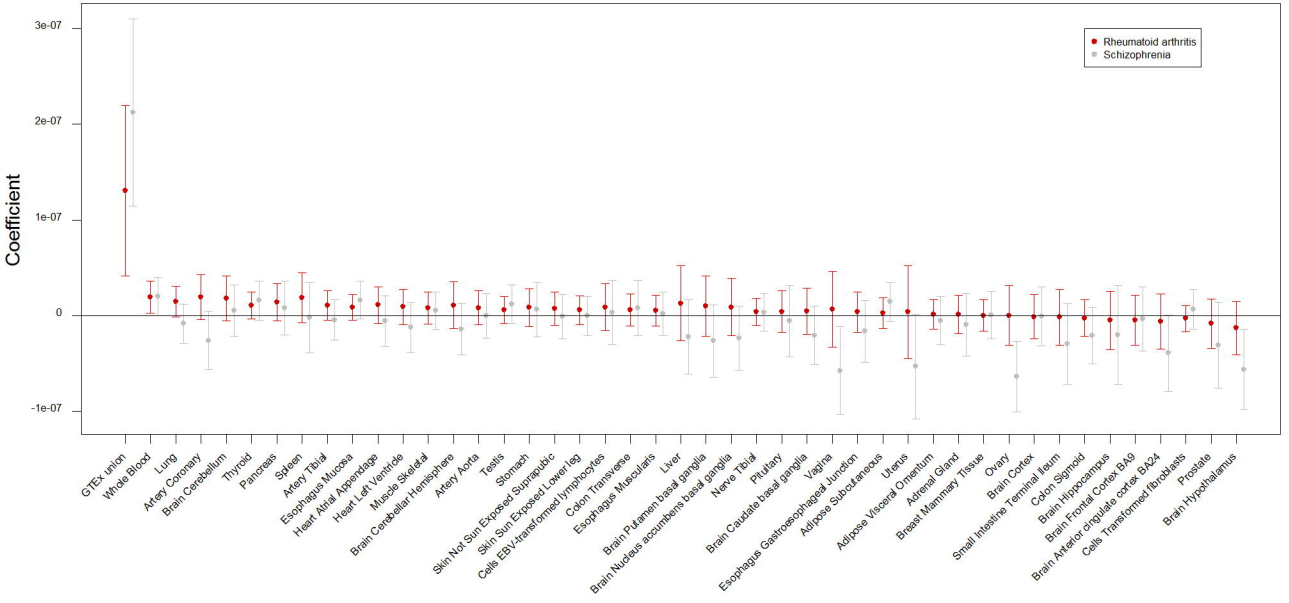
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Rheumatoid arthritis
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GTEx union
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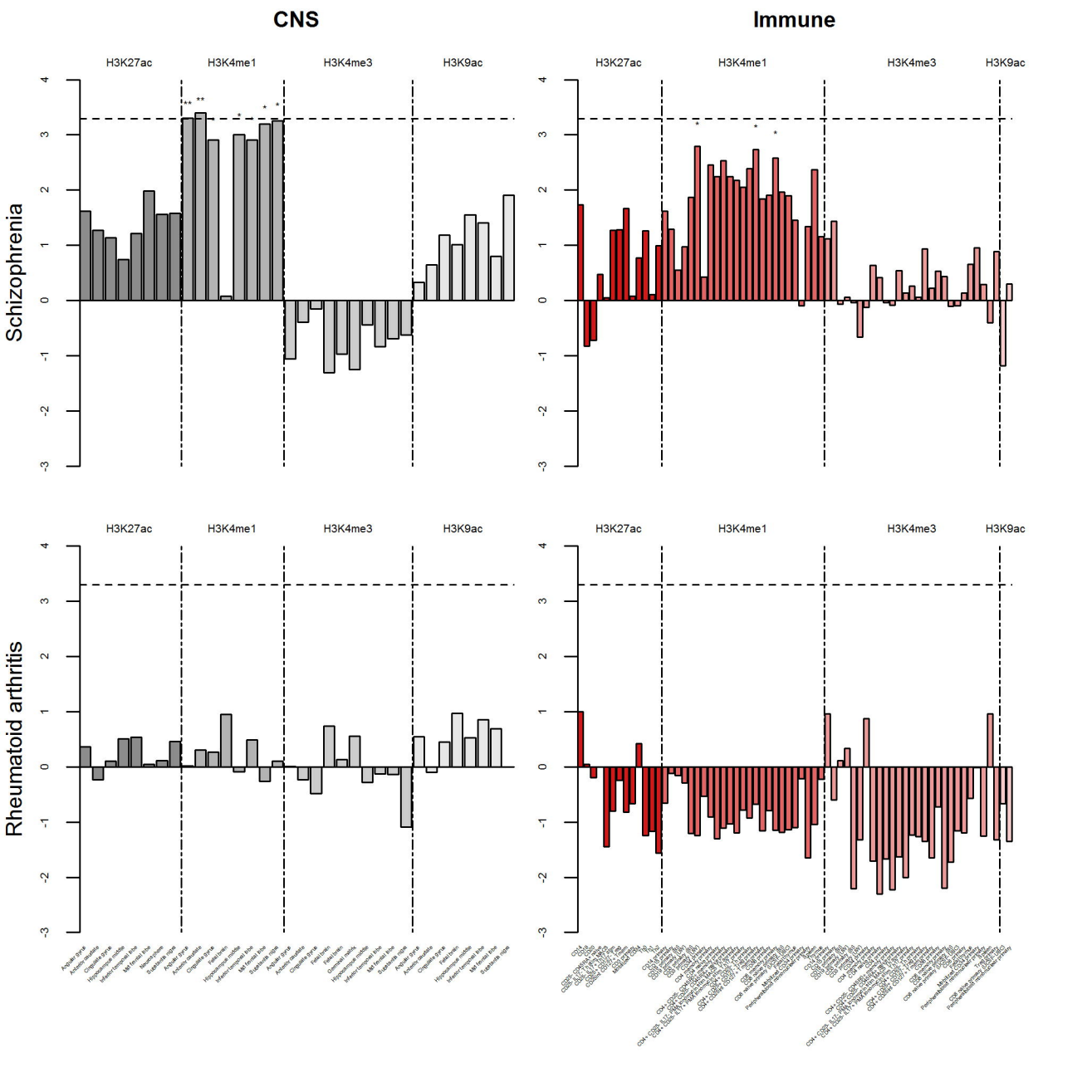
Artery Coronary
Brain Cerebellum
Thyroid
Pancreas
Spleen
Artery Tibial
Esophagus Mucosa
Heart Atrial Appendage
Heart Left Ventricle
Muscle Skeletal
Brain Cerebellar Hemisphere
Artery Aorta
Testis
Stomach
Skin Not Sun Exposed Suprapubic
Skin Sun Exposed Lower leg
Cells EBV-transformed lymphocytes
Colon Transverse
Esophagus Muscularis
Liver
Brain Putamen basal ganglia
Brain Nucleus accumbens basal ganglia
Nerve Tibial
Pituitary
Brain Caudate basal ganglia
Vagina
Esophagus Gastroesophageal Junction
Adipose Subcutaneous
Uterus
Adipose Visceral Omentum
Adrenal Gland
Breast Mammary Tissue
Ovary
Brain Cortex
Small Intestine Terminal Ileum
Colon Sigmoid
Brain Hippocampus
Brain Frontal Cortex BA9
Brain Anterior cingulate cortex BA24
Cells Transformed fibroblasts
Prostate
Brain Hypothalamus


CNS
Immune
Schizophrenia
Rheumatoid arthritis
H3K27ac
H3K4me1
H3K4me3
H3K9ac
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