Identifying and exploiting trait-relevant tissues with multiple functional annotations in genome-wide association studies

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Abstract

Genome-wide association studies (GWASs) have identified many disease associated loci, the majority of which have unknown biological functions. Understanding the mechanism underlying trait associations requires identifying trait-relevant tissues and investigating associations in a trait-specific fashion. Here, we extend the widely used linear mixed model to incorporate multiple SNP functional annotations from omics studies with GWAS summary statistics to facilitate the identification of trait-relevant tissues, with which to further construct powerful association tests. Specifically, we rely on a generalized estimating equation based algorithm for parameter inference, a mixture modeling framework for trait-tissue relevance classification, and a weighted sequence kernel association test constructed based on the identified trait-relevant tissues for powerful association analysis. We refer to our analytic procedure as the Scalable Multiple Annotation integration for trait-Relevant Tissue identification and usage (SMART). With extensive simulations, we show how our method can make use of multiple complementary annotations to improve the accuracy for identifying trait-relevant tissues. In addition, our procedure allows us to make use of the inferred trait-relevant tissues, for the first time, to construct more powerful SNP set tests. We apply our method for an in-depth analysis of 43 traits from 28 GWASs using tissue-specific annotations in 105 tissues derived from ENCODE and Roadmap. Our results reveal new trait-tissue relevance, pinpoint important annotations that are informative of trait-tissue relationship, and illustrate how we can use the inferred trait-relevant tissues to construct more powerful association tests in the Wellcome trust case control consortium study.

Key words

Author Summary

Identifying trait-relevant tissues is an important step towards understanding disease etiology. Computational methods have been recently developed to integrate SNP functional annotations generated from omics studies to genome-wide association studies (GWASs) to infer trait-relevant tissues. However, two important questions remain to be answered. First, with the increasing number and types of functional annotations nowadays, how do we integrate multiple annotations jointly into GWASs in a trait-specific fashion to take advantage of the complementary information contained in these annotations to optimize the performance of trait-relevant tissue inference? Second, what to do with the inferred trait-relevant tissues? Here, we develop a new statistical method and software to make progress on both fronts. For the first question, we extend the commonly used linear mixed model, with new algorithms and inference strategies, to incorporate multiple annotations in a trait-specific fashion to improve trait-relevant tissue inference accuracy. For the second question, we rely on the close relationship between our proposed method and the widely-used sequence kernel association test, and use the inferred trait-relevant tissues, for the first time, to construct more powerful association tests. We illustrate the benefits of our method through extensive simulations and applications to a wide range of real data sets.

Introduction

Genome-wide association studies (GWASs) have identified thousands of genetic loci associated with complex traits and common diseases. However, the majority (~90%) of these associated loci reside in noncoding regions and have unknown biological functions [1]. Systematic characterization of the biological function of genetic variants thus represents an important step for further investigating the molecular mechanisms underlying the identified disease associations. Functional characterization of genetic variants is challenging because the function and genetic effects of variants on most traits are likely acted through a tissue-specific fashion, despite their tissue-wide presence (certainly with the notable exception of somatic mutations) [2-4]. For example, it is well recognized that many psychiatric disorders, such as bipolar and schizophrenia, are consequences of dysfunctions of various genes, pathways as well as regulatory elements in neuronal and glia cells, resulting from brain-specific genetic effects of polymorphisms [5-9]. Therefore, characterizing the function of variants in various brain regions can help elucidate the biology of psychiatric disorders. For most complex traits, however, their trait-relevant tissues are often obscure. As a result, identifying trait-relevant tissues and characterizing the functions of genetic variants within relevant tissues holds the key for furthering our understanding of disease etiology and the genetic basis of phenotypic variation [10-16].

Both experimental and computational studies have recently produced a rich resource of variant annotations that can help characterize the function of genetic variants in a tissue-dependent fashion [17-21]. For example, the ENCODE and Roadmap epigenomics projects collect various measurements of histone modification, open chromatin, and methylation from more than a hundred different tissue and cell types, where each epigenetic mark characterizes a specific aspect of variant function [22,23]. Similarly, the GTEx project produces gene expression measurements from multiple tissues and quantifies variant function in terms of its ability to regulate gene expression levels in the given tissue [24]. Besides the experimental efforts, many computational methods have also been developed to create synthetic functional annotations for variants in a tissue-dependent manner. For example, the chromHMM converts measurements of multiple histone modifications in each tissue into 15 chromatin states that have more biologically interpretable functions than the original histone occupancy based annotations [25,26]. Similarly, several other methods provide different ways to summarize multiple SNP annotations into a single, potentially more interpretable annotation for various tissues [27,28].

With the large and growing number of tissue-specific variant annotations, however, one naturally wonders how these different annotations can be incorporated together to facilitate the identification of trait-relevant tissues. Several statistical methods have been recently developed to test the role of various functional annotations in predicting the variant effect sizes or causality for GWAS traits [10-16,29-31]. These methods often test one annotation at a time and produce a test statistic signifying the importance of the given annotation for a GWAS trait. By comparing the test statistics of univariate annotation from different tissues and ordering tissues by the magnitude of the test statistics, existing methods can be used to identify tissue relevance for a given trait [10,16]. However, examining one variant annotation at a time can be inefficient as it may fail to incorporate the rich information contained in various other annotations that likely characterize other aspects of variant function [27,28,32]. For example, some annotations are

103 designed to evaluate evolutionary conservation of a variant, while some other annotations are
104 designed to quantify its biochemical functionality [29,33]. Even annotations that belong to the
105 same general category may characterize substantially different functions of a variant. For
106 example, different histone modifications are used to annotate variants by different functional
107 genomic regions: H3K4me3 annotates promoter; H3K4me1 annotates enhancer; H3K36me3
108 annotates transcribed regions; H3K27me3 annotates polycomb repression; H3K9me3 annotates
109 heterochromatin; and H3K9ac annotates both enhancer and promoter [22,34]. Therefore, testing
110 one annotation at a time may be suboptimal, and it would be ideal to incorporate multiple
111 sources of information together to identify trait-relevant tissues. Besides the potential loss of
112 inference efficiency, examining one annotation at a time can sometimes lead to incoherent results
113 on the identification of trait-relevant tissues: partly due to a lack of statistical power, the trait-
114 relevant tissues inferred by different SNP annotations may not always agree, and it is often not
115 straightforward to consolidate results from using different annotations [27,28].

117 Despite the potential inefficiency due to the use of univariate annotation tests, several studies
118 have explored the feasibility of inferring trait-relevant tissues for various complex traits using
119 SNP functional annotations [16,31,35,36]. While the inferred trait-tissue relevance often makes
120 biological sense, it is unclear how to further make use of these inferred trait-relevant tissues to
121 benefit future association studies [11,16]. In principal, levering the information learned from the
122 identified trait-relevant tissues could enable powerful association tests, as the functional
123 annotations in the trait-relevant tissues could contain important SNP causality and effect size
124 information. In practice, however, incorporating trait-relevant tissue information into association
125 tests is challenging, partly because the existing statistical methods for identifying trait-relevant
126 tissues mainly rely on polygenic models [16,31,35,36] while the existing statistical methods for
127 association tests mostly rely on univariate tests or sparse regression models [37-40]. The
128 disparity between the methods used for trait-tissue relevance inference and the methods used for
129 association tests make it hard to share information across the two different tasks.

131 Here, we develop a simple method to address the above two challenges. First, we incorporate
132 multiple binary and/or continuous annotations to facilitate the identification of trait-relevant
133 tissues for GWAS traits. To do so, we modify the commonly used linear mixed model [38,41-45]
134 to relate variant effect sizes to variant annotations by introducing variant specific variance
135 components that are functions of multiple annotations. We quantify and evaluate the joint
136 contribution of multiple annotations to genetic effect sizes by performing parameter inference
137 using the widely used generalized estimation equation (GEE) [46]. Our GEE-based algorithm is
138 closely related to the recent LDSC [16], ployGEE [47], and MQS methods [48], allows for the
139 use of summary statistics, and naturally accounts for the correlation among summary statistics
140 due to linkage disequilibrium. With GEE statistics, we further apply mixture models to classify
141 tissues into two categories -- those that are relevant to the trait and those that are not -- thus
142 formulating the task of identifying trait-relevant tissues into a classification problem. Second, our
143 method is closely related to the sequence kernel association test (SKAT) [49-51], and this
144 relationship allows us to apply parameter estimates from the inferred trait-relevant tissues as SNP
145 weights to construct SNP set test and power new association studies. We refer to our overall
146 analytic procedure as the Scalable Multiple Annotation integration for trait-Relevant Tissue
147 identification (SMART). We provide an overview of our method in the Materials and Methods
148 section, with details described in the Supplementary Text. With simulations, we show that,

149   compared with analyzing one annotation at a time, analyzing multiple annotations jointly can
150   improve power for the identification of trait-relevant tissues. In addition, we show that, using
151   parameter estimates from inferred trait-relevant tissues as SNP weights leads to more powerful
152   SNP set tests than the standard SKAT [49-51]. We apply our method for an in-depth analysis of
153   43 GWAS traits with multiple functional annotations in more than one hundred tissues derived
154   from ENCODE and Roadmap. We show how our method and analysis can help provide
155   biological insights for the genetic basis of complex traits and benefit future association studies.
156   The SMART method is implemented as an R package, freely available at
157   http://www.xzlab.org/software.html.

Materials and Methods

Method Overview

We consider a simple extension of the linear mixed model to evaluate jointly the contribution of multiple SNP annotations. To do so, we first consider the following multiple linear regression model that relates genotypes to phenotypes

$$y = X\beta + \epsilon, \qquad \epsilon_i \sim N(0, \sigma_e^2), \tag{1}$$

where y is an n-vector of phenotypes; X is an n by m matrix of genotypes; β is an m-vector of effect sizes; and ϵ is an n-vector of residual errors; each element ϵ_i is independent and identically distributed from a normal distribution with variance σ_e^2. We center the phenotype y and standardize each column of the genotype matrix X to have zero mean and unit variance, allowing us to ignore the intercept in the model.

Because $p \gg n$, we have to make further modeling assumptions on the SNP effect sizes β to make the model identifiable. We do so by incorporating SNP annotation information and making the effect size β_j of j-th SNP depending on its annotations. Specifically, we assume that all SNPs are characterized by a same set of c annotations. For the j-th SNP, we denote $A_j = \left(1, C_{j1}, C_{j2}, \cdots, C_{jc}\right)^T$ as a $(c+1)$-vector of realized annotation values including a value of one that corresponds to the intercept. These annotations can be either discrete or continuous. For example, one annotation could be a binary indicator on whether the SNP resides in exonic regions, while another annotation could be a continuous value of the CADD score [18] of the SNP. Because our model includes an intercept (more details in the next paragraph), we require that any linear combination of these annotations does not sum to a vector of one's across SNPs in order to avoid identifiability issues − a requirement holds for standard linear regression models. For example, we cannot include two non-overlapping annotations that form a partition of the genome (i.e. $C_{j1} = 1$ when $C_{j2} = 0$, and $C_{j1} = 0$ when $C_{j2} = 1$). Our coding scheme is conventionally referred to as the reference coding scheme. To simplify presentation, we assemble the annotation vectors across all SNPs into an m by $(c+1)$ annotation matrix A, where each row contains the annotation vector for the corresponding SNP.

We assume that the annotations for a given SNP influence its effect size. In particular, we assume that each effect size β_j is independent and follows a normal distribution with mean zero and a variance σ_j^2 that is SNP specific. The SNP-specific variance assumption generalizes the standard LMM assumption where every SNP is assumed to share a common variance [37,52]. We further impose an extra layer of hierarchy by assuming that the SNP specific variance is a function of the annotation vector, or

$$\beta_j \sim N\left(0, \sigma_j^2/m\right), \qquad \sigma_j^2 = A_j\,\alpha^*, \tag{2}$$

where $\alpha^* = \binom{\alpha_0}{\alpha}$ is a $(c+1)$-vector of coefficients that include an intercept α_0 and a c-vector of annotation coefficients α. Each annotation coefficient is large when the corresponding annotation is predictive of the SNP effect size. Therefore, the annotation coefficients can be used to evaluate the importance of annotations. Above, we center the 2nd to the $(c+1)$-th columns of the annotation matrix A to have mean zero across SNPs. After centering, the ratio $m\alpha_0/(m\alpha_0 + \sigma_e^2)$ has the natural interpretation of SNP heritability, which is defined as $h^2 = E(\sum\beta_j^2)/(E(\sum\beta_j^2) + \sigma_e^2)$,

200 roughly following [16], where E represents prior expectation. The intercept α_0 effectively
201 determines how large a typical SNP effect size would be, while the other annotation coefficients
202 determine how the SNP effect size variance would vary around the average depending on what
203 annotations the SNP has. Note that the assumed linear relationship between the SNP specific
204 variance and annotations also naturally extends the modeling assumptions made in LDSC [16]
205 and MQS [48], both of which examine one annotation at a time in the presence of multiple
206 binary annotations, though LDSC has also been recently extended to examine one annotation at a
207 time in the presence of continuous annotations [31]. In addition, our polygenic modeling
208 assumption complements alternative approaches in using sparse models for integrating functional
209 annotations [11,12,40,53].

211 For inference on the annotation coefficients (α), we follow the main idea of LDSC and MQS in
212 using the marginal χ^2 statistics. Using marginal statistics allows our method to be applied to data
213 where only summary statistics are available. Unlike the detailed algorithms of LDSC or MQS
214 that were initially designed to examine one annotation at a time in the presence of multiple
215 binary annotations, however, we applied the generalized estimating equation (GEE) [46,54]
216 inference method that allows for the joint inference of multiple binary and continuous
217 annotations (details in Supplementary Text). GEE is widely used for modeling correlated data
218 and is particularly suitable here to account for the correlation among the marginal χ^2 statistics
219 due to linkage disequilibrium. In the case of binary annotations, the results of our GEE on each
220 annotation by using a diagonal matrix as the working covariance matrix can reduce to that of
221 LDSC and MQS, while the results of our GEE by using an LD based general working covariance
222 matrix can reduce to that of polyGEE [47]. Importantly, just like other summary statistics based
223 methods, GEE inference can be carried out using summary statistics that include marginal χ^2
224 statistics and the m by m SNP correlation matrix. The SNP correlation matrix can be obtained
225 from a reference panel, by using, for example, the genotypes from the 1,000 Genomes Project
226 [55]. To facilitate both computation and memory storage, we further approximate the SNP
227 correlation matrix by a block diagonal matrix (details in Supplementary Text), allowing us to
228 capture the main block-wise linkage disequilibrium pattern commonly observed in the human
229 genome [40,56-58]. Finally, with GEE, we obtain both point estimates $\hat{\alpha}$ and their variance $V(\hat{\alpha})$
230 for all annotation coefficients in a closed form. We can then compute the multivariate Wald
231 statistic $\hat{\alpha}^T V(\hat{\alpha})^{-1} \hat{\alpha}$ which can be used as a measurement of trait-tissue relevance.

233 Previous approaches to identify trait-relevant tissues examines one (univariate) Wald statistics at
234 a time, and uses an asymptotic normal test to obtain a p-value to identify significant trait-tissue
235 pairs. Because one annotation in one tissue is often highly correlated with the same annotation in
236 other tissues as well as other annotations in other tissues, the p-values for even the trait-irrelevant
237 tissues are often significant due to the annotation correlation across annotations and tissues.
238 Indeed, as previous studies have shown, even in simple simulations, trait-irrelevant tissues can be
239 falsely identified as trait-relevant in 20% of the simulation replicates [16]. As a consequence,
240 previous studies have to use a set of baseline annotations as covariates to reduce the cross-tissue
241 correlation among annotations, thus reducing false positives. However, it is often unclear how
242 many and what types of baseline variables one should include for a given data set: using a small
243 number of baseline covariates may not control for false positives well, while using a large
244 number of covariates may reduce the power to detect the true trait-relevant tissues. Indeed, the
245 use of baseline variables seems to be highly dependent on data sets (with varying sample sizes

246   and SNP numbers), and needs adjustment in different data sets to achieve sensible results [16].
247
248   Here, we present an alternative strategy for identifying trait-relevant tissues. Specifically, for
249   each trait in turn, we model the multivariate Wald statistics across tissues with a mixture of two
250   non-central chi-squared distributions to classify tissues into two groups. The two non-central chi-
251   squared distributions have the same degrees of freedom that equals to the number of annotations
252   fitted in GEE (i.e. c), but different noncentrality parameters. The chi-squared distribution with
253   the small noncentrality parameter represents the empirical null distribution that contains tissues
254   irrelevant to the trait. The small, nonzero, noncentrality parameter characterizes the fact that
255   these irrelevant tissues tend to have Wald statistics larger than what would be expected under the
256   theoretical null distribution (i.e. central chi-squared) simply due to annotation correlation across
257   tissues. In contrast, the chi-squared distribution with the large non-central parameter represents
258   the alternative model that contains tissues relevant to the trait. The large noncentrality parameter
259   characterizes the fact that these relevant tissues tend to have Wald statistics larger than those
260   from the irrelevant tissues. By classifying tissues into two groups, we can identify tissues with
261   strong trait-relevance without the need to explicitly model the empirical null distribution using a
262   data generative model. Therefore, our strategy effectively formulates the task of identifying trait-
263   relevant tissues as a classification problem instead of a testing problem. By modeling the
264   empirical null distribution directly, we can reduce false discoveries and potentially gain power at
265   a given false discovery rate (FDR). We also note that this classification strategy follows closely
266   recent applications of mixture models to estimate the empirical null distribution in other
267   genomics settings [59,60]. Technically, we use the expectation-maximization (EM) algorithm to
268   fit the mixture model and infer the two noncentrality parameters as well as the proportion of
269   alternatives from data at hand (details in the Supplementary Text). For each tissue in turn, we
270   then obtain the inferred posterior probability (PP) of it being in the alternative model as its
271   evidence for trait-relevance. We use these inferred posterior probabilities (ranging between 0 and
272   1) for all following analyses. Note that while our linear mixed model itself does not explicitly
273   model the correlation structure among annotations across tissues by incorporating all annotations
274   from all tissues into a single model, our mixture model and classification strategy can implicitly
275   account for the annotation correlation across tissues.
276
277   Finally, we ask the question of how to make use of the inferred trait-relevant tissues to enable
278   more powerful future association studies. We note that our model defined in equations (1) and
279   (2) is closely related to the sequence kernel association test (SKAT) model [49-51] for SNP set
280   test. In particular, the SNP specific variance σ_j^2 in our model can be naturally interpreted as the
281   SNP specific weight in the SKAT [49-51] framework. Because of this close relationship between
282   our model and SKAT [49-51], we propose to use the estimated SNP specific variance $\hat{\sigma}_j^2$ in the
283   top trait-relevant tissue from our model as SNP weights to perform SKAT [49-51] analysis in
284   new association studies. Intuitively, if a SNP tends to have a large effect size, then weighting it
285   high in the subsequent SNP set analysis can help achieve greater association mapping power. We
286   examine this intuition with both simulations and real data applications. Note that our weighted
287   SKAT [49-51] approach is related to a recent method, FST, which also extends SKAT to
288   accommodate multiple functional annotations [32]. However, our method borrows information
289   across all SNPs to infer trait-relevant tissues and estimate annotation coefficients, and further
290   relies on the estimated annotation coefficients in the trait-relevant tissues to construct SNP
291   specific weights for SKAT analysis. In contrast, FST [32] examines one gene at a time, calculates

292 a test statistic for each annotation in turn, and effectively chooses the minimal test statistics
293 among all these annotations as the final statistics for testing. In addition, while our method is
294 polygenic in nature, the idea of using SNP specific weights to construct test statistics is also
295 related to a recent study that uses functional annotations to design SNP specific weights in sparse
296 regression models to improve disease risk prediction performance [61].
297

Tissue-Specific SNP Annotations

299

300 We used tissue-specific SNP annotations from the ENCODE [23] and the Roadmap [22] projects
301 in the present study. Specifically, we downloaded the broadPeak files from the Roadmap
302 Epigenomics web portal (http://egg2.wustl.edu/roadmap/web_portal/). The broadPeak files
303 contain peak regions for four histone marks (H3K27me3, H3K36me3, H3K4me1, H3K4me3)
304 from 16 cell lines in the ENCODE project and 111 tissues from the Roadmap project (release 9).
305 Among the 127 tissue/cell types, we excluded ESC, IPSC, and ES-derived cell lines to focus on
306 the remaining 105 tissue/cell types (Table S1). Following previous studies [16,22,27], we further
307 classified 105 tissues into 10 tissue groups based on anatomy (BloodImmune, Adipose,
308 AdrenalPancreas, BoneConnective, Cardiovascular, CNS, Gastrointestinal, Liver, Muscle, Other;
309 Table S1). For each tissue and each histone mark in turn, we created a binary histone mark
310 annotation indicating whether the SNP resides inside the peak regions of the histone mark. The
311 average proportions of SNPs residing in each of the four mark labeled regions across the 105
312 tissues are 25.75% for H3K27me3, 18.51% for H3K36me3, 17.98% for H3K4me1, 10.69% for
313 H3K4me3 (Table S1). In addition to the binary annotations, for each tissue group and each
314 histone mark in turn, we averaged the binary annotation indicator across all tissue types within
315 the tissue group and used the average value as a new, continuous, tissue group level histone mark
316 annotation. Therefore, we obtained both tissue-specific binary histone mark annotations and
317 tissue-group-specific continuous histone mark annotations.
318

319 Besides the above histone mark annotations, we also obtained SNP annotations based on 15
320 chromatin states (TssA, TssAFlnk, TxFlnk, Tx, TxWk, EnhG, Enh, ZNFRpts, Het, TssBiv,
321 BivFlnk, EnhBiv, ReprPC, ReprPCWk and Quies) inferred from ChromHMM [62] in the 105
322 tissues. In particular, we downloaded the posterior probabilities of each of the 15 states for each
323 genomic location in different tissues from the Roadmap Epigenomics web portal. For each tissue
324 group and each posterior probabilities in turn, we then averaged the posterior probabilities across
325 all tissue types within the tissue group and used the average value tissue as tissue group specific
326 continuous ChromHMM annotation.
327

Simulations

329

330 We performed two sets of simulations to illustrate the benefits of our method in terms of (1)
331 using multiple SNP annotations and (2) enabling more powerful SNP set tests. For all
332 simulations, we used real genotypes from the Genetic Epidemiology Research Study on Adult
333 Health and Aging (GERA; dbGaP accession number phs000674.v2.p2) [63,64]. The original
334 genotype data of the GERA study consists of 675,367 SNPs on 62,313 individuals. We removed
335 SNPs with a missingness percentage above 0.05, a minor allele frequency (MAF) below 0.05,
336 and a Hardy-Weinberg equilibrium test p-value below 10^{-4}. We then randomly selected 10,000
337 individuals with European ancestry, and obtained the first 27,640 (or 10,000) SNPs on

338 chromosome one to perform the first (or the second) set of simulations.

339

340 For the first set of simulations, we obtained two histone marks (H3K4me1 and H3K4me3) from
341 ten different tissue groups from the ENCODE and Roadmap projects, and used them as SNP
342 annotations (details in the previous subsection). Among the ten tissue groups, we randomly
343 selected one as the trait-relevant tissue group in each simulation replicate. We designated all
344 SNPs to be causal, and simulated the causal SNP effects independently from a normal
345 distribution with a SNP-specific variance determined by annotations in the trait-relevant tissue.
346 In particular, we set the variance intercept (i.e. α_0) to be 0.1 and we varied each of the two
347 annotation coefficients (i.e. α_1, α_2) from -0.1 to 0.5 (-0.1/0/0.05/0.1/0.25/0.5) to cover a range of
348 possible values estimated from real data (details in Real Data Applications). We performed 1,000
349 simulation replicates for each combination of the two annotation coefficients (α_1, α_2). Note that
350 the median estimates of the two annotations across 43 GWAS traits (details in Real Data
351 Applications) is close to $(\alpha_1, \alpha_2)_m = (0.1, 0.05)$. We simulated the residual errors from a normal
352 distribution with variance 0.9, so that the resulting trait has a SNP heritability of 0.1, which
353 corresponds to the median SNP heritability estimate across 43 traits in the real data analysis. We
354 then summed all genetic effects and the residual errors together to form the simulated
355 phenotypes. With genotypes and simulated phenotypes, we fitted a linear regression model for
356 one SNP at a time and computed marginal χ^2 statistics. We further paired these marginal
357 statistics with a SNP correlation matrix estimated using 503 individuals of European ancestry
358 from the 1,000 Genomes Project [55]. We then examined the ten candidate tissues in turn using
359 either two annotations together or one annotation at a time. For additional comparisons at the
360 median setting $(\alpha_1, \alpha_2)_m = (0.1, 0.05)$, we also included LDSC [16], which in default includes
361 75 baseline annotations as covariates. We used this first set of simulations for two purposes. In
362 the Supplementary Text, we used simulations to illustrate the benefits of using mixture models to
363 post-process the Wald statistics in order to address correlations among annotations and reduce
364 false positives (Figure S1). In the main text, we used simulations to illustrate the benefits of
365 modeling multiple annotations jointly.

366

367 For the second set of simulations, we used 10,000 SNPs and divided them into 100 blocks with
368 100 SNPs inside each block. For the null simulations, we set the effect sizes of all SNPs to be
369 zero and performed 50,000 simulation replicates. For the alternative simulations, we randomly
370 selected 10 non-adjacent blocks as causal blocks and we randomly selected 20% SNPs inside
371 these causal blocks to be causal SNPs (i.e. a total of 200 causal SNPs). We then simulated ten
372 tissue-specific annotation sets, each with two annotations, which are simulated to correlate with
373 SNP causality [30]. Specifically, the annotation values for the non-causal SNPs are sampled from
374 a normal distribution with mean 0 and variance 1. The causal SNPs are randomly divided into
375 three groups: for the first annotation, its annotations values for the first group are sampled from a
376 normal distribution with mean 0 and variance 1 while its annotations values for the second and
377 third groups are sampled from a normal distribution with mean 10 and variance 1; for the second
378 annotation, its annotations values for the second group are sampled from a normal distribution
379 with mean 0 and variance 1 while its annotations values for the first and third groups are sampled
380 from a normal distribution with mean 10 and variance 1. The proportion of the three groups of
381 causal SNPs are set to be either (1/2, 1/2, 0), (1/3, 1/3, 1/3) or (0, 0, 1). Because two annotations
382 share similar annotation values in the third group of causal SNPs, the proportion of the third
383 group determines the correlation between the two annotations for causal SNPs within the

384 annotation set. Therefore, the selected proportion of the third group SNPs being 0, 33% and
385 100% correspond to low, median and high correlation between the two annotations in causal
386 SNPs, respectively. Once we had the annotations, we simulated the effect sizes for causal SNPs
387 independently from a normal distribution with a SNP-specific variance determined by the
388 designated annotation set. Specifically, we set $\alpha_0 = 0.5$ and chose either $(\alpha_1, \alpha_2) = (0.4, 0.4)$ (in
389 the case of two informative annotations) or $(\alpha_1, \alpha_2) = (0.4, 0)$ (in the case of one informative
390 annotation). These parameters were selected to ensure that the 10 causal blocks explain a large
391 proportion of variance in phenotypes (per-block PVE > 0.01; Figure S2) so that we will have
392 reasonable power to detect them. Certainly, power is a continuous function of per-block PVE and
393 is non-zero even for small values of per-block PVE. We simulated the residual errors from a
394 normal distribution with variance 0.5. We summed all genetic effects and the residual errors
395 together to form the simulated phenotypes. We then randomly divided the 10,000 individuals into
396 two sets: a training set with 7,000 individuals and a test set of 3,000 individuals. In the training
397 set, we followed the same procedure described in the previous paragraph to obtain marginal χ^2
398 statistics in the data and SNP correlation matrix from a reference panel to fit our model. We
399 applied the parameter estimates from the best trait-relevant tissue determined in the training set
400 to compute the SNP specific variance $\hat{\sigma}_j^2$ as SNP weights. For the computed variance, we
401 subtracted from them the minimal variance across SNPs and added a small constant (10^{-15}) to
402 ensure that all weights are positive. We then multiplied the resulting SNP weights with the
403 posterior probability (PP) of the best trait-relevant tissue and further added a value of 1-PP to all
404 SNPs, thus effectively obtaining a set of averaged SNP weights by using both the constructed
405 SNP weights in the identified trait-relevant tissue and the equal SNP weights. Averaging the
406 constructed weights and the equal weights using PP ensures the robustness of our method and
407 guards against the special case where none of the tissues are trait-relevant: in this case, the
408 resulting SNP weights would equal to the equal weights due to a small PP value and would thus
409 still be effective in the subsequent SNP set analysis. We finally applied the SNP weights
410 constructed in the training data to the test data to perform SNP set analysis. We performed 1,000
411 simulation replicates for each alternative simulation setting. We divided these replicates into 10
412 sets, each with 100 replicates, and computed the power to detect the causal blocks in each set.
413 We report the mean and variance of these power values across 10 sets.

GWAS Summary Statistics

417 We obtained summary statistics in the form of marginal z-scores for 43 traits from 28 GWAS
418 studies. Details are provided in Table S2. These studies collect a wide range of complex traits
419 and diseases that can be classified into six phenotype categories [28,65]: anthropometric traits
420 (e.g. height and BMI), hematological traits (e.g. MCHC and RBC), autoimmune diseases (e.g.
421 CD and IBD), neurological diseases (e.g. Alzheimer's disease and Schizophrenia), metabolic
422 traits (e.g. FG and HDL), and social traits (e.g. ever smoked and college completion). We
423 removed SNPs within the major histocompatibility complex (MHC) region (Chr6: 25Mb-34Mb)
424 following [16]. We then intersected the SNPs from all the studies and retained a common set of
425 622,026 SNPs for analysis. We paired the marginal z-scores from these studies with the SNP
426 correlation matrix estimated using 503 individuals of European ancestry from the 1,000
427 Genomes Project [55] for inference. Finally, after the analysis, we computed correlation among
428 traits in terms of their tissue relevance and used the Bayesian information criterion (BIC)
429 implemented in the clustering package mclust [66] in R with the standard option EEI to classify

430 traits. Clustering with BIC automatically inferred a total of five main trait clusters.

431

Investigate Trait-Tissue Relevance via PubMed Search

433

434 We rely on previous literature to partially validate the inferred trait-relevant tissue results in real
435 data. We reasoned that, if a tissue is indeed relevant to a given trait, then there would be
436 extensive prior biomedical researches carried out on the tissue for the trait. Therefore, the
437 number of previous publications on a trait-tissue pair can serve as a useful indicator on the
438 potential relevance and importance of the tissue for the trait. To estimate the number of previous
439 publications on trait-tissue pairs, we conducted a literature search on PubMed
440 (https://www.ncbi.nlm.nih.gov/pubmed/). Specifically, for each trait-tissue pair, we used the
441 names of trait and tissue as input and counted the number of publications that contain the input
442 values either in the abstract or in the title. For traits, we used trait names directly. For tissues, we
443 excluded the "Other" tissue group and focused on the nine remaining tissue groups. For these
444 remaining tissue groups, we used the following key words in addition to the tissue group name in
445 the PubMed search: (1) CNS: brain, central nervous system, neuron, glia and CNS; (2)
446 BloodImmune: blood, T-cell, B-cell, thymus and immune system; (3) Adipose: adipose. (4)
447 AdrenalPancreas: adrenal, pancreas; (5) BoneConnective: bone, fibroblast and connective tissue;
448 (6) Cardiovascular: heart, cardiovascular; (7) Gastrointestinal: gastrointestinal, esophagus,
449 stomach, intestine and rectum; (8) Liver: liver; (9) Muscle: muscle. For example, for the
450 schizophrenia-CNS trait-tissue pair, we conducted the search by using "schizophrenia
451 [Title/Abstract] AND (CNS [Title/Abstract] OR brain [Title/Abstract] OR central nervous system
452 [Title/Abstract] OR neuron [Title/Abstract] OR glia [Title/Abstract])", which yielded 17,720 hits.
453 The number of publications on each trait-tissue pair from the PubMed search is listed in Table S3
454 (the search was carried out on June 23, 2017). For each trait in turn, we further normalized the
455 data by dividing the number of publications for a tissue by the total number of publications
456 across all tissues for the trait. We used the resulting proportion for the final analysis.

457

SNP Set Test in WTCCC

459

460 Because of the close relationship between our method and the sequence kernel association test
461 (SKAT [49-51]) (details in Method Overview), we propose to use the estimated SNP specific
462 variance in the top trait-relevant tissue from our method as SNP weights in SKAT [49-51] to
463 perform SNP set test in new association studies. To examine the utility of this association
464 mapping strategy in real data, we estimated annotation coefficients in consortium studies, applied
465 them to construct SNP weights (details in the above Simulations subsection), with which we
466 performed SKAT [49-51] for the corresponding traits in the Wellcome Trust Case Control
467 Consortium (WTCCC) study [67]. The WTCCC data consists of about 14,000 cases from seven
468 common diseases and 2,938 shared controls. The cases include 1,963 individuals with type 1
469 diabetes (T1D), 1,748 individuals with Crohn's disease (CD), 1,860 individuals with rheumatoid
470 arthritis (RA), 1,868 individuals with bipolar disorder (BD), 1,924 individuals with type 2
471 diabetes (T2D), 1,926 individuals with coronary artery disease (CAD), and 1,952 individuals
472 with hypertension (HT). We excluded HT and considered the remaining six diseases for which
473 we had summary statistics in other larger consortium studies. We obtained quality controlled
474 genotypes from WTCCC [67] and imputed missing genotypes using BIMBAM [68] to obtain a

475 total of 458,868 SNPs that are shared across all individuals. The genotypes were further imputed
476 by SHAPEIT [69,70] and IMPUTE2 [71] with the 1,000 Genomes Project [55] as a reference.
477 We removed SNPs with a Hardy-Weinberg equilibrium p-value $< 10^{-4}$ or a minor allele
478 frequency < 0.05, and intersected SNPs from WTCCC with the consortium data to obtain a final
479 set of 335,170 overlapped SNPs. Meanwhile, we obtained genome locations for a set of 19,189
480 protein coding genes from GENCODE project [72]. We intersected SNPs with these genes and
481 identified gene-harboring SNPs that reside within 10 kb upstream of the transcription start site
482 and 10 kb downstream of the transcription end site. To perform gene-set test, we focused on
483 5,588 genes that have at least 10 SNPs, with an average of 29.6 SNPs inside each gene and a
484 total of 153,813 gene-harboring SNPs. For each gene in turn, we computed SNP-specific
485 variance using annotation coefficient estimates from the best trait-relevant tissue inferred with
486 consortium study summary statistics for the corresponding trait. We used the SNP-specific
487 variance as SNP weights. As in simulations, for these weights, we subtracted from them the
488 minimal weight across SNPs and added a small constant (10^{-15}) to ensure that all weights are
489 positive. We then multiplied the resulting SNP weights with the posterior probability (PP) of the
490 best trait-relevant tissue and further added a value of 1-PP to all SNPs as the final SNP weights
491 to perform SKAT [49-51] analysis. The SNP-weights for the 43 traits can be downloaded from
492 http://www.xzlab.org/.
493

Results

Simulations: Multiple Annotations versus Single Annotation

Our first set of simulations are used to illustrate the benefits of using multiple annotations to identify trait-relevant tissues. Details of simulations are provided in Materials and Methods. Briefly, we obtained 27,640 SNPs from 10,000 randomly selected individuals in the GERA study [63,64] and simulated phenotypes. We considered two histone annotations (H3K4me1, H3K4me3) from ten tissue groups (Table S1), among which we randomly designated one as the trait-relevant tissue. We then simulated SNP effect sizes under a polygenic model based on the two annotations in the trait-relevant tissue. We added genetic effects with residual errors to form simulated phenotypes. We obtained summary statistics from the data and considered three different approaches to identify trait-relevant tissues:

(1) SMART. We analyzed two annotations jointly and computed a single multivariate Wald statistic for each tissue using our procedure. We then applied an EM algorithm and a mixture model on the multivariate Wald statistics to further classify tissues into two groups. We used the posterior probability of a tissue being trait-relevant to measure trait-tissue relevance.

(2) Uni. We analyzed one annotation at a time and computed two univariate Wald statistics for each tissue using our procedure. We then applied an EM algorithm to classify these Wald statistics into two groups. For each tissue and each annotation, we obtained the posterior probability of being a trait-relevant tissue to measure trait-tissue relevance.

(3) UniMax. We analyzed one annotation at a time. For each tissue, we computed two univariate Wald statistic using our procedure and selected among them the larger statistic as a measurement of trait-tissue relevance. We then applied an EM algorithm to classify these Wald statistics into two groups. For each tissue, we obtained the posterior probability of its being a trait-relevant tissue to measure trait-tissue relevance.

Above, we have included two versions of univariate tests: Uni and UniMax. While the Uni approach is widely applied in previous studies [16,27,28,48], the UniMax approach can be statistically more appropriate than Uni for summarizing tissue-level evidence. We considered a range of realistic annotation coefficient combinations (i.e. (α_1, α_2)). For each combination, we performed 1,000 simulation replicates. For each method, we computed the power of various methods in detecting the trait-relevant tissue at a false discovery rate (FDR) of 0.1 (Figure 1A). In the majority of settings, analyzing multiple annotations jointly also improves power compared with analyzing one annotation at a time. For example, based on power at 10% FDR, SMART is ranked as the best method in 15 out of 25 simulation settings where both annotations have non-zero effects, while UniMax is the best in 10 settings (Figure 1A). While the performance of SMART is often followed by UniMax, the power improvement of SMART compared with UniMax can be large (median improvement = 9.2%). Certainly, in the special cases where one annotation coefficient is exactly zero or close to zero, then SMART is often outperformed by UniMax, presumably due to its smaller degree of freedom there. For example, among the 11 settings where at least one annotation has zero effects (grey area, Figure 1A), SMART is ranked as the best method only 4 times, while UniMax is ranked as the best method 7 times. Finally, to further explore the characteristics of annotations that can influence the power of SMART in identifying trait-relevant tissues, we simulated annotations that have various genome-occupancy characteristics and that have various annotation effect sizes and signs (Supplementary Text). We

540 show that the power of SMART increases with increasing annotation coefficients, is not sensitive
541 to the signs of annotations, and is relatively stable with respect to the genome-occupancy of the
542 annotations as we have standardized the annotations to have mean zero and standard deviation
543 one across the genome (Figure S3).
544
545 We examine in detail a simulation setting where (α_1, α_2) are chosen to be close to the median
546 estimates $(0.1, 0.05)$ from the real data sets (i.e. gold shade in Figure 1A and Figure S1). Note
547 that even though these parameters are chosen based on real data, we have much less SNPs or
548 samples in the simulations than in real data and are thus underpowered in simulations. In any
549 case, we first obtained annotation coefficient estimates $(\hat{\alpha}_1, \hat{\alpha}_2)$ across simulation replicates in
550 this setting. We found that the estimates are centered around the truth as one would expect
551 (Figure 1B), suggesting accurate parameter estimation by our approach. Next, in addition to the
552 six approaches listed above, we also included a UniMax_LDSC approach into comparison. In the
553 UniMax_LDSC approach, we applied LDSC to analyze one trait at a time and used the
554 maximum Wald statistics among the two to measure trait-tissue relevance. Different from the
555 UniMax_Wald, however, UniMax_LDSC used a set of 75 baseline annotations to address
556 correlation among annotations. As a result, UniMax_LDSC performs similarly as UniMax in
557 terms of power to detect trait relevant tissues at different FDR thresholds (Figure 1C), suggesting
558 that using mixture modeling is competitive compared to using covariates to control for
559 annotation correlation across tissues. Because both UniMax_LDSC and UniMax use only one
560 annotation, they are often less powerful compared to SMART that models two annotations
561 together (Figure 1C).
562

Simulations: Construct Powerful SNP Set Test

564
565 Our second set of simulations is intended to illustrate the benefits of our method in using inferred
566 trait-relevant tissue to enable more powerful SNP set tests. Here, we ask the question of how to
567 make use of the inferred trait-relevant tissues to enable more powerful future association studies.
568 As explained in the Method Overview section, our model is closely related to the sequence
569 kernel association test (SKAT) [49-51] for SNP set test. In particular, the SNP specific variance
570 in our model can be naturally interpreted as the SNP specific weight in the SKAT [49-51]
571 framework. Because of this close relationship between our model and SKAT [49-51], we propose
572 to use the estimated SNP specific variance in the top trait-relevant tissue from our model as SNP
573 weights to perform analysis in new association studies. Intuitively, if a SNP tends to have a large
574 effect size, then weighting it high in the subsequent SNP set analysis can help achieve greater
575 association mapping power. To explore the possibility of using the inferred SNP-specific
576 variance estimate $\hat{\sigma}_j^2$ as *a priori* weight to construct SNP set test in the SKAT framework [49-
577 51], we obtained 10,000 SNPs from the same set of 10,000 individuals in the GERA study
578 [63,64] and simulated phenotypes (Materials and Methods). To do so, we divided these SNPs
579 evenly into 100 blocks and randomly selected 10 blocks to be causal blocks. In each casual
580 block, we further selected 20 SNPs to be causal SNPs. We then simulated ten tissue-specific
581 annotation sets with two annotations within each set and designated one set as the trait-relevant
582 tissue. We simulated causal SNP effect sizes based on the two annotations from the trait-relevant
583 tissue and added residual errors to form the simulated phenotypes. Afterwards, we divided
584 individuals randomly into two sets: a training set of 7,000 individuals and a test set of 3,000
585 individuals. We applied SMART_EM and UniMax_EM in the training set to identify trait-

586 relevant tissues and to estimate annotation coefficients. We then applied the following weighting
587 options to perform SKAT [49-51] analysis in the test set:
588 (1) EqualWeight, where we weight all SNPs equally.
589 (2) TissueWeight_Oracle, where we use the true coefficients from the correct trait-relevant tissue
590 to construct SNP weights. This represents an up limit of power we can possibly achieve.
591 (3) TissueWeight_SMART, where we fitted SMART_EM in the training data and applied the
592 coefficient estimates for the two annotations in the inferred trait-relevant tissue to construct SNP
593 weights.
594 (4) TissueWeight_UniMax, where we fitted UniMax_EM in the training data and applied the
595 coefficient estimate for the annotation with the larger Wald statistics in the inferred trait-relevant
596 tissue to construct SNP weights.
597
598 We first simulated 50,000 replicates under the null where there is no causal SNP so that both α_0
599 and (α_1, α_2) are 0. We used the null simulations to examine the type I error control for various
600 methods and we found that all these methods are well behaved (Figure 2A). Next, we simulated
601 1,000 replicates under the alternative where we have non-zero α_0 and (α_1, α_2). We divided SNPs
602 into 100 blocks, among which 10 are causal. We compared different methods in terms of their
603 power to identify the causal blocks. In the simulations, we generated two annotations whose
604 values in the trait-relevant tissue are predictive of SNP causality. The annotation values for the
605 two annotations are almost identical in a certain proportion of causal SNPs (chosen to be 0%,
606 33%, or 100%) so that the two annotations can contain complementary information (in the case
607 of 0%) or overlapping information (in the case of 100%). Intuitively, information overlapping in
608 the two annotations would reduce the relative power gain of using multiple annotations versus
609 using a single annotation in constructing SNP set tests. As one would expect, in all settings,
610 constructing SNP weights using the true coefficients from the correct trait-relevant tissue (i.e.
611 TissueWeight_Oracle; red bars in Figure 2B and C) achieves the greatest power compared with
612 the other methods. For example, compared with using equal weights, using the oracle weights
613 improves power by 14.1% on average (median = 13.7%) across all settings. Importantly,
614 constructing SNP weights using the estimated coefficients from the inferred trait-relevant tissue
615 weight (i.e. TissueWeight_SMART; green bars in Figure 2 B and C) can often achieve almost
616 identical power as TissueWeight_Oracle. Comparing between TissueWeight_SMART and
617 TissueWeight_UniMax, when both annotations have non-zero coefficients, we found that using
618 multiple annotations often leads to greater power gain than using a single annotation. However,
619 as one would expect, when the two annotations contain overlapping information (e.g. in the case
620 of 100%), then using one annotation yields similar power as using two annotations (green vs blue
621 in Figure 2B). In the special case where only one annotation has a non-zero coefficient, then
622 using multiple annotations also has similar power compared with using a single annotation, even
623 when the two annotations contain complementary information (green vs blue in Figure 2C).
624
625 Next, we explore how various simulation parameters influence the weighted SKAT power
626 (Supplementary Text). Here, we also include TissueWeight_UniMaxLDSC, where we applied
627 LDSC with the UniMax procedure in the training data and used the coefficient estimate for the
628 annotation with the larger Wald statistics in the inferred trait-relevant tissue to construct SNP
629 weights. In this set of simulations, we varied the annotation coefficients and varied the number of
630 causal blocks. The results are presented in Supplementary Figure S4. With simulations, we show
631 that the power of SNP set test primarily depends on the phenotype variance explained (PVE) by

632   each causal block (i.e. per-block PVE) as well as annotation coefficients, and increases with
633   increasing per-block PVE or annotation coefficients. In contrast, power is not influenced by the
634   number of blocks when per-block PVE is fixed to be a constant, though it would decrease with
635   increasing number of blocks when the total PVE is fixed (as per-block PVE is negatively
636   correlated with number of blocks in this case). Importantly, TissueWeight_SMART outperforms
637   TissueWeight_UniMax and TissueWeight_UniMaxLDSC in most scenarios and outperforms
638   EqualWeight in all scenarios.

Real Data Applications

Data processing and analysis overview

We applied our method to analyze 43 traits from 29 GWAS studies (Table S2). For these analyses, we obtained tissue-specific SNP annotations in 105 tissues from 10 tissue groups in the ENCODE [23] and Roadmap [22] projects and processed these annotations into three sets (details in Materials and Methods; Table S1): (1) four binary annotations (H3K27me3, H3K36me3, H3K4me1, and H3K4me3) in 105 tissues constructed based on histone mark occupancy; (2) four continuous annotations in 10 tissue groups (BloodImmune, Adipose, AdrenalPancreas, BoneConnective, Cardiovascular, CNS, Gastrointestinal, Liver, Muscle, and Other) based on averaging binary annotations across tissues within each tissue group; and (3) posterior probabilities of the 15 ChromHMM [62] states in the 10 tissue groups. For each trait in turn, we paired the three sets of annotations with GWAS summary statistics to identify trait-relevant tissues. Data processing and analysis details are described in the Materials and Methods.

Trait tissue relevance determined by SMART is largely consistent with PubMed literature and highlights the importance of modeling multiple annotations

Besides applying our method to infer trait relevant tissues, we first rely on the knowledge gained from previous biomedical literature to measure trait-tissue relevance. To do so, we conducted a PubMed literature search and counted the number of publications existed for each trait-tissue pair. We reasoned that, if a tissue is indeed relevant to a given trait, then there would be a fair number of studies performed on the tissue for the given trait. Therefore, the number of publications carried out on a trait-tissue pair would be a good indicator on their relevance. Next, for each trait in turn, we normalized the count data by computing the proportion of previous publications performed on each of the nine tissue groups (i.e. the ten tissue groups minus the "Other" group), resulting in for each trait a vector of nine proportion values that sum to one (details in Materials and Methods). The number of total publications and proportion values for all traits are summarized in Table S4. The PubMed literature search results are generally consistent with what we would expect. For example, for schizophrenia (SCZ), 63.8% of the previous literatures are focused on CNS, with the rest of the literature scattered across other tissues. The proportion of literature carried out on each trait-tissue pair obtained in PubMed thus provides a reasonable *a priori* measure of trait-tissue relevance. We use these measurements to validate some of our analysis results using tissue specific annotations.

We then applied our method to jointly analyze multiple annotations for each of the three sets of tissue-specific annotations described above. We denote the analysis on annotation set (1) as **HB** (i.e. histone marks, binary), analysis on annotation set (2) as **HC** (i.e. histone marks, continuous), and analysis on annotation set (3) as **cHMM** (i.e. ChromHMM annotation). For **HC** and **cHMM**, we obtained the posterior probability values (PPs) from each of the 10 tissue groups for each trait. For **HB**, we first obtained PPs from each of the 105 tissues for each trait. For each trait in turn, we then averaged these PP values within each tissue group and used the averaged tissue group level PP values for the following analyses – this way we can perform comparisons at the tissue group level across different annotation sets. As a comparison, we also applied our method to each of the three annotation sets and performed univariate analysis that corresponds to the

685 UniMax procedure explained in the simulation section. These univariate analyses include
686 **HBuMax**, which is a univariate analysis of the annotation set (1); **HCuMax**, which is a
687 univariate analysis of the annotation set (2); **cHMMuMax**, which is a univariate analysis of the
688 annotation set (3); and **HBuMaxLDSC**, which is a univariate analysis on the binary annotation
689 set (1) using LDSC. In these univariate analyses, for each trait in turn, we first selected the
690 annotation with the maximum Wald statistic in every tissue (or tissue group). We then computed
691 the PPs of the selected mark in all tissues (or tissue groups). When necessary, we further
692 averaged PPs (for **HBuMax**) or Wald statistics (for **HBuMaxLDSC**) within each tissue group to
693 allow for comparison at the tissue group level. Overall, we obtained 10 tissue group level PP
694 values or Wald statistics for every trait from each of the five different approaches. We list the top
695 trait-relevant tissue groups with the largest PP value or Wald statistics identified by each of the
696 above approaches in Table S3, with the corresponding tissue group PPs listed in the same table.
697 The tissue group PPs from HC are also plotted in Figure S5.
698
699 The results from those different approaches are largely consistent with the PubMed search
700 results, though notable deviations exist. For example, PubMed search identified CNS to be the
701 most relevant tissue to five neurological traits (ADD, BIP, SCZ, Autism and Alzheimer).
702 Approaches using annotations also identified CNS as the most trait-relevant tissue for four of the
703 five neurological traits (ADD, BIP, SCZ and Autism). However, for Alzheimer's disease, using
704 tissue-specific annotations revealed BloodImmune tissue as a trait-relevant tissue, which is
705 consistent with recent discoveries that inflammation and microglia are important for Alzheimer's
706 disease etiology [73,74]. As another example, PubMed search identified liver to be the most
707 relevant tissue for hematological traits (MCHC, MCH, MCV, MPV, PLT and RBC), presumably
708 because of liver's important role in producing extrarenal erythropoietin [75]. In contrast, using
709 tissue-specific annotation highlighted BloodImmune tissue as the most relevant tissue for
710 hematological traits. The similarity and difference between SMART and PubMed search results
711 highlight the importance of using different information to infer trait tissue relevance.
712
713 We further quantify the similarity between various approaches and PubMed results. To do so, we
714 compare the tissue group level PP values from the annotation integration approaches to the
715 proportion of publications on each tissue group obtained from PubMed search. For each trait and
716 each approach in turn, we computed the correlation between the PP vector for the nine tissue
717 groups and the corresponding proportion values from PubMed search (Figure 3C). We reasoned
718 that, if an approach makes good use of the annotation information, then the trait tissue relevance
719 inferred by this approach would be consistent with the trait tissue relevance measured by
720 PubMed search. Indeed, the Spearman's rank correlations between different integrative
721 approaches and the PubMed search are reasonable, with an median (average) value of 0.474
722 (0.420), 0.417 (0.379), 0.283 (0.242), 0.433 (0.397), 0.433 (0.376), 0.417 (0.360) and 0.417
723 (0.344) for **HB, HBuMax, HBuMaxLDSC, HC, HCuMax, cHMM** and **cHMMuMax**,
724 respectively. The correlation results also suggest that, for the same annotation set, using multiple
725 annotations often yields better performance than using one annotation alone (i.e. **HB** vs
726 **HBuMax** or **HBuMaxLDSC, HC** vs **HCuMax**, and **cHMM** vs **cHMMuMax**). Finally,
727 comparing different annotation sets, we found that using 15 chromatin states (i.e. **cHMM** and
728 **cHMMuMax**) often result in lower correlation than using the annotations based on histone
729 occupancy, suggesting that post-processing histone occupancy data into chromatin states may
730 lose important trait-tissue relevance information, dovetailing earlier findings [76].

731

732

Tissue relevance analysis reveals important histone markers in predicting SNP effects and
classifies 43 traits into five main clusters

735

To characterize trait-tissue relevance at the tissue group level, we focused on the results from the *HC* approach in more details and examined the annotation coefficients for the four histone marks inferred from the most trait-relevant tissue. We show the estimates and their significance for individual traits in Figure 3A and then grouped coefficients across 43 traits in Figure 3B. Overall, among the four histone marks, two of them have positive coefficient estimates: the coefficient estimates for H3K4me1 are positive for 42 out of 43 traits, while the coefficient estimates for H3K4me3 are positive for 32 traits (Figure 3B). The positive coefficients for the two histone marks are consistent with their role in marking promotors and enhancers, which are enriched in or near association loci identified by multiple GWASs [11,45]. In contrast, the coefficient estimates of H3K27me3 and H3K36me3 are mostly estimated to be close to zero, with approximately random positive or negative signs (positive signs in 22 traits for H3K27me3, and in 25 traits for H3K36me3; Figure 3A). The near-zero estimates of H3K27me3 and H3K36me3 suggests that SNP effect sizes in polycomb repression regions and transcribed regions often do not differ much from the rest of the genome. In terms of the magnitude of the estimated coefficients, two of the four marks (H3K4me3 and H3K4me1) have large effect estimates, as well as high estimation variation, across all examined traits (Figure 3B). The large coefficient estimates for H3K4me3 and H3K4me1 suggest that both promotor regions and enhancer regions are highly predictive of SNP effect sizes and are often the most informative for inferring trait-tissue relevance.

755

The results with the *HC* approach are also consistent with what we see in the simulations. In particular, while our extended linear mixed model itself does not explicitly model the correlation among annotations across tissues, our mixture modeling and classification strategy implicitly accounts for annotation correlation across tissues and allows us to identify multiple trait-relevant tissues for a given trait when they are present. Indeed, examining the tissue group PPs from HC (Figure S5), we found that, among the 43 GWAS traits, more than half of them have one trait-relevant tissue with PP>0.5, while 4 of them have two or more trait-relevant tissues with PPs>0.5. For example, consistent with [16], the CNS tissue group was identified as the trait-relevant tissue for SCZ, BIP, YE and Ever smoked. Consistent with [16], the blood immune tissue group was identified as the trait-relevant tissues for CD, RA and UC. While consistent with [16,27], multiple tissue groups, including bone connective, muscle, cardiovascular and adipose, were identified as relevant for height.

768

To further characterize trait-tissue relevance at the tissue level, we examined the results from the *HB* approach in details. The annotation set (1) contains binary annotations for 105 tissues that belong to 10 tissue groups. We have only focused on examining group-level results from this set of annotations so far. Here, we focus instead on the PP values for the 105 tissues directly; thus we have a 105-vector of PP values for every trait. We relied on the PP values to rank tissues for every trait. The tissue rank list for each trait represents the tissue footprint of each trait: the trait-relevant tissues are ranked high in the list while the trait-irrelevant tissues are ranked low in the list. With the tissue rank list, we assess the similarity between GWAS traits in terms of their

777 tissue relevance by hierarchical clustering (Figure 4). We also computed pair-wise spearman
778 correlation between traits based on the tissue rank list (Figure 5). Overall, applying the Bayesian
779 information criterion (BIC) to the correlation plot using mclust [66] revealed five main trait
780 clusters.

782 The first and second trait clusters contain psychiatric disorders (i.e. SCZ, BIP, Autism, DS,
783 Neuroticism and ADD) and neurological related traits (e.g. College, YE, Menarche, Child_Obes,
784 Child_BMI, and EverSmoked). For these two clusters, the CNS tissue tends to be identified as
785 the most trait-relevant, consist with previous studies [16,27]. Among these traits, BIP, Menarche,
786 College, YE, BIPSCZ, SCZ, DS, Neuroticism are highly correlated with each other and all belong to
787 the first trait cluster; while ADD, Autism, EverSmoked, Child_BMI, Child_Obes are all grouped
788 into the second trait cluster. Among the psychiatric trait pairs in the first two clusters, SCZ and
789 BIP pair has the highest correlation (spearman correlation = 0.561; versus median/mean
790 correlation = 0.098/0.167; BIPSCZ are excluded), suggesting that SCZ and BIP are more similar
791 to each other in terms of tissue relevance footprint compared with the other trait pairs. The third
792 trait cluster contains traits that are often related to several tissue groups. Specifically, the
793 anthropometric traits (i.e. BL, BW, FNBMD, LNBMD and Height) are related to the bone,
794 connective and gastrointestinal tissues; while the metabolic traits (i.e. FG, T2D and HR) are
795 related to the gastrointestinal, liver and adipose tissues. The fourth trait cluster mainly contains
796 two categories of traits that include immune diseases (e.g. RA, Lupus, T1D, UC, PBC, CD and
797 IBD) and hematological traits (e.g. MCHC, MCH, MCV, PLT, RBC and MPV). Both these two
798 categories are related to blood immune tissues. However, the fourth cluster also contains
799 Alzheimer's disease. The classification of Alzheimer's disease in the fourth cluster rather than in
800 the first two clusters presumably reflects the close relationship of the disease to both
801 BloodImmune and CNS [28,74]. Finally, the fifth trait cluster mainly contains metabolic traits
802 (TC, TG, LDL, HDL and CAD) that are related to gastrointestinal and blood immune tissues.
803 Note that traits from the last three clusters tend to have positive correlations among each other,
804 while have negative correlations with traits from the first two clusters (Figure 5).

806 **Using Trait-relevant Tissue Results in More Powerful SNP Set Tests**

808 Finally, we explored the use of annotation coefficient estimates from the inferred trait-relevant
809 tissues to construct SNP set tests in a separate data, the Wellcome trust cast control consortium
810 (WTCCC) study. WTCCC contains the six common diseases that include T1D, T2D, CD, BIP,
811 RA and CAD. We focused on a set of 5,588 genes and used 153,813 SNPs inside these genes to
812 perform SNP set test using SKAT [49-51] (details in Materials and Methods). As in simulations,
813 we considered three different SNP weights for SKAT test: (1) SNP weights constructed by the
814 multivariate analysis approaches of SMART (i.e. *HC* and *HB*); (2) SNP weights constructed by
815 the univariate maximal statistics approach (*HCuMax, HBuMaxLDSC* and *HBuMax*); and (3)
816 equal SNP weights (*EqualWeight*). We apply different weights to each of the six diseases. We
817 first display the quantile-quantile (QQ) plot of –log10 p-values from SKAT in Figure 6 (for CD)
818 and Figure S6 (for T1D, T2D, BIP, RA and CAD), which, consistent with simulations, suggests
819 proper control of type I error. In the analysis, different approaches identified a different number
820 of associated genes that pass the Bonferroni corrected genome-wide significance threshold
821 (8.95×10^{-6}), and these numbers range from 12-15 (the union of them contains 17 genes). These
822 genes are associated with either CD, RA, T1D or T2D, and have all been validated either in the
823 original WTCCC study or in other GWASs of the same trait (Table 1). Consistent with

824   simulations, we found that SNP set tests using weights constructed from the trait-relevant tissue
825   achieves higher power compared with using equal weights. For example, the *HC* approach or the
826   *HB* approach identified 15 genes, 3 more than that identified using equal weights (Table 1). In
827   particular, the *HC* approach identified *C1orf141* [77] and *BSN* [78] for CD as well as *FTO* [79]
828   for T2D, and neither of these were identified by the equal weights approach. While the HB
829   approach identified *BSN* [78] and *SLC22A5* [78] for CD as well as *FTO* [79] for T2D, and
830   neither of these were identified by the equal weights approach. Finally, within each annotation
831   set, using multiple annotations identified slightly more genes than using one annotation at a time
832   (i.e. *HB* **vs.** *HBuMax* or *HBuMaxLDSC* and *HC* vs. *HCuMax*), again consistent with the
833   simulation results.

Discussion

We have presented a simple modification of the commonly used linear mixed model to integrate multiple SNP annotations with GWAS traits to facilitate the identification of trait-relevant tissues. We have described an accompanying GEE based parameter inference algorithm that makes use of summary statistics and naturally accounts for genetic correlation due to linkage disequilibrium. We have shown how the task of identifying trait-relevant tissues can be formulated into a classification problem and how mixture modeling can facilitate the inference of trait-relevant tissues in the presence of annotation correlation across tissues. We have also illustrated how the link between our extended linear mixed model and the commonly used SKAT can enable more powerful SNP set tests in new association studies. With both simulations and an in-depth analysis of 43 GWAS traits, we have illustrated the benefits of modeling multiple annotations jointly.

Our approach complements several recently developed methods that aim to derive a single, interpretable synthetic annotation by combining information of multiple annotations in a tissue specific fashion [17,20,27,28]. Most of these methods rely on multiple annotation information and use clustering algorithms to cluster SNPs into two categories. The posterior probability of SNPs in the category with the smaller number of SNPs thus becomes a synthetic annotation and is often interpreted as the posterior probability of being a "causal" or "functional" SNP. While these synthetic annotations have the benefits of simplicity and potential interpretability, they often have the drawback of being derived without taking into account the GWAS trait of interest. Arguably, functions of genetic variants depend on traits and clustering SNPs without considering the trait of interest may be suboptimal. Our approach complements these previous methods in that we effectively derive a synthetic annotation by taking GWAS traits into account. In particular, our method can be viewed as a supervised approach to combine multiple annotations into a single annotation, where the single annotation is represented as a weighted summation of the multiple annotations, with the weights being the estimated annotation coefficients inferred directly using the GWAS trait. Therefore, the approach we develop effectively takes the trait of interest into account. Certainly, both our approach and these previous approaches make a key modeling assumption that multiple annotations in the trait-relevant tissue are more relevant to SNP effect sizes or causality as compared with annotations in trait-irrelevant tissues. While it is a reasonable assumption for histone occupancy based annotations we examine here, this assumption may not hold well for certain annotations and for certain complex traits. For example, it is possible the classification of trait-relevant tissue depends on what annotation one examines: the SNP effect sizes can be predicted well by using one annotation in one tissue, or by using another annotation in a different tissue. To briefly explore the utility of our method in the case of multiple trait-relevant tissues, we performed a simulation study that is similar to the polygenic scenario presented in the results section but with two trait-relevant tissues: we used one annotation from one tissue and another annotation from another tissue to simulate SNP effect sizes. In this setting, as one might expect, the difference between the multivariate approach and the univariate approach is small (Figure S7). Therefore, developing method for the case of multiple trait-relevant tissues is an interesting future direction.

We rely on a polygenic model to evaluate the contribution of annotations to SNP effect sizes and infer trait-relevant tissues. Our polygenic model assumes that all SNP effect sizes are non-zero

880 and follow a normal distribution with SNP-specific variance that is a function of multiple
881 annotations. Therefore, our approach is different from several previous approaches that rely on a
882 sparse model to evaluate the contribution of annotations to SNP causality [11,12,27,28,40,53] .
883 While sparse models can be used to directly link annotation coefficients to the causality of SNPs,
884 they often encounter severe computational burdens due to linkage disequilibrium among SNPs.
885 For example, the recent sparse model bfGWAS [40] has to divide genome into thousands of
886 approximately independent blocks and perform analysis within each block separately; and even
887 with such a simplified algorithm it can take a sparse model days to analyze a GWAS data with
888 tens of thousands of individuals and millions of SNPs. In contrast, a key advantage of our
889 polygenic model and its GEE based inference algorithm is their ability to properly account for
890 linkage disequilibrium while being computationally trackable. Indeed, it only take about 20
891 minutes to analyze each of trait-tissue pair in our real data application with hundreds of
892 thousands of individuals and millions of SNPs. Certainly, the polygenic modeling assumption
893 that all SNPs have non-zero effects may not be realistic for certain traits and developing both
894 realistic and computationally efficient methods is an important future direction.
895
896 We have focused primarily on using tissue-specific annotations based on histone occupancy from
897 the ENCODE and ROADMAP projects. Other tissue-specific annotations are nowadays readily
898 available. For example, the GTEx project measures expression quantitative trait loci (eQTL)
899 information in 53 tissues, many of which overlap with that in ROADMAP. Our method can
900 easily incorporate multiple annotations from different data sources and include both eQTL
901 annotations from GTEx and histone annotations from ROADMAP, though caution needs to be
902 made to account for accuracy difference in these eQTL annotations from different tissues due to
903 sample size variation. In any case, jointly analyzing multiple sources of annotations will likely
904 improve power further in identifying trait-relevant tissues in the future.
905
906 In the real data application, we have attempted to infer fine-scale trait-tissue relevance by using
907 105 tissues instead of the 10 tissue groups using the **HB** approach. The inferred top-ranking
908 tissue types from the **HB** approach for each of the 43 GWAS traits are listed in Supplementary
909 Table S5. As expected, most of these top-ranking tissues belong to the top-ranking tissue group
910 (median = 70.5% across traits), suggesting relatively stable inference results whether tissues or
911 tissue groups were used in the analysis. For example, all of the top-ranking tissues (with PP >
912 0.5) for ever smoked and YE belong to the CNS tissue group, and 28 of the 39 top-ranking
913 tissues for CD belong to the blood immune tissue group. We have attempted to further quantify
914 the tissue-level relevance results by comparing them to the corresponding PubMed search
915 results, as we have done in the main text for the tissue group analysis. However, we found that
916 PubMed search results are unable to distinguish fine-scale tissue types for most traits. Therefore,
917 we had to rely on prior biology knowledge obtained in various other studies to validate our tissue
918 relevance analysis. In many cases, the top-ranking tissue fits our prior expectation. However, we
919 also acknowledge that identifying relevant tissues from >100 tissue types is indeed a challenging
920 task. Specifically, for 34 out of 43 traits, the PPs for more than half of the tissues within the
921 corresponding top-ranking tissue group are greater than 0.5, suggesting that it is often difficult to
922 identify a single trait-relevant tissue within the tissue group. Alternative approaches to explore
923 fine-scale trait-tissue relevance have been suggested before. For example, a two-step analysis
924 procedure was proposed to first identify trait-relevant tissue group and then identify trait-relevant
925 tissue within the tissue group [80]. In addition, using synthetic annotations generated from

926　Genoskyline [28] or FUN-LDA [81] could be particularly useful for identifying fine scale trait-
927　relevant tissues. Our method can be easily adapted to incorporate a two-step analysis procedure
928　and/or accommodate synthetic annotations, and has the potential to yield better trait-tissue
929　relevance resolution in the future.
930

931　Finally, while we have mainly focused on inferring trait-relevant tissues, we have also explored
932　the feasibility of using inferred trait-relevant tissues and the estimated annotation coefficients to
933　enable more powerful SNP set test in future GWASs. In practice, multiple annotation sets can be
934　used to construct SNP set tests (e.g. HC and HB annotations sets as used in our real data
935　application). It is often difficult *a priori* to determine which annotation set would yield the best
936　results. Therefore, we recommend analyzing all of these annotation sets separately and choose
937　the one that yields the highest power, as we have done in the real data application. In addition,
938　sometimes the trait of interest may have multiple relevant tissues. In this case, we can apply the
939　PPs from the identified trait-relevant tissues (with PP>0.5) to weight the corresponding estimated
940　annotation coefficients from these tissues to form a set of weighted annotation coefficients, in
941　line with the Bayesian model averaging idea. Finally, while incorporating annotation information
942　does increase SNP set test power, we also found that such power improvement in realistic
943　settings depends on traits and can be variable. The variability in power improvement of our
944　method is consistent with many previous studies that have shown similar variability in power
945　improvement by integrating SNP annotations into single SNP association tests [11,40]. However,
946　increasing sample size and the development of better SNP annotations will likely facilitate the
947　adaption of various annotation integration methods in the near future.

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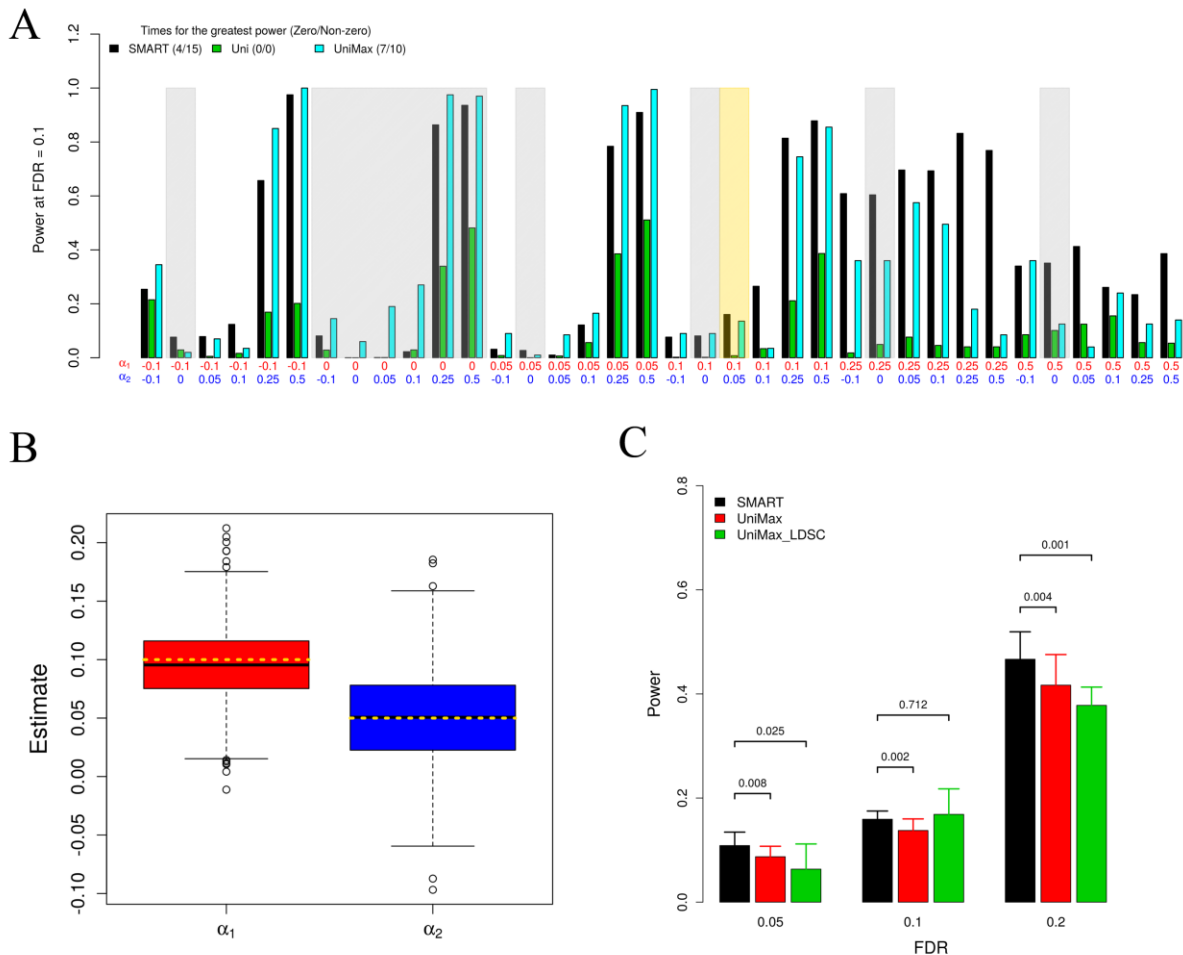
1149
1150 **Figure 1** Simulation results for comparing using multiple annotations versus a single annotation. (A) Power to
1151 detect trait-relevant tissues by different approaches in various settings at a fixed FDR of 0.1. x-axis shows the values
1152 of the two annotation coefficients used in the simulations. Settings where at least one annotation coefficient is zero
1153 are shaded in grey. The setting where the annotation coefficients equal to the median estimates from real data (i.e.
1154 $\alpha = (0.1, 0.05)$) is shaded in gold. The first number for each method in the figure legend represents the number of
1155 times each method is ranked as the best in 25 simulation settings where none of the annotations have zero
1156 coefficients; while the second number represents the number of times each method is ranked as the best in 11
1157 simulation settings where at least one annotation has a zero coefficient. (B) Annotation coefficient estimates by
1158 SMART are centered around the truth (horizontal dotted gold lines). (C) Mean power (y-axis) to detect trait-relevant
1159 tissues by different approaches at different FDR values (x-axis). Error bar shows the standard deviation computed
1160 across 10 simulation groups, each of which contains 1,000 simulation replicates (i.e. a total of 10,000 simulations).
1161 *p*-values from the paired t-test are used to compare methods at different FDR cutoffs. Note that the error bar is large
1162 due to the small number of simulation replicates within each simulation group. For (B) and (C), simulations were
1163 done at $\alpha = (0.1, 0.05)$. FDR, false discovery rate.
1164
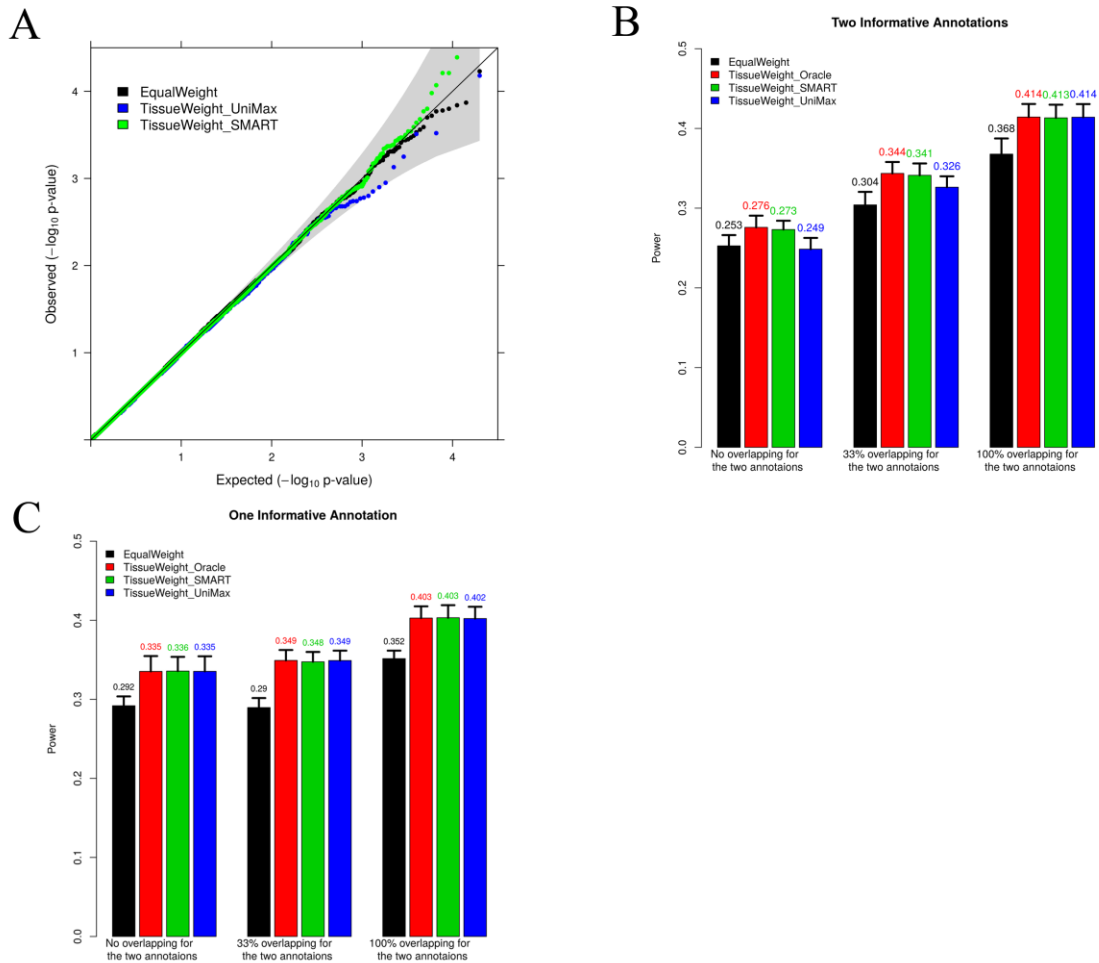
1165
1166 **Figure 2** Simulation results for using different weights to construct SNP set tests. (A) QQ plot of -log10 p values
1167 from SNP set tests using different SNP weights under the null simulations. Tests using different weights all control
1168 type I error well. (B) Power to detect causal blocks by SNP set tests using different SNP weights in the simulation
1169 setting where $\alpha = (0.4, 0.4)$. (C) Power to detect causal blocks by SNP set tests using different SNP weights in the
1170 simulation setting where $\alpha = (0.4, 0)$. For both (B) and (C), Power are evaluated at a genome-wide significance
1171 threshold of 1×10^{-4}. Standard errors are computed across 1,000 simulation replicates. The x-axis shows the
1172 proportion of causal SNPs that have identical values for the two annotations, which measures correlation between
1173 the two annotations.
1174
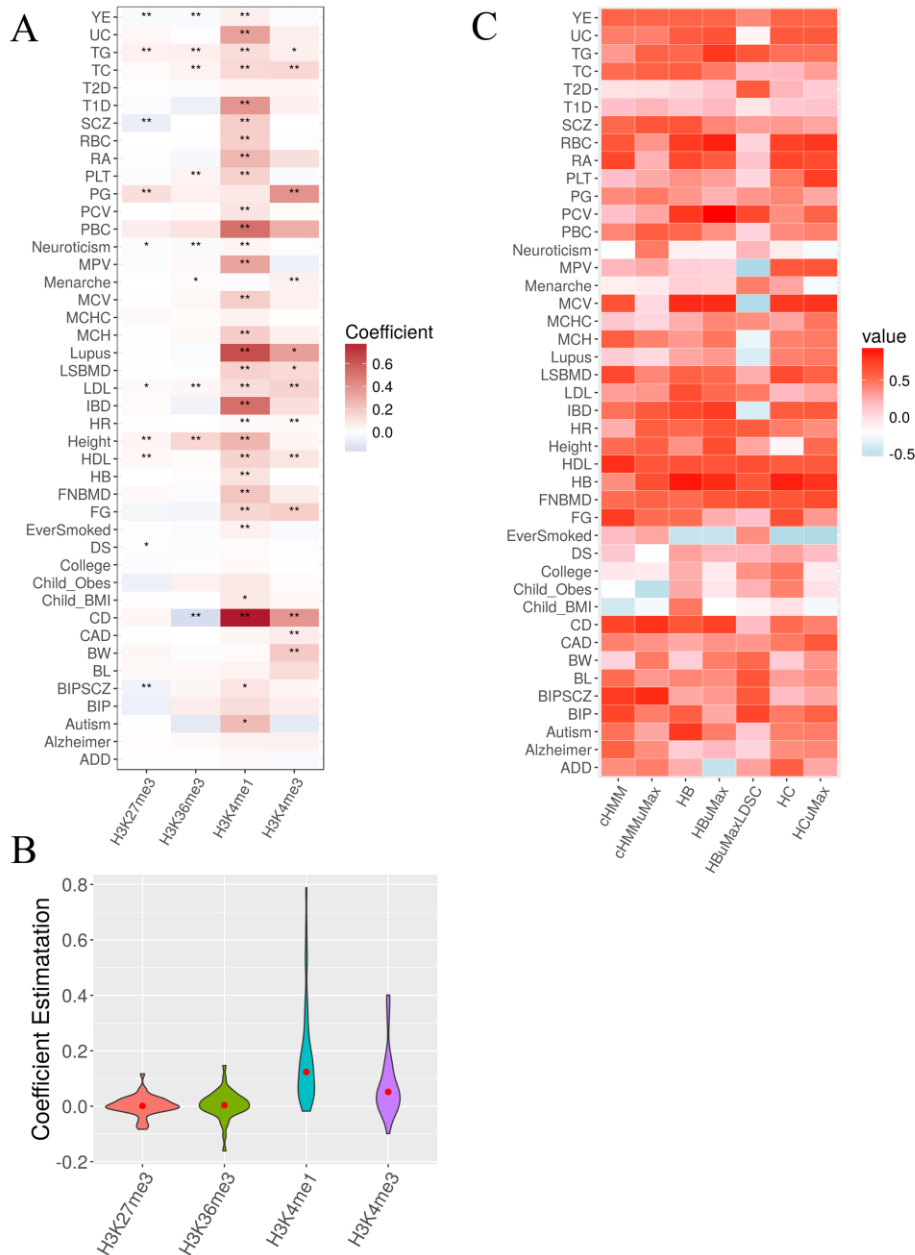
Figure 3 Inferring tissue relevance for 43 GWAS traits using SNP annotations (A) Heatmap displays the annotation coefficient estimates for the four histone marks (y-axis) in the most trait relevant tissue for 43 traits (x-axis). Color captures the sign and magnitude of the estimates, while the number of stars represent the significance of the estimates after Bonferroni correlation for the 43 * 10 *4 = 1,720 hypotheses tested (*: $p < 0.05$; **: $p < 0.01$). (B) Boxplot shows the coefficient estimates for the four histone marks in the most trait relevant tissue across 43 traits. (C) Heatmap displays correlation between different annotation integration approaches (y-axis) and the PubMed search approach for 43 GWAS traits (x-axis). For Uni and SMART approaches, correlations are computed between the average posterior probability vectors of the nine tissue groups from different annotation integration approaches and the proportion of existing publications on the same nine tissue groups from PubMed search; For UniMax_LDSC approach, correlations are computed between the average Wald statistic vectors of the nine tissue groups and the proportion of existing publications on the same nine tissue groups from PubMed search. Color captures the sign and magnitude of the estimates.
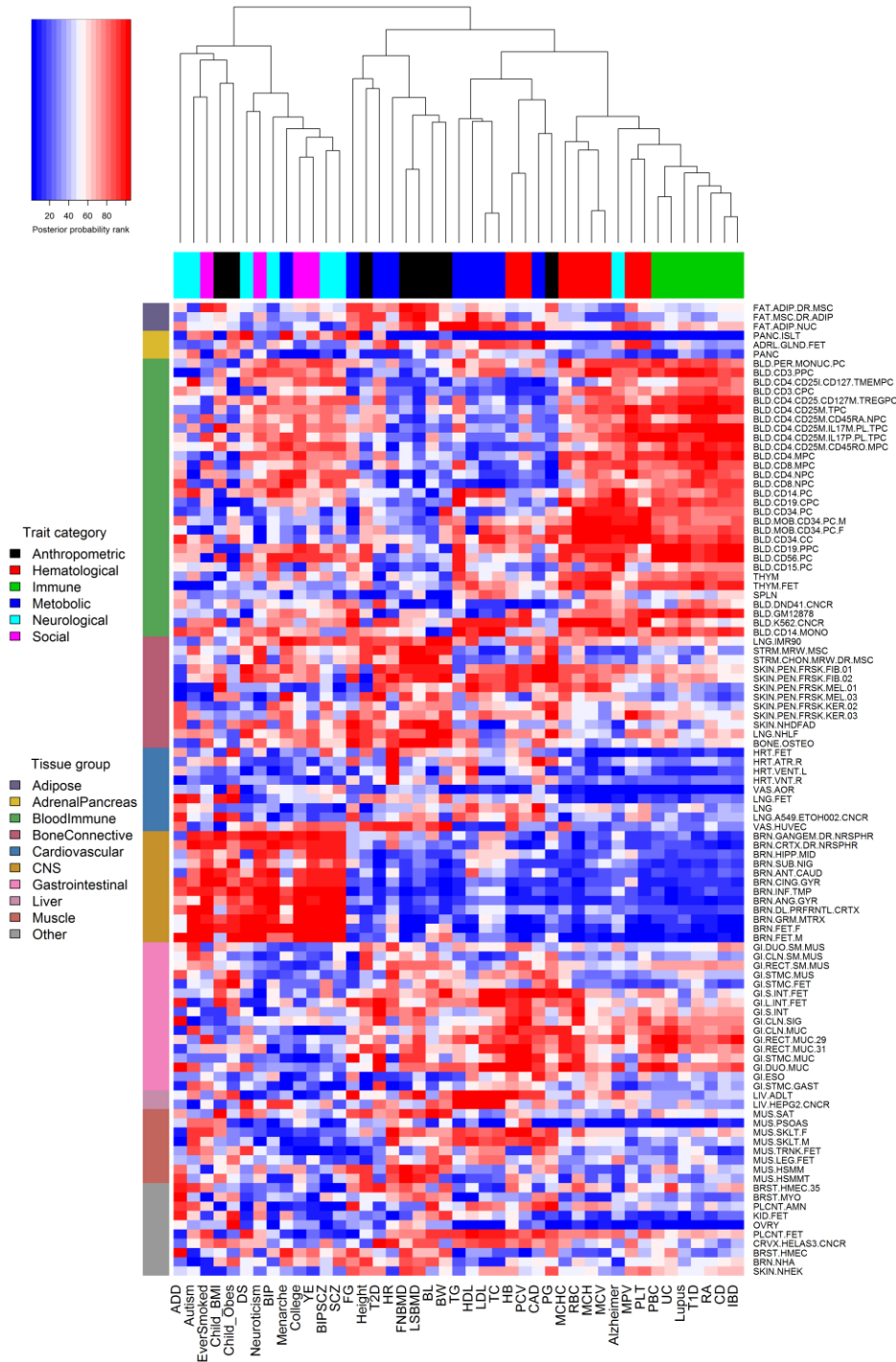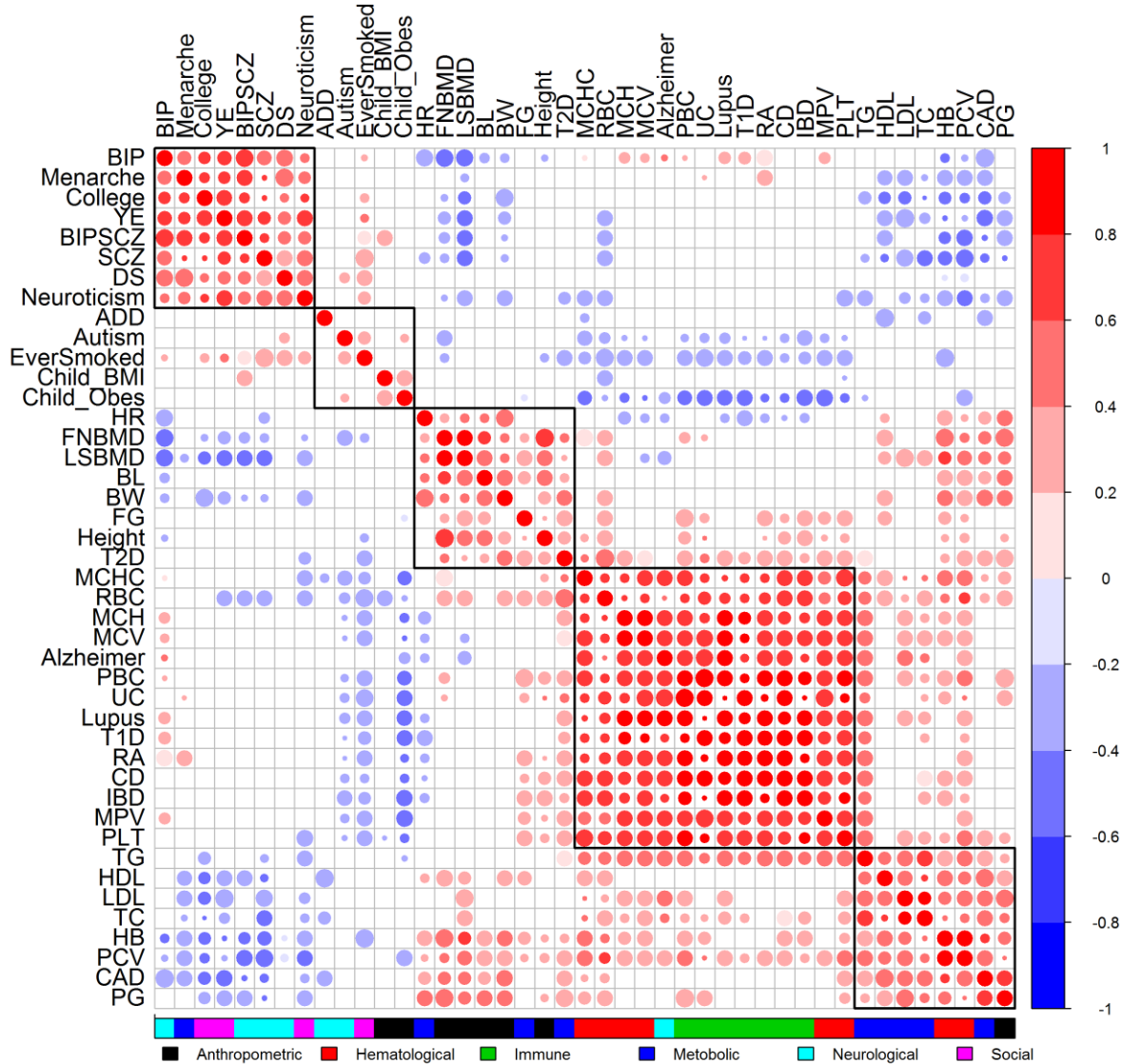
Figure 4 Heatmap displays the rank of 105 tissues (y-axis) in terms of their relevance for each of the 43 GWAS traits (x-axis). Traits are organized by hierarchical clustering. Tissues are organized into ten tissue groups.

Figure 5 Correlation plot displays the relationship among 43 traits. Color of the circles in the correlation plot represents the sign and magnitude of the correlation coefficient (red: positive; blue: negative). No circle (while space) indicates no significant correlation (p > 0.05). Size of the circle indicates significance (large: p<0.001; median: p<0.01; small: p<0.05).
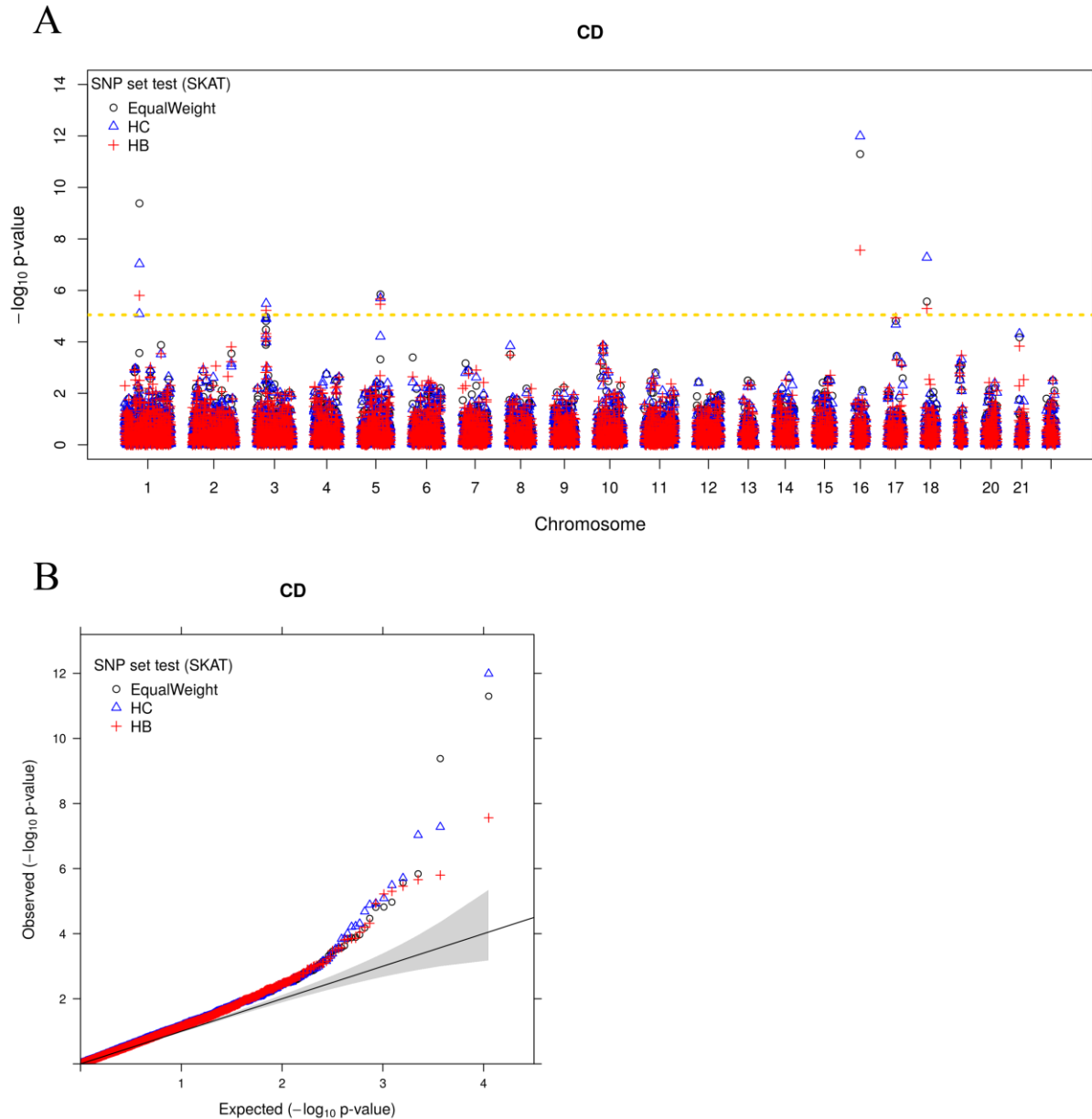
Figure 6 SNP set test results on Crohn's disease (CD) using different SNP weights. (A) Manhattan plot shows association signal across genes (x-axis) detected by SNP set tests using three different sets of SNP weights. EqualWeight (black): equal SNP weights. HC (red): SNP weights constructed using the estimated coefficient parameters for continuous histone mark based annotations in the GWAS consortium study. HB (green): SNP weights constructed using the estimated coefficient parameters for binary histone mark based annotations in the GWAS consortium study. The gold dashed line represents genome-wide significance threshold (8.95×10^{-6}). (B) The same results are displayed with QQ plot of -log10 p-values. Grey shaded area represents the 95% point-wise confidence interval.

Supporting Information Legends

Figure S1 Simulation results for comparing using multiple annotations versus using a single annotation. Power to detect trait-relevant tissues by different approaches in various settings at a fixed FDR of 0.05 (A), 0.1(B), or 0.2 (B). x-axis shows the values of the two annotation coefficients used in the simulations. Settings where at least one annotation coefficient is zero are shaded in grey. The setting where the annotation coefficients equal to the median estimates from real data (i.e. $\alpha = (0.1, 0.05)$) is shaded in gold.

Figure S2 Per-block PVE of the ten causal blocks for the second set simulations. (A) The cases of one informative annotations at $\alpha_0 = 0.5$ and $(\alpha_1, \alpha_2) = (0.4, 0)$; (B) The cases of two informative annotations at $\alpha_0 = 0.5$ and $(\alpha_1, \alpha_2) = (0.4, 0.4)$.The bar indicates the standard error across simulation replicates.

Figure S3 Various annotation characteristics influence the power in identifying trait-relevant tissues in simulations. Methods for comparison include SMART (red), UniMax (green), and UniMaxLDSC (blue). Area under the curve (AUC) is used to measure method performance. (A) Power to identify trait-relevant tissue generally increases with increasingly large annotation coefficients when the two coefficients have the same sign. (B) Power also increases with increasingly large annotation coefficients when the two coefficients have the opposite sign. (C) Power is relatively stable with the genome coverage of the two annotations varied from 4%, 8% to 12%.

Figure S4 Various factors influence the power of SNP set analysis in simulations. Left columns (A, D, G): annotation coefficients are fixed to be (1, 1) while the number of causal blocks changes from 5, 10, 20 to 50. Middle columns (B, E, H): the number of causal blocks is fixed to be 10 while the annotation coefficients change from (0.01, 0.01), (0.3, 0.3), (0.6, 0.6) to (1, 1). Right columns (C, F, I): per-block PVE are approximately fixed while the number of causal blocks and annotation coefficients vary. Top rows (A, B, C) show the average proportion of phenotype variance explained (PVE) by non-causal or causal blocks. Middle rows (D, E, F) show the fold enrichment. Bottom rows (G, H, I) show SNP set analysis power for various methods.

Figure S5 Posterior probabilities of 10 tissue groups for being relevant to each of the 43 GWAS traits by HC. The gold dashed line represents a horizontal line at 0.5.

Figure S6 Manhattan and QQ plots display the SNP set test results for five common diseases in WTCCC using different SNP weights. Results are shown for rheumatoid arthritis (RA; A), cardiovascular disease (CAD; B), bipolar disease (BIP; C), type II diabetes (T2D; D), and type I diabetes (T1D; E). For comparison, association results based on univariate SNP tests are also shown in F-K. EqualWeight (black): equal SNP weights. *HC* (blue): SNP weights constructed using the estimated coefficient parameters for continuous histone mark based annotations in a GWAS consortium study. *HB* (red): SNP weights constructed using the estimated coefficient parameters for binary histone mark based annotations in a GWAS consortium study. For Manhattan plots, gold dashed lines represent genome-wide significance thresholds: 0.05/153,813 for univariate tests and 0.05/5,588 for SNP set tests. For QQ plots, grey shaded area represents the 95% point-wise confidence interval.

Figure S7 Simulation results for SKAT. As the second set of the simulations, 10,000 individuals and 10,000 SNPs were selected from GERA study. The SNPs were divided into 100 blocks with 100 SNPs in each block. Two histone marks were simulated for 40% SNPs in the causal blocks of the trait-relevant tissue. Left panel (A, D, G): Fix the annotation effect (1, 1) and change the number of causal blocks; Middle panel (B, E, H): Fix the number of causal blocks 10, and the change the annotation effects (0.01, 0.01), (0.3, 0.3), (0.6, 0.6) and (1, 1); Right panel (C, F, I): Fix the per-block PVE, and change the number of causal blocks and annotation effects.

1256 **Table 1 Association results for SNP set tests in WTCCC using different SNP weights. Results are shown for 17**
1257 **genes identified to be significant by at least one SNP weighting option in four dieseases from the WTCCC**
1258 **data (CD, RA, T1D and T2D). All these genes have been previously identified to be associated with the**
1259 **corresponding trait (cited references). Approaches that yield a p-value passing the genome-wide significance**
1260 **threshold (8.95x10^{-6}) are highlighted in bold.**

Trait	Gene	Chr	Locus start	Locus end	Number of SNPs in gene	HC	HCuMax	HB	HBuMax	HBuMaxLDSC	EqualWeight
CD	*C1orf141 [77]*	1	67557859	67600639	18	*8.17e-06*	*4.99e-06*	0.00316	0.00548	**1.02E-08**	0.000271
	IL23R [82,83]	1	67632083	67725662	29	*9.33e-08*	*3.66e-07*	*1.58e-06*	*5.19e-09*	0.000271	*4.16e-10*
	DAG1 [84]	3	49506146	49573048	15	1.29E-05	1.35E-05	0.000911	*2.84e-06*	**4.16E-10**	1.55E-05
	BSN [78]	3	49591922	49708978	26	*3.27e-06*	*2.22e-06*	*5.97e-06*	*1.43e-06*	1.01E-05	1.07E-05
	SLC22A5 [78]	5	131705444	131731306	16	6.14E-05	2.46E-05	*3.47e-06*	*1.54e-06*	8.98E-05	0.000477
	C5orf56 [85]	5	131746328	131811736	21	*1.96e-06*	*1.81e-06*	*2.17e-06*	*1.43e-06*	*1.68e-06*	*1.43e-06*
	NOD2 [83]	16	50727514	50766988	11	*1.01e-12*	*6.24e-13*	*2.74e-08*	*1.51e-12*	*1.84e-06*	*5.04e-12*
	PTPN2 [86,87]	18	12785477	12884337	17	*5.26e-08*	*8.04e-08*	*5.05e-06*	*1.77e-07*	**1.50E-12**	*2.71e-06*
RA	*MAGI3 [88]*	1	113933371	114228545	53	*3.99e-06*	3.44E-05	*6.8e-06*	0.0117	**4.66E-07**	*2.07e-06*
	RSBN1 [89]	1	114304454	114355098	12	*8.07e-07*	*8.85e-07*	*9.36e-07*	*6.89e-07*	*2.55e-06*	*3.01e-07*
	PTPN22 [82,86]	1	114356433	114414381	17	*5.09e-06*	*2.24e-06*	*7.43e-07*	*7.44e-07*	*9.68E-08*	*2.02e-07*
T1D	*MAGI3 [90]*	1	113933371	114228545	53	*6.16e-08*	*1.21e-07*	*9.65e-09*	*4.4e-07*	*1.95E-07*	*7.47e-10*
	RSBN1 [91]	1	114304454	114355098	12	*8.89e-08*	*1.04e-07*	*2.46e-07*	*9.63e-08*	**8.47E-10**	*6.76e-08*
	PTPN22 [91]	1	114356433	114414381	17	*9.22e-07*	*7.18e-07*	*2.28e-06*	*1.29e-07*	*4.10E-08*	*2.81e-08*
	CLEC16A [92]	16	11038345	11276046	55	*3.49e-07*	*3.42e-07*	*2.26e-07*	*3.19e-07*	*3.27E-08*	*7.69e-07*
T2D	*TSPAN8 [93]*	12	71518865	71835678	38	*8.64e-06*	1.01E-05	*3.29e-06*	*2.84e-06*	*9.10E-07*	*8.26e-07*
	FTO [79]	16	53737875	54155853	61	*2.6e-06*	*1.05e-06*	*6.16e-06*	8.43E-05	0.000152	0.000245
	Total					*15*	*13*	*15*	*14*	*14*	*12*

1261
1262 **Table S1** Information for the tissue-specific SNP annotations obtained based on histone occupancy data in the
1263 ENCODE and Roadmap projects. The table lists ID, tissue group, epigenome name and mnemonic, tissue types, and
1264 genome-wide percentage of mark occupancy for the four histone marks (H3K27me3, H3K36m3, H3K4me1,
1265 H3K4me3).
1266
1267 **Table S2** Information for the summary statistics of 43 traits from 29 GWAS studies. The table lists the phenotype
1268 name, category, abbreviation, number of individuals, reference, and downloaded websites for each of the 43 traits.
1269
1270 **Table S3** The most relevant tissue group for each trait determined by various methods. Parenthesis shows either the
1271 proportion of existing publications for the tissue group (for PubMed search), the tissue group level posterior
1272 probability for other approaches (HC, HCuMax, HB, HBuMax, Chmm, cHMMuMax), or the tissue group level
1273 Wald statistics for HBuMaxLDSC.
1274
1275 **Table S4** PubMed search results show the number (in parenthesis) and the normalized proportion of publications on
1276 each pair of tissue group (columns) and trait (rows). The PubMed search was performed on June 23, 2017. For each
1277 GWAS trait, the tissue group with the largest proportion of existing publications are highlighted in red. The
1278 proportion values in each row sum to one.
1279
1280 **Table S5** The posterior probability of 105 tissues with four histone marks for 43 complex traits inferred by SMART.
1281
1282