Bayesian reassessment of the epigenetic architecture of complex traits

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1 Abstract

Epigenetic DNA modification is partly under genetic control, and occurs in response to a wide range of environmental exposures. Linking epigenetic marks to clinical outcomes may provide greater insight into underlying molecular processes of disease, assist in the identification of therapeutic targets, and improve risk prediction. Here, we present a statistical approach, based on Bayesian inference, that estimates associations between disease risk and all measured epigenetic probes jointly, automatically controlling for both data structure (including cell-count effects, relatedness, and experimental batch effects) and correlations among probes. We benchmark our approach in simulation study, finding improved estimation of probe associations across a wide range of scenarios over existing approaches. Our method estimates the total proportion of disease risk captured by epigenetic probe variation, and when we applied it to measures of body mass index (BMI) and cigarette consumption behaviour in 5,101 individuals, we find that 66.7% (95% CI 60.0-72.8) of the variation in BMI and 67.7% (95% CI 58.4-76.9) of the variation in cigarette consumption can be captured by methylation array data from whole blood, independent of the variation explained by single nucleotide polymorphism markers. We find novel associations, with smoking behaviour associated with a methylation probe at the MNDA gene with >95% posterior inclusion probability, which is a myeloid cell nuclear differentiation antigen gene previously implicated as a biomarker for inflammation and non-Hodgkin lymphoma risk. We conduct unique genome-wide enrichment analyses, identifying blood cholesterol, lipid transport and sterol metabolism pathways for BMI, and response to xenobiotic stimulus and negative regulation of RNA polymerase II promoter transcription for smoking, all with >95% posterior inclusion probability of having methylation probes with associations >1.5 times larger than the average. Finally, we improve phenotypic prediction in two independent cohorts by 28.7% and 10.2% for BMI and smoking respectively over a LASSO model. These results imply that probe measures may capture large amounts of variance because they are likely a consequence of the phenotype rather than a cause. As a result, 'omics' data may enable accurate characterization of disease progression and identification of individuals who are on a path to disease. Our approach facilitates better understanding of the underlying epigenetic architecture of complex common disease and is applicable to any kind of genomics data.

2 Introduction

Data characterizing gene expression, protein structure, or epigenetic modifications such as DNA methylation, histone marks and nucleosome positioning are becoming increasingly available. Epigenetic marks reflect a wide range of environmental exposures and genetic influences, are critical for regulating gene and non-coding RNA expression [1], and have been shown to be associated either as a cause or consequence with disease [2]. The identification of clinically relevant epigenetic loci can provide insight into the molecular underpinning of disease [3], leading to identification of biologically relevant therapeutic targets [4] and potentially epigenetic-guided clinical decision making [5].

Most studies testing for association between 'omics' data and complex traits utilize methodology from genome-wide associations studies, meaning that probe effects are tested one at a time [6]. This methodology does not account for correlations among probes and leads to model overfitting, poor effect size estimation, and poor calibration of prediction due to omitted variable bias [7]. Additionally, data structure such as intra-sample cellular heterogeneity, sample relatedness, population stratification, or experimental design effects are a major challenge [8] and result in more cross-chromosome correlation than genetic data. This structure, in conjunction with the fact that cases and controls typically differ in their cell-type composition, can result in spurious associations and many statistical algorithms have been proposed to tackle these potential biases [7, 9, 10]. However, all current statistical approaches rely upon corrections for structure that require a choice of either a suitable reference profile of representative cell types, or a limited number of pre-selected variables computed from the methylation data (e.g. Surrogate Variable Analysis [9], RefFreeEWAS [11], EWASher [12], or ReFACTor [13]), with the underlying assumption that all confounders are reflected by a sparse set of latent covariates and methylation sites.

Here, we present an alternative approach, based on Bayesian inference, that: (i) estimates probe effects on an outcome jointly and conditionally on each other whilst controlling for other covariates such as sex and age, avoiding model over-fitting and controlling for both data structure (including cell-count effects) and the correlations among probes; (ii) does not require any knowledge of cell-type composition or any selection of proxy confounder variables (i.e., accounts for both known and unknown confounders); (iii) estimates the total proportion of disease risk accounted for by the probe effects (cumulative proportion of variance explained); (iv) estimates probe effects conditional on other sources of data such as single nucleotide polymorphism data, enabling a determination of the unique contribution of different data types; (v) gives an in-depth understanding of the genome-wide range of probe effects on the phenotype, in terms of the likely number of independent effects and their variance explained; (vi) enables unique genome-wide enrichment analyses, describing the variance explained and number of trait-associated probes of each annotation; and (vii) provides improved estimation of biomarker effects, which could be used for disease risk assessment. The approach is similar to, but more flexible than linear mixed model analyses recently proposed in genome-wide association studies [14], and we demonstrate properties (i) through (vii) with theory, simulation and then empirical analysis of body-mass index (BMI) and smoking behaviour for over 5000 individuals with methylation probe measures [15].

3 Results

3.1 Methods overview

Our approach assumes that the observed phenotype $\mathbf{y}$ is reflected by a linear combination of genetic effects (β_G) estimated from single nucleotide polymorphism (SNP) data, epigenetic effects (β_{cpg}) estimated from probes on an array, along with age and sex specific effects (α, γ), such that:

$$\mathbf{y} = \alpha \text{age} + \gamma \text{sex} + \mathbf{X}_{cpg}\beta_{cpg} + \mathbf{X}_G\beta_G + \epsilon$$

with the effects β_G, β_{cpg}, α and γ being estimated in a Bayesian statistical model. We assign to each type of effect a prior distribution, which is a mixture of Gaussian distributions and a discrete "spike" at zero. This allows for non-identifiable effects to be excluded from the model, while the rest are estimated jointly (and conditionally on each other given our algorithm). Controlling for all different covariates and their effects

while estimating each individual effect, better alleviates problems related to correlations and structure in the marker data as we show in our simulation study (**fig.**1, also see Methods). This is because each probe estimate is made conditionally after accounting for the SNP markers and the other 'omics' probes in the model, which capture, and thus account for, genetic relationships in the data [16] and capture structural effects (such as cell-count effects, experimental batch effects, or population structure).

As described above, we fit both SNP and epigenetic probe data together, as it allows a determination of the unique contribution of each data source. However, our software implementation of this modelling framework, (BayesRR, which is freely available, see URLs) is entirely flexible. Any number of data sources can be modelled together, each with separate mixtures, making it applicable to any kind of genetic or epigenetic data. Furthermore, if only epigenetic probe data are available, estimates of the probe effects can still be obtained jointly, avoiding model over-fitting and controlling for both data structure (including cell-count effects) and correlations among probes (**fig.**1, also see Methods). Additionally, other major covariates could be included, including genetic loci of large effect such as HLA in immunodisease or APOE4 variant in Alzheimer disease. This flexibility is important as data sets will likely be variable in their structure and the degree to which different 'omics' measures are correlated.

3.2 Simulation study

We simulated methylation data for 2000 individuals at 103638 probes. We reproduced cell-type proportion variation present in real methylation probe data, using a recently proposed simulation model [13]. Our first simulation scenario, was a "sparse" setting, where a phenotype is determined by only 100 differentially methylated probes (see Methods in **sec.**5.1), which cumulatively explained 60% of the phenotypic variance in the trait. We applied our BayesRR method and computed the mean over the samples of the posterior distribution to obtain our parameter estimates (see Methods **sec.**5.1). We show (**fig.1a**) that our approach outperforms comparable methods in the literature: single-probe linear regression with a Bonferroni corrected p-value threshold (GWAS approach), ridge regression (ridge approach) [17] and LASSO (lasso approach) [18] by metrics such as the correlation of the estimated effects with the true simulated values ($\rho\left(\beta, \hat{\beta}\right)$), and the mean squared error (MSE). We also simulated different levels of correlation between the phenotype and the cell-type proportions, which is shown in the panel $||\rho(\mathbf{y}, \mathbf{R})||$, finding that approaches which fit probe effects jointly generally provide estimates that are unbiased of cell-count confounding. However, our proposed approach gave accurate estimation of the proportion of phenotypic variance explained by the probes, represented by the panel σ^2_{cg} in **fig.1a** across different scenarios. We tested our method's performance for a wide range of simulation parameters, showing improved accuracy over the other methods in each scenario (see supplementary fig.S1 and fig.S2).

We then examined whether methylation probe effects can be estimated conditionally on the SNP marker effects to determine the unique contribution of each type of marker. We simulated correlated genetic and epigenetic effects, with 100 epigenetic effects drawn from a normal distribution $\mathcal{N}(0, 0.5/100)$, and a combination of 100 genetic effects drawn from a normal distribution $\mathcal{N}(0, 0.2/100)$ and 900 smaller genetic effects drawn from $\mathcal{N}(0, 0.01/900)$. We find that our approach can better distinguish between the variance explained by genetic markers and methylation probes, but with higher variability in the error of estimates (**fig.**1b). In the following section we illustrate the additional advantages of working with a posterior distribution to elucidate the architecture of epigenetic effects whilst accounting for the uncertainty of our model given the phenotypic data.

Finally we performed a comparison with a linear mixed effects model where probe values are used to calculate a covariance matrix, which is then used in a restricted maximum likelihood estimation (REML) approach [14]. As this model assumes probe effects come from a single distribution, and that a covariance matrix among all probes is informative as to the covariance matrix amoung probes that are associated with the phenotype, we compared the approaches across two levels of sparsity, the first where a phenotype is influenced by 100 probes (**fig.**1**c**) and the second where a phenotype is influenced by 1000 probes (**fig.1d**). Both the linear mixed model and BayesRR provide unbiased estimates of the proportion of phenotypic variance captured by the probes, with the error variance of each approach dependent upon the underlying effect size distribution (**fig.1c** and **d**). The estimated effects from the linear mixed model showed reduced

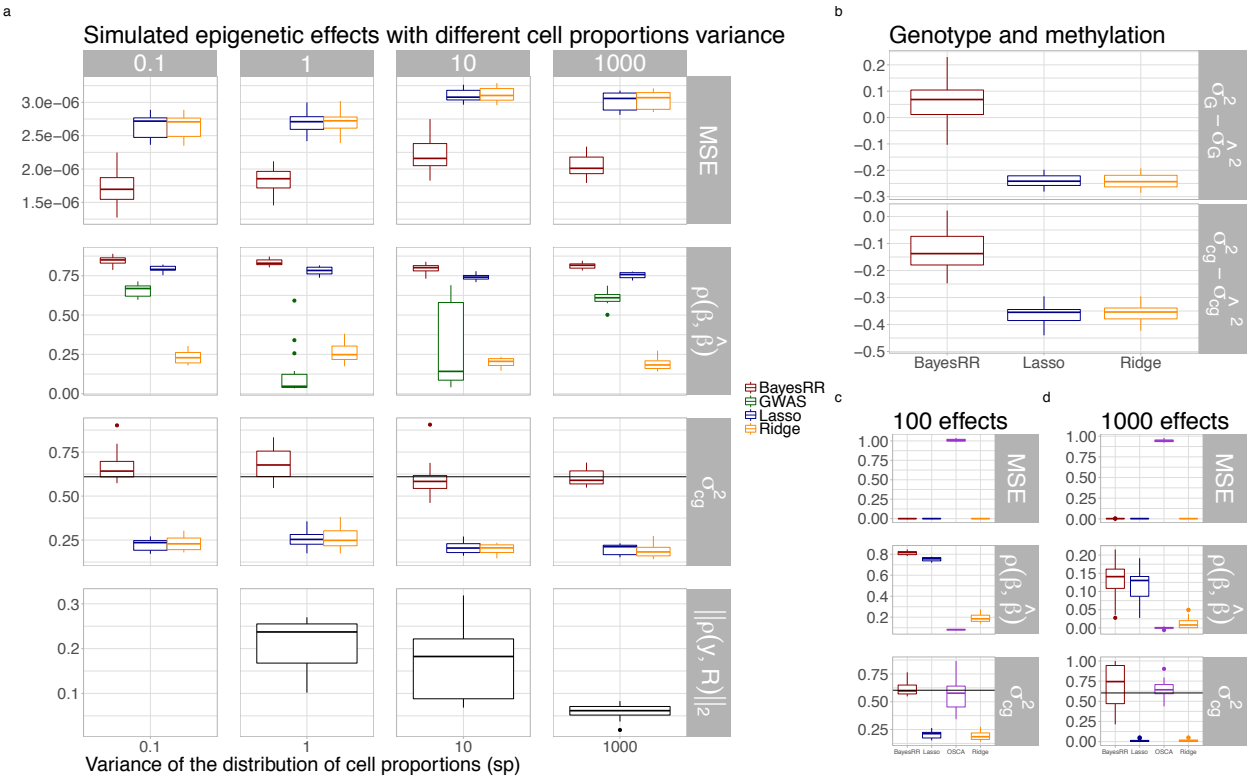

Figure 1. Simulation study: a. Simulation results of methylation marker effects for a phenotype influenced by 100 methylation probes. Top panel shows mean square error (MSE) between true and estimated coefficients for single probe regression (GWAS) estimation, Ridge regression, Lasso, and BayesRR. The correlation between true effects and estimates($\rho(\beta, \hat{\beta})$) and the phenotypic variance explained by the probes (σ^2_{cg}) are then shown with black lines showing the true value. Finally, to illustrate the degree of confounding, we show the norm of the correlation vector between the phenotype and the cell-type proportions ($||\rho(\mathbf{y}, \mathbf{R})||$) for each simulation scenario. **b**. Simulation results of methylation marker effects for a phenotype influenced by both 100 methylation probes and 1000 SNP markers, showing the difference between the true and the estimated phenotypic variance explained by genetic markers ($\sigma^2_G - \hat{\sigma^2_G}$) and epigenetic probes ($\sigma^2_{cg} - \hat{\sigma^2_{cg}}$). **c,d** Comparisons of the previous methods with OSCA for two different levels of sparsity, with 100 non-zero effects and 1000 non-zero effects respectively.

correlation with the true effects as compared to BayesRR, demonstrating that BayesRR will provide improved performance in both sparse and non-sparse regimes (**fig.**1**c** and **d**).

3.3 Application to body mass index and smoking

We applied our BayesRR approach to two lifestyle factors, smoking and body mass index, that are correlated with numerous health outcomes across the lifecourse. Previous studies have shown that smoking produces a strong alteration in methylation levels which at the same time, are related to the etiology of smoking-related disease [19], and BMI has also been associated with methylation levels and adipose-related traits [20]. Here, we present results from a converged set of four models for each trait, each model having different starting values, applied to 5,101 individuals of the Generation Scotland cohort (see Methods in **sec.**5.5.1).

Our approach facilitates the estimation of the total phenotypic variation attributable to the SNP markers and methylation probes (**fig.**2 and summary in **table** S1 and **table** S2). For BMI, 66.74% (95% CI 59.99-72.80) of the phenotypic variance of BMI was captured by methylation probes, with 65.47% (95% CI 53.75-77.28) of this attributable to 143.66 (95% CI 116.25-168.10) probes that each explain <1% of the

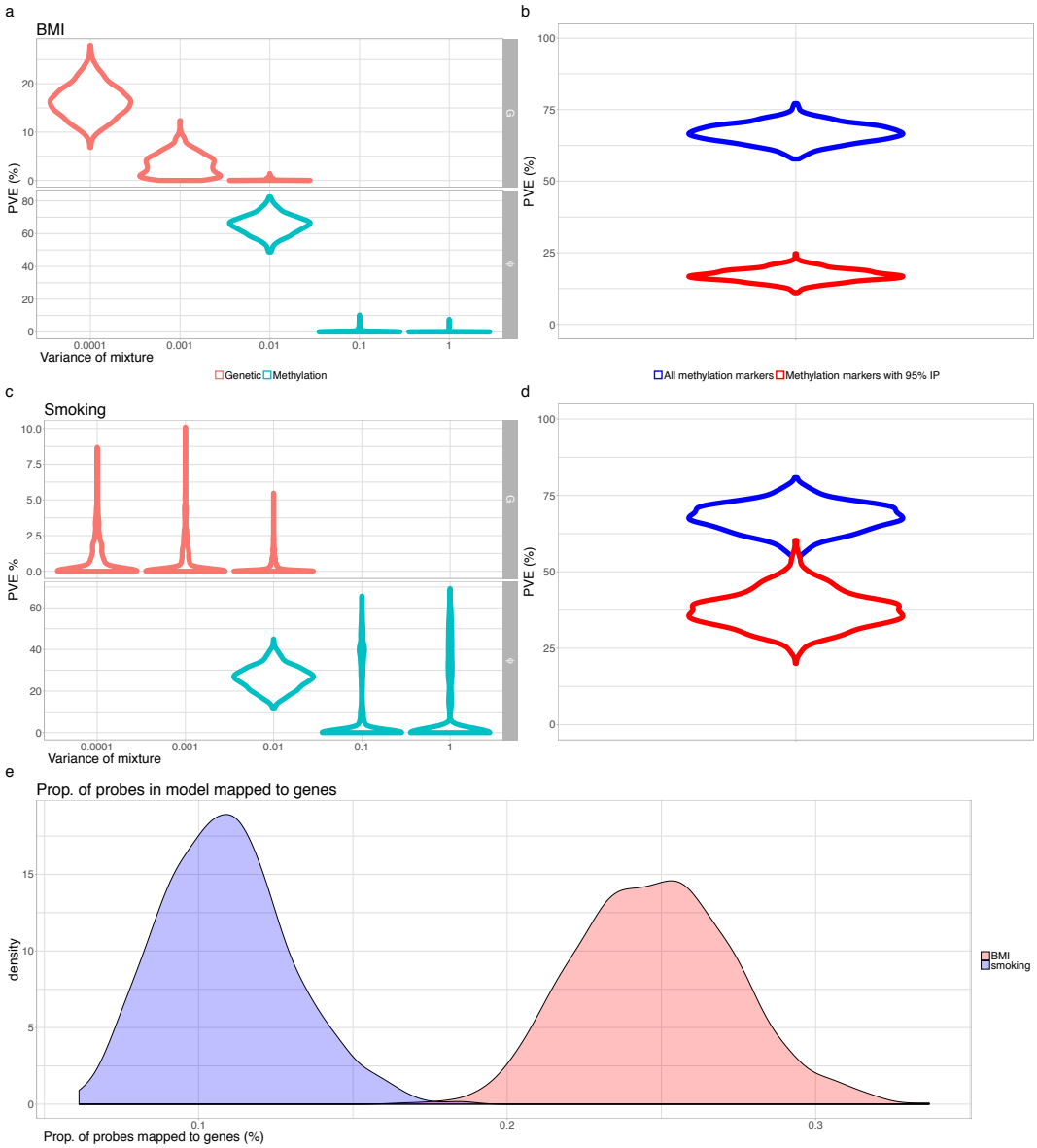

Figure 2. Biomarker architecture: a. Phenotypic variance of BMI explained by the three mixtures for single nucleotide polymorphism markers (SNP; Genetic) and methylation probes, with mixture variances (0.0001,0.001,0.01) and (0.01,0.1,1) respectively. **b**. For BMI, the phenotypic variance explained by all markers in the model (blue) and for the markers with 95% posterior inclusion probability (IP; red) is shown. **c**. For cigarette consumption, the phenotypic variance explained by the mixtures for the SNPs and methylation probes, with same mixture specific variances as for BMI. **d**. Phenotypic variance explained by all markers in the model (blue) and variance explained by the markers with 95%IP for cigarette consumption. **e**. Distribution of proportion of all methylation probes in model for BMI (red) and smoking(blue).

phenotypic variance. The remaining third of the phenotypic variance explained by methylation probes, was attributable to 10 probes with 95% inclusion probability (IP), which cumulatively explain 17.11% (95% CI 13.18-21.16) of the phenotypic variance of BMI **fig.2b**. This suggests that most epigenetic probe effects for BMI are relatively small, but larger than SNP marker effects, which cumulatively explain an additional 19.89%(CI 13.69-25.57) of the phenotypic variance **fig.2a**. In total, the variance captured by both methylation probes and SNP markers was estimated as 86.63% (95% CI 73.68-98.37). We repeated the analysis but excluded close relatives and modelled only the methylation probe effects, finding 69.55% (95% CI 57.35-78.32) of the phenotypic variance in the remaining 2614 unrelated individuals was associated with methylation probe variation. This implies that our estimates of the variance captured by methylation probes, are independent of the variance attributable to SNP markers and do not reflect family effects.

For smoking behaviour, defined as the number of pack years, we find that 67.68% (95% CI 58.41-76.86) of phenotypic variance is captured by methylation probes **fig.**2. In contrast to BMI, we find evidence for 5 probes with 95%IP, which contribute to almost a half (37.26%, 95% CI 27.01-49.5) of the phenotypic variance **fig.**2. The remaining 26.3% (95% CI 15.27-37.10) of phenotypic variance was attributable to 56.33 (95% CI 35-77) methylation probes of effect size <1% **fig.**2. Of the probes mapped to genes, 0.25% (95% CI 0.20-0.30) are in the model for BMI, more than double of the 0.11% (95% CI 0.07-0.15) for smoking behaviour **fig.**2. In total, the variance captured by both methylation probes and SNP markers was estimated as 69.54% (95% CI 58.41-84.21). Again, we repeated the analysis but excluded close relatives and modelled only the methylation probe effects, finding 73.83% (95% CI 54.33-88.26) of the phenotypic variance was captured by methylation probe variation, which implies that our estimates are independent of the variance attributable to SNP markers and do not reflect family effects. We also used a linear mixed effects model where probe values are used to calculate a co-variance matrix, which is then used in a restricted maximum likelihood estimation (REML) approach [14], but this approach did not produce a converged set of estimates for either phenotype, with or without relatives in the data. Taken together, these results highlight the ability of our approach to describe the architecture of epigenetic associations, in terms of the likely number and effect size of associated probes, and our results imply a higher degree of polygenicity of epigenetic probe associations, spread throughout the genome, for BMI as opposed to smoking behaviour.

We then proceeded to derive annotation information from the posterior distribution over effects. First, we looked for Gene Ontology (GO) enrichment for the probes whose IP was >95% and compared these to previous findings using the EWAS catalog. We replicate previous associations with BMI and smoking, finding enrichment for probes with >95%IP corresponding to GO terms of thrombin-related pathways for smoking(**table** S7) and lipid transport for BMI(**table** S6). We find two additional related terms for BMI of lipids and triglycerides (**fig.3a**), and one additional probe for smoking behaviour that has not been previously associated to any trait in the EWAS catalogue, probe *cg16663980* that is annotated for the *MNDA* gene, a myeloid cell nuclear differentiation antigen previously implicated as a biomarker for inflammation and non-Hodgkin lymphoma risk (see Methods **sec.**m:enrich; **fig.3b**). For both traits, probes with >95% IP were also associated with alcohol consumption.

We then take advantage of the fact that if we use the posterior distribution over all effects, we can derive a posterior distribution over GO terms and devise a definition of enrichment (see Methods **sec.**5.5.2). Under our enrichment statistic, we can measure those GO terms which explain a greater proportion of phenotypic variance than expected, given the proportion of probes that map to the GO term (**fig.3e** for BMI,**fig.3f** for smoking). Then, using a ROPE decision rule [21], we can define a term as being significantly enriched if the IP of the GO term in the model is >95%, and if 95% of the posterior distribution of enrichment is outside the interval $(0.5, 1.5)$. We sorted significantly enriched terms by their mean enrichment and generated a tree map of the terms using REVIGO [22].

For BMI, there is a preponderance of lipid transport, cholesterol transport and sterol metabolism(**fig.**S13), and for smoking, response to xenobiotic stimulus and interestingly negative regulation of transcription from RNA polymerase II promoter (**fig.**S14). Taken together, this demonstrates the novel findings and additional inference that can be obtained from conducting whole-genome enrichment analyses, rather than testing for enrichment at only those effects that are singularly found to be above a significance threshold.

We repeated our whole-genome enrichment, mapping probes to genes that are differentially expressed across tissues, to ask whether associations between phenotype and methylation assessed in whole blood can

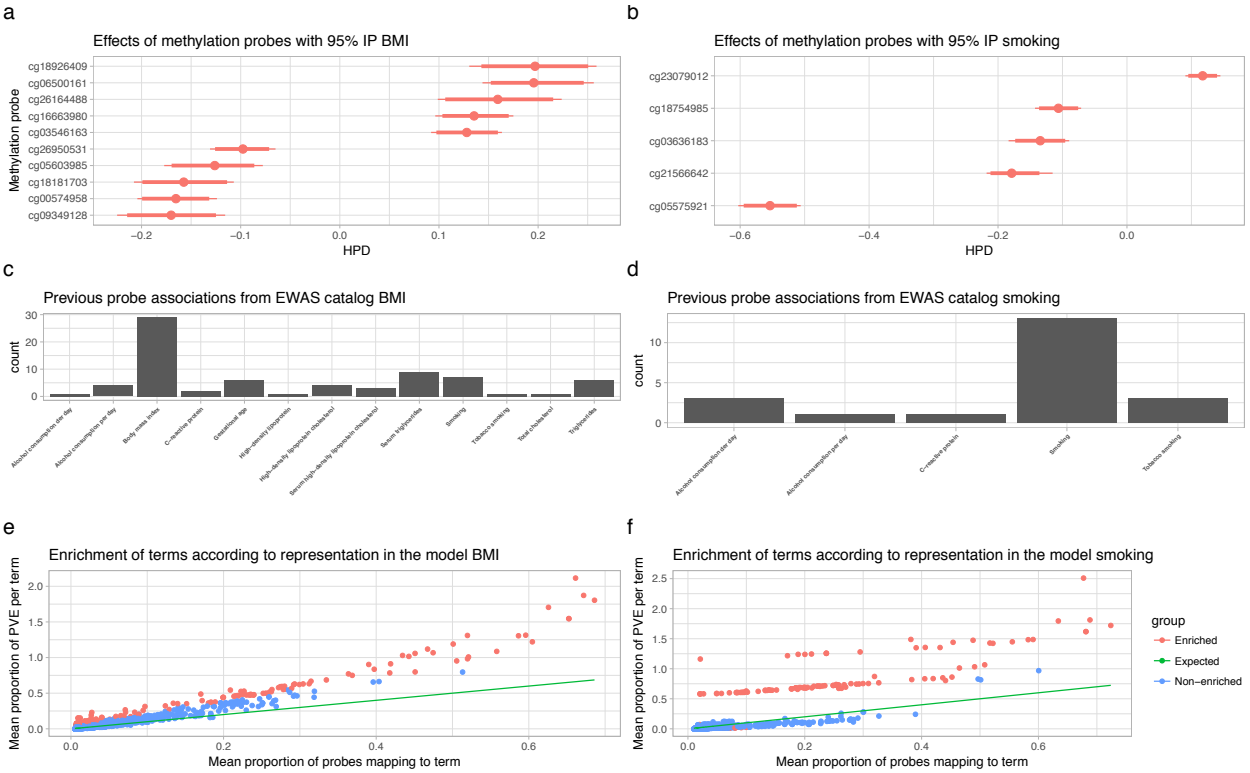

Figure 3. Annotation replication and enrichment analysis: a., b. Posterior distribution of effect sizes for methylation probes with 95% posterior inclusion probability (IP) for BMI and smoking respectively. **c.**,**d.** Previous associations found for the probes with 95% IP according to the EWAS catalog. **e.**,**f.** Results of a whole-genome enrichment analysis of all methylation probes in the model. Proportion of phenotypic variance explained by methylation probes is plotted against the proportion of probes mapping to each enrichment term tested (BMI left, smoking right). The one-to-one line represents the expected value of proportion of phenotypic variance explained if all probes explained the same amount of variance among annotation terms. Significantly enriched terms are those defined as having both IP >95% and enrichment of >95% IP of being >1.5.

be linked to tissue specific gene expression. We selected genes in the upper 99% percentile (those differentially over-expressed) and the lower 1% percentile (those differentially repressed) of those that show differential expression across tissues in the GTEX [23] and Depict [24] data (see Methods **sec.**5.5.2). We find only one significantly enriched term for BMI in GTEX repressed genes: *"Cells Transformed fibroblasts"*, one significantly enriched term in DEPICT over-expressed genes: *"KEGG ABC TRANSPORTERS"*, and one significantly enriched term for repressed genes in DEPICT: *"KEGG TRYPTOPHAN METABOLISM"*; with no term significantly enriched for smoking. These results suggest that while we can capture a large amount of phenotypic variance from methylation in whole blood, the probes of strongest effect may only reflect specific processes in the tissues sampled that are a consequence of differences among individuals in smoking behaviour or BMI.

Finally, we use the estimated methylation probe effects to predict BMI and smoking behaviour in two independent cohorts: The Lothian Birth Cohort 1936 (LBC) and the Accessible Resource of Integrated Epigenomics Studies (ARIES) dataset (see Methods **sec.**5.5.4 and **sec.**5.5.5). We compared the prediction accuracy gained from our approach to recently obtained estimates from another model based on the LASSO estimator by using the R^2 metric. For BMI, we achieve R^2 of 15.7% for adult BMI in LBC, and in the ARIES dataset we achieve R^2 of 3.56% for birth weight, 0.81% for BMI at age 7, 6.27% for BMI age 15, 11.65% for BMI in adult males, and 16.26% for BMI in adult females **table** 1. The increase in prediction accuracy with age in the ARIES results implies that methylation associations are a consequence of BMI, rather than a cause. Overall, these values amount to an improvement of 28.7% in comparison to the LASSO predictor in the LBC. For smoking, we observed values of 46.49% for LBC and 34.66% for males in ARIES, a 10.2% improvement over the LASSO predictor **table** 1. This replicates previous results showing that methylation profiles predicted BMI independently of genetic profiles in an additive manner [25] and shows that our approach can better capture the overall distribution of effects, including small effects, whilst accurately estimating larger effects, leading to improved phenotypic prediction.

Following [26], the squared correlation between a phenotype in an independent sample and a predictor of the phenotype can be approximated given the sample size of the initial study, the expected variance explained by the covariates, and the effective number of independent covariates. Assuming an effective number of covariates of 20,000 (approximate number of protein coding genes) and a variance explained of 70%, an R^2 of 12% is expected. If the initial study sample size increased to 100,000 individuals than an R^2 of over 60% is expected, which in combination with SNP array data, would lead to a predictor of BMI with an R^2 of nearly 80% from a single blood test.

The theory described above does not account for the fact that 'omics' probe variation may be a consequence of the phenotype and thus in a regression equation, phenotypic variance will appear on both sides. If the consequential effects are large then it is conceivable that all phenotypic variance may be attributable to probe effects within this type of analysis. Additionally, given the highly variable nature of 'omics' measures, and the considerable changes with age that occur [27], it may also may also be likely that the phenotypic variance attributable to the probes differs across cohorts.

4 Discussion

We present a statistical model for joint inference of genetic and epigenetic effects over complex phenotypic traits. Our method has the advantage of controlling for all factors at once and performing statistical inference jointly on all of the model parameters and adjusting estimates conditionally on each other. For both BMI and cigarette consumption, a large amount of phenotypic variance is captured by epigenetic markers in the training data set, which may be expected as trait-associated DNA methylation probe variation is likely to a large degree to be a consequence of the phenotype, as evidenced in our enrichment analyses and the prediction results from the ARIES study. These consequential effects lead to the expectation that 'omics' data may capture large amount of phenotypic variance. Thus, if applied to common complex disease, the model we present may enable accurate characterization of disease progression and better identification of individuals who are on a "path" to disease where future diagnosis is likely (i.e. those that are pre-diabetic, in the early stages of dementia, etc.). It remains to be seen whether such large amounts of phenotypic variance can be captured by a methylation array for common complex disease, but our prediction

Trait	Method	R^2 in cohort (%)						
		GS	LBC1936	ARIES				
				A.0	A.7	A.15	A.FOF	A.FOM.
BMI	LASSO	-	12.2	1.07	0.13	2.95	9.37	14.95
$\log(kg/m^2)$	Bayes	-	15.7	3.56	0.81	6.27	11.65	16.26
Smoking	LASSO	-	42.18	-	-	-	24.71	-
$log(p.p.y.^a + 1)$	Bayes	-	46.49	-	-	-	34.66	-

Table 1. Replication study: A phenotypic predictor was created in the Lothian Birth Cohort data 1936 (LBC1936) and Accessible Resource of Integrated Epigenomics Studies (ARIES) cohorts from the methylation effects estimated in the Generation Scotland (GS) data. The prediction accuracy as measured by the R^2 statistic is presented as compared to LASSO estimates of the methylation effects. In the ARIES cohort, A.0 refers to measures at birth, A.7 refers to measures at age 7, A.15 refers to measures at age 15, A.FOF refers to adult males (fathers), and A.FOM refers to females (mothers).

[a]packs per year

results shows that our approach can better describe the overall distribution of associations leading to improved phenotypic prediction.

By working in a Bayesian framework we derive a rich representation of the estimated effects through probability distributions, where all markers are taken into account and for which we can assess genome-wide enrichment of relevant biological features. From these distributions, we conclude that from the same set of probes in the same individuals, two example phenotypes show different architecture in the distribution of their effects, with the distribution of effects for cigarette consumption being more concentrated in a few epigenetic markers (5 markers with 95% IP explaining approx. 37%), while for BMI we have more probes associated with the phenotype (10 markers with 95% IP explain only 17%). We find novel associations as compared to previous approaches, with smoking behaviour associated with a myeloid cell nuclear differentiation antigen gene previously implicated as a biomarker for inflammation and non-Hodgkin lymphoma risk. Our genome-wide enrichment analyses, identified blood cholesterol, lipid transport and sterol metabolism pathways for BMI, and response to xenobiotic stimulus and negative regulation of RNA polymerase II promoter transcription for smoking, all with >95% posterior inclusion probability of having methylation probes with effects sizes >1.5 times larger than the average. Therefore, the approach we propose provides a more complete characterization of the molecular networks associated with disease.

There are a number of important considerations and caveats. It is important to punctuate that the inferred associations only relate to the present state of the biomarkers and are not intended to capture any causality between methylation status and outcome. Given the highly variable nature of 'omics' measures, the variation across data sets in the degree of confounding by experimental biases or unwanted biological variation that will contribute to the variation captured by probes, and the considerable changes with age that occur [27], it is highly unlikely that the phenotypic variance attributable to probes is stable across cohorts and with age. Determining biomarkers for future disease outcomes requires a different experimental design, for example longitudinal studies with a baseline, along with methodological extensions for causal inference within this framework, which our future work will focus on. Additionally, while we extend the model to ask how much additional phenotypic variance of each trait can be captured by methylation probes from whole blood above that captured by a SNP array, partitioning the phenotypic variance explained exactly may be difficult in data sets where factors are highly correlated. Furthermore, while we present a whole-genome enrichment approach, identifying novel pathways is currently limited and technological improvements are required to improve our ability to capture, define, and understand epigenetic marker variation. Finally, Bayesian inference comes at increased computational cost and requires the specification of prior distributions, for example here, that effects can be well described by a series of Gaussian distributions. A Student-t likelihood could be a path worth exploring as its inferences could be more robust to outliers [28] and additionally, although a Gaussian model may still be applied to categorical "disease or not" measurements,

developing an extension to model binary response variables and explore performance in unbalanced case-control settings will likely be worthwhile.

In conclusion, our model can be applied to any kind of 'omics' data providing unbiased estimates of marker effects, conditional on other markers, covariates and on the data structure. By operating in a Bayesian framework the uncertainties over the estimates given the data are represented explicitly, helping the researcher to interpret and draw conclusions over the architecture of the variance in the trait. We provide freely-available software with source code available to facilitate further replication and potential applications of the methodology (see URLs).

5 Materials and methods

Statistical model

We assume additive probe effects $\beta_{cpg} \in \mathbb{R}^{\mathrm{M_{cpg}} \times 1}$, genetic effects $\beta_G \in \mathbb{R}^{\mathrm{M_G} \times 1}$, age and sex effects α, γ associated over a vector of measurements over a trait $\mathbf{y} \in \mathbb{R}^{\mathrm{N} \times 1}$ such that,

$$\mathbf{y} = \alpha \mathrm{age} + \gamma \mathrm{sex} + \mathbf{X}_{cpg}\beta_{cpg} + \mathbf{X}_G\beta_G + \epsilon \tag{1}$$

where $\epsilon \sim \mathcal{N}\left(0, \sigma_\epsilon^2 \mathbf{I}_N\right)$, the methylation matrix $\mathbf{X}_M$ and the genotype matrix $\mathbf{X}_G$ have been centered and scaled to unit variance. We assume that only a subset of $\Theta = \{\beta_M, \beta_G, \alpha, \gamma\}$ have an identifiable effect over trait $\mathbf{y}$, as such, and proceeding in a Bayesian framework, we assign a sparsity inducing prior over Θ. The chosen prior follows the formulation of [29], which is a mixture of L Gaussian probability densities and a discrete "spike" at zero. As such, each $\Theta_i \in \Theta$ is distributed according to:

$$\Theta_i \sim \pi_0\delta_0 + \pi_1\mathcal{N}\left(0, \sigma_1^2\right) + \pi_2\mathcal{N}\left(0, \sigma_2^2\right) + \ldots + \pi_L\mathcal{N}\left(0, \sigma_L^2\right)$$

where $\{\pi_0, \pi_1, \pi_2, \ldots, \pi_L\}$ are the mixture proportions and $\left\{\sigma_0^2, \sigma_1^2, \sigma_2^2, \ldots, \sigma_L^2\right\}$ are the mixture-specific variances and δ_0 is a discrete probability mass at zero.

We further constrain the prior by assuming a single parameter representing the total variance explained by the effects σ^2, and the component-specific variances are proportional to σ^2, that is

$$\begin{bmatrix} \sigma_1^2 \\ \sigma_2^2 \\ \vdots \\ \sigma_L^2 \end{bmatrix} = \sigma^2 \begin{bmatrix} C_1 \\ C_2 \\ \vdots \\ C_L \end{bmatrix}$$

with $\{C_1, C_2, \ldots, C_L\}$ being constants.

We expand on the previous formulation by allowing different subsets of Θ to have specific σ^2 and π parameters. In our case, we assign to the genetic effects β_G a set of mixture variances $C_G = \{0.0001, 0.001, 0.01\}$, a proportion parameter π_G and variance parameter σ_G^2. We assign to the methylation probes, age and sex effects $\phi = \{\beta_{cpg}, \alpha, \gamma\}$ the same prior variances $C_\phi = \{0.01, 0.1, 1\}$ and parameters π_ϕ, σ_ϕ^2

The rest of the model follows the prior hierarchy of [29] but with additional parameters for groups G and ϕ.

$$\begin{aligned}
\pi_G &\sim \mathrm{Dirichlet}\left(\mathbf{p_G}\right) \\
\pi_\phi &\sim \mathrm{Dirichlet}\left(\mathbf{p}_\phi\right) \\
\sigma_G^2 &\sim \mathrm{Inv-Scaled}\chi^2\left(\mathrm{v}_0, \mathrm{s}_0^2\right) \\
\sigma_\phi^2 &\sim \mathrm{Inv-Scaled}\chi^2\left(\mathrm{v}_0, \mathrm{s}_0^2\right) \\
\sigma_\epsilon^2 &\sim \mathrm{Inv-Scaled}\chi^2\left(\mathrm{v}_0, \mathrm{s}_0^2\right)
\end{aligned}$$

with the respective hyper parameters $\left\{\mathbf{p}_G, \mathbf{p}_\phi, \mathrm{v}_0, \mathrm{s}_0^2\right\}$ such that the prior distributions are weakly informative, $\mathbf{p}_G = \mathbf{p}_\phi = (1,1,1)$,$\mathrm{v}_0 = \mathrm{s}_0^2 = 0.001$.

Model Inference

Inference of the probabilistic model, follows a Gibbs sampling algorithm. Here the joint posterior probability density of parameters $\left(\Theta, \mu, \sigma_\epsilon^2, \sigma_G^2, \sigma_\phi^2, \pi_G, \pi_\phi\right)$ conditioned on observed covariates $\mathbf{Z} = \left[\begin{array}{cccc} \mathbf{X}_G & \mathbf{X}_{cpg} & age & sex \end{array}\right]$ and observed phenotype $\mathbf{y}$ is denoted as $p\left(\Theta, \mu, \sigma_\epsilon^2, \sigma_G^2, \sigma_\phi^2, \pi_G, \pi_\phi | \mathbf{Z}, \mathbf{y}\right)$ and decomposed according to the conditional distributions over each parameter:

$$\begin{aligned} p\left(\Theta, \mu, \sigma_\epsilon^2, \sigma_G^2, \sigma_\phi^2, \pi_G, \pi_\phi | Z, \mathbf{y}\right) \approx\; & p\left(\mu | \Theta, \sigma_\epsilon^2 Z, \mathbf{y}\right) \\ & \times p\left(\Theta | \sigma_G^2, \sigma_\phi^2, \mu, \sigma_\epsilon^2, Z, \mathbf{y}\right) \\ & \times p\left(\sigma_G^2 | \beta_G, \pi_G\right) \\ & \times p\left(\pi_G | \beta_G, \sigma_G^2\right) \\ & \times p\left(\sigma_\phi^2 | \beta_\phi, \pi_\phi\right) \\ & \times p\left(\pi_\phi | \beta_\phi, \sigma_\phi^2\right) \\ & \times p\left(\sigma_\epsilon^2 | \mu, \Theta, Z, \mathbf{y}\right). \end{aligned} \tag{2}$$

Given the prior distributions presented in eq.3, the conditional distributions are:

$$p\left(\mu | \Theta, \sigma_\epsilon^2 Z, \mathbf{y}\right) \propto \mathcal{N}\left(\frac{\sum_{i=1}^N \left(\mathbf{y}_i - \mathbf{Z_i}\Theta\right)}{N}, \frac{\sigma_\epsilon^2}{N}\right) \tag{3}$$

$$p\left(\sigma_G^2 | \beta_G, \pi_G\right) \propto \mathrm{Inv-Scaled}\chi^2\left(m_G + \mathrm{v}_0, \frac{m_G \sum_{i=1}^{M_G} \beta_{Gi} + \mathrm{v}_0 S_0^2}{\mathrm{v}_0 + m_G}\right) \tag{4}$$

$$p\left(\pi_G | \beta_G, \sigma_G^2\right) \propto \mathrm{Dirichlet}\left(\mathbf{p}_\phi + \#\mathbf{K}_\mathrm{G}\right) \tag{5}$$

$$p\left(\sigma_\phi^2 | \beta_\phi, \pi_\phi\right) \propto \mathrm{Inv-Scaled}\chi^2\left(m_\phi + \mathrm{v}_0, \frac{m_\phi \sum_{i=1}^{M_G} \beta_{\phi i} + \mathrm{v}_0 S_0^2}{\mathrm{v}_0 + m_\phi}\right) \tag{6}$$

$$p\left(\pi_\phi | \beta_\phi, \sigma_\phi^2\right) \propto \mathrm{Dirichlet}\left(\mathbf{p}_\phi + \#\mathbf{K}_\phi\right) \tag{7}$$

$$p\left(\sigma_\epsilon^2 | \mu, \Theta, Z, \mathbf{y}\right) \propto \mathrm{Inv-Scaled}\chi^2\left(\mathrm{v}_0 + N, \frac{\sum_{i=1}^N \left(\mathbf{y}_i - \mu - \mathbf{Z}_i\Theta\right)^2 + \mathrm{v}_0 S_0^2}{\mathrm{v}_0 + N}\right) \tag{8}$$

$$\tag{9}$$

Where m_G and m_ϕ are the number of markers in each respective category in a sample and $\#\mathbf{K}_G$,$\#\mathbf{K}_\phi$ are vectors which contain the number of markers in each mixture for the respective categories.

Residual updating algorithm

The most computationally expensive step of sampling from the distribution in eq. 3 involves drawing from the conditional distribution

$$p\left(\Theta | \sigma_G^2, \sigma_\phi^2, \mu, \sigma_\epsilon^2, Z, \mathbf{y}\right)$$

if conditioned on the Markov blanket of effects Θ, the distribution is a multivariate normal with mean $\mathbf{m}$ and co-variance Σ such that

$$\mathbf{m} = \Sigma \mathbf{Z}^T \mathbf{y}$$

$$\Sigma = \sigma_\epsilon^{-2}\left(\mathbf{Z}^T\mathbf{Z} + \frac{\sigma_\epsilon^2}{\sigma_l^2}\mathbf{I}\right)^{-1}$$

with σ_l^2 being the mixture-specific variance and the residual's variance σ_ϵ^2. Inverting matrix Σ is of complexity $\mathcal{O}\left((M_G + M_\phi)^3\right)$. If we use the properties of multivariate Gaussian distributions, we can decompose $p\left(\Theta|\sigma_G^2, \sigma_\phi^2, \mu, \sigma_\epsilon^2, Z, \mathbf{y}\right) \propto \prod_{i=1}^{M_G+M_{\phi+2}} p\left(\Theta_i|\Theta_{\setminus i}\sigma_G^2, \sigma_\phi^2, \mu, \sigma_\epsilon^2, Z, \mathbf{y}\right)$, where $\Theta_{\setminus i}$ represents all the effects except effect Θ_i. Then each individual update consists of :

$$p\left(\Theta_i|\Theta_{\setminus i}\sigma_G^2, \sigma_\phi^2, \mu, \sigma_\epsilon^2, Z, \mathbf{y}\right) \propto \mathcal{N}\left(\mu_i, \Sigma_{li}\right)$$

with

$$\mu_i = \Sigma_i \mathbf{Z}_i^T\left(\mathbf{y} - \mu - \mathbf{Z}_{\setminus i}\Theta_{\setminus i}\right)$$
$$\Sigma_{li} = \sigma_\epsilon^{-2}\left(\mathbf{Z}_i^T\mathbf{Z}_i + \frac{\sigma_\epsilon^2}{\sigma_l^2}\right)^{-1}.$$

This obviates the necessity of inverting matrix Σ, if in addition we keep in memory the vector of residuals $\epsilon = \mathbf{y} - \mu - \mathbf{Z}\Theta$, then we can compute efficiently $\mathbf{y} - \mu - \mathbf{Z}_i\Theta_i$ by the update $\mathbf{y} - \mu - \mathbf{Z}_i\Theta_i = \epsilon + \mathbf{Z}_i\Theta_i = \tilde{\mathbf{y}}$, thus sampling from the joint distribution with a complexity $\mathcal{O}\left(M_G + M_\phi\right)$. Mixing and convergence issues that may arise in this formulation, have been shown to be alleviated by randomly choosing an effect Θ_i to update, as seen in successful implementations of the algorithm [29].

Drawing from the mixtures

To select the mixture l from which to draw the the effect Θ_i we must evaluate the likelihood ratio between all the mixtures. Using the log-likelihood $\mathcal{L}$, this amounts to:

$$\mathcal{L}\left(i,l\right)\begin{cases}\log\pi_0 - \frac{1}{2}\left|N\log\sigma_\epsilon^2\right| - \frac{1}{2\sigma_\epsilon^2}\sum_{i=1}^N \tilde{\mathbf{y}}_i & l = \delta_0\\ \log\pi_k - \frac{1}{2}\left|N\log\Sigma_{li}\right| - \frac{1}{2}\mu_i^2\Sigma_{li}^{-1} & rest\end{cases}$$

Finally, the probability of drawing effect Θ from mixture l is given by:

$$p\left(l\right) = \frac{1}{\sum_{j=1}^L \exp[\mathcal{L}\left(i,j\right) - \mathcal{L}\left(i,l\right)]}$$

Software implementation

The algorithm was implemented in C++-11.0, with an interface with R through Rcpp [30], and with the help of the templated matrix algebra library Eigen [31, 32]. Source code available in `https://github.com/ctggroup/BayesRRcpp`.

5.1 Simulation study of methylation data

We use a generative model of methylation levels as in [13], where the matrix $\mathbf{O} \in \mathbb{R}^{\mathrm{N}\times\mathrm{M}}$ represents the methylation levels for M probes in N individuals. This matrix can be decomposed in a matrix of K cell proportions for N individuals, which we denote $\mathbf{R} \in \mathbb{R}^{\mathrm{N}\times\mathrm{K}}$, and a matrix of cell-specific methylation levels $\mathbf{S} \in \mathbb{R}^{\mathrm{K}\times\mathrm{M}}$. The decomposition assumes i.i.d. observation noise such that

$$\mathbf{O} = \mathbf{M} + \vartheta$$

Algorithm 1 Algorithm for sampling over the posterior distribution $p(\mu, \beta, \epsilon, \sigma_\epsilon, \theta)$, each sample $(\mu, \beta, \epsilon, \sigma_\epsilon, \theta)$ is stored in a synchronised queue for a consumer thread to store in disk.. $\mathbf{X}_{marker_j}$ represents column of $\mathbf{X}$ corresponding to the column j of the vector $marker$. Given that $marker$ is shuffled before sampling the effects, this is equivalent to permuting the order of the effects to be sampled.

Input: genotype matrix $\mathbf{X}_G$, methylation probe matrix $\mathbf{X}_{cpg}$, age and sex, vector of trait measurements $\mathbf{y}$, prior hyperparameters $\left\{\mathbf{p}_G, \mathbf{p}_\phi, \mathrm{v}_0, \mathrm{s}_0^2\right\}$, number of iterations I.
output: mean μ, effects vector $\Theta = \{\beta_M, \beta_G, \alpha, \gamma\}$, residual vector ϵ, residuals variance σ_ϵ^2 and posterior parameters, $\sigma_G^2, \sigma_\phi^2$

1. Initialize $\Theta, \mu, \sigma_\epsilon^2, \sigma_G^2, \sigma_\phi^2, \pi_G, \pi_\phi$
2. $effects$= $(1 \ldots M_G, (M_G + 1) \ldots (M_G + M_\phi), (M_G + M_\phi + 1), (M_G + M_\phi + 2))$
3. set $\mathbf{Z} = \left[\begin{array}{cccc} \mathbf{X}_G & \mathbf{X}_{cpg} & age & sex \end{array}\right]$
4. $\epsilon = \mathbf{y} - \mu - \mathbf{Z}\Theta$
5. For i in 1...I
   (a) sample $\mu =$
   (b) $shuffle(effects)$
   (c) For j in $1 \ldots (M_G + M_\phi + 2)$
      i. $\tilde{y} = \epsilon + \mathbf{Z}_{effect_j}\Theta_{effect_j}$
      ii. Sample Θ_{effect_j}
      iii. $\epsilon = \tilde{y} - \mathbf{Z}_{effect_j}\mathbf{\Theta}_{effect_j}$
   (d) sample σ_ϵ^2
   (e) sample σ_G^2
   (f) sample σ_ϕ^2
   (g) $enqueue(\mu, \beta, \epsilon, \sigma_\epsilon, \theta)$

where the observation noise $\vartheta_{i,j} \sim \mathcal{N}\left(0, \nu_j^2\right)$, such that $i \in (1 \dots N)$ and $j \in (1 \dots M)$. The methylation level matrix M is decomposed in

$$\mathbf{M} = \mathbf{RS}$$

For the simulation, each row i of $\mathbf{R}$ is distributed according to

$$r_i \sim \text{Dirichlet}\left(\theta\right)$$

and each of the methylation levels $s_{ij} \in \mathbb{R}$ are distributed as follows for the differentially methylated regions (DMR)

$$s_{ij} \sim \mathcal{N}_{(0,1)}\left(0, \tau^2\right) \tag{10}$$

being $\mathcal{N}_{(0,1)}$ the truncated normal distribution with support $[0, 1]$. For the non-DMR we set the methylation levels to a base value

For these simulations we relied on software kindly provided by the authors [13]. We performed a slight modification to be able to change the variance of the cell proportions matrix $\mathbf{P}$. For each simulation we generated a matrix of $N = 2000$ and $M = 103638$. The simulation parameters were in accordance to [13]:

- Proportion of differentially methylated probes (p).
- Variance of the DMRs(τ).
- Variance of the cell proportions (sp).
- Variance of the measurement noise (ϑ)

We assume 100 probes exert an effect over phenotypic trait $\mathbf{y}$, thus for each probe selected we denote β_d as the effect corresponding to a probe, and their respective effects are drawn from

$$\beta_d \sim \mathcal{N}\left(0, \sigma_\beta^2\right)$$

the rest of the effects are assign a value of 0. Finally we simulate $\mathbf{y}$ from the linear model $\mathbf{y} = \mathbf{MB} + \epsilon$ with σ_ϵ^2 =0.6 and $\sigma_\beta^2 = \frac{0.5}{100}$ where the VE by the probes amounts to 0.6. For each of the following scenarios, 15 simulations were performed:

- $p \in \{0.1, 0.3, 0.7, 0.9\}$,$\tau = 0.07$,$sp = 1000$,$\vartheta = 0.01$
- $p = 0.15$,$\tau \in \{0.01, 0.03, 0.05, 0.09\}$, $sp = 1000$,$\vartheta = 0.01$
- $p = 0.15$,$\tau = 0.07$,$sp \in \{0.001, 0.1, 1, 10, 1000\}$,$\vartheta = 0.01$
- $p = 0.15$,$\tau = 0.07$,$sp = 1000$,$\vartheta \in \{0.01, 0.025, 0.05, 0.075\}$, for this case the simulated model is $\mathbf{y} = \mathbf{OB} + \epsilon$.

which amounts to 255 simulated data sets in total.

5.2 Inference over simulations of methylation effects

For each of the simulations we ran our method for the observed phenotype $\mathbf{y}$ centered and scaled to variance 1, the observed methylation matrix $\mathbf{O}$ as inputs and with mixture variances (0.1, 0.01, 0.001, 0.0001), for 20000 samples with 10000 samples of burn-in after which a thinning of 10 samples was used to select samples of the posterior for the simulation.

5.2.1 Competing methods

For comparisons with our method we chose the common EWAS methodology, which is derived from the GWAS methodology: we run a set of 103638 linear regressions using the function lm() from R version 3.4.2, and accepted the effect sizes whose p-value was less than 0.05/103638. We ran ridge regression and lasso estimation with 10-fold cross validation using the default settings of package glmnet [33] version 2.0-16. Previous experiments suggested that best performance was achieved by leaving the phenotype vector $\mathbf{y}$ un-scaled. Posterior statistics were obtained for the simulations and shown in **fig.**S1, **fig.**S2 and **fig.**S3. We also compared our approach to a linear mixed effects model where probe values are used to calculate a covariance matrix, which is then used in a restricted maximum likelihood estimation (REML) approach [14].

5.3 Simulations of genotype and methylation effects

We simulated a methylation matrix $\mathbf{M}$ with parameters $p = 0.15$,$\tau = 0.07$,$sp = 1000$,$\vartheta = 0.01$ as above. Then we generated a genotype matrix $\mathbf{X} \in \mathbb{R}^{1000\times 103638}$. For each of the DMRS with non-zero effects in $\mathbf{M}$ we select column j of X to have a correlated genotype by sampling its elements from the distribution:

$$X_{ij} \sim Binomial\left(2, \frac{1}{1+\exp\left(10 - c * M_{ij}\right)}\right)$$

by sampling c from an uniform distribution between 20 and 25 for each column, we achieve a correlation between 0 and 0.6 among genotype and methylation levels.

Having both matrices $\mathbf{O}$ (the noisy observations over matrix $\mathbf{M}$) and $\mathbf{X}$ centered and scaled, we generated 100 methylation effects $\beta_{cg} \sim \mathcal{N}\left(0, \frac{0.5}{100}\right)$, 100 larger genotypic effects $\beta_g \sim \mathcal{N}\left(0, \frac{0.2}{100}\right)$ and 900 small genotypic effects $\beta_g \sim \mathcal{N}\left(0, \frac{0.1}{900}\right)$. Thus the model for the simulated genotype is $\mathbf{y} = \mathbf{O}\beta_{cg} + \mathbf{X}\beta_g + \epsilon$, with $\epsilon \sim \mathcal{N}\left(0, 0.2\right)$

We repeated the process 15 times to have the same number of simulated data sets.

5.4 Inference over simulated genotype and methylation effects

For each of the simulated data sets we ran our method for 20000 samples, with a burnin of 10000 and a thinning of 10 samples. The mixture variances were set to (0.1, 0.01, 0.001, 0.0001) for methylation effects and to (0.01, 0.001, 0.0001, 0.00001) for genotype effects.

5.4.1 Competing methods

For comparisons with other methods we followed the same methodology as for the methylation-only comparison. The only variant being that for the GWAS-like method we adjusted the phenotype by the first ten principal components of the genotype matrix and then regressed the residuals against the scaled methylation matrix. The methods were compared over the estimation of the true genetic and epigenetic VE and power to estimate the true effects. Results shown in **fig.**S4

5.5 Data

5.5.1 Generation Scotland

Generation Scotland: the Scottish Family Health Study is a large population-based, family-structured cohort of over 24,000 individuals aged 18-99 years. The study baseline took place between 2006-2011 and included detailed cognitive, physical, and health questionnaires, along with sample donation for genetic and biomarker data. DNA methylation data from whole blood was obtained on a subset of 5,200 participants. The Illumina HumanMethylationEPIC Bead Chips array was used to measure methylation and quality control details have been reported previously [27]. Briefly, outliers based on the visual inspection of methylated to unmethylated log intensities were excluded, along with poorly performing probes and samples, and sex mismatches (predicted based on genetics versus questionnaire data) yielding an analysis dataset of 5,101. As reported in McCartney et al. [27], further filtering was performed to exclude non-autosomal CpG sites and sites that were

exclusive to the EPIC array. This allowed for the predictors to be applied to datasets that collected DNA methylation using an earlier version of the Illumina arrays (450k array) giving a total of 370,262 probes.

After the quality control steps described above, we integrated the SNP marker and methylation matrices, along with the log-transformed age and the sex of the individuals (encoded as 1 for Female). All matrices and phenotypes were centered and scaled to variance 1. The data was used as input for our Bayesian model, with parameters (0.0001, 0.001, 0.01) for genetic effects mixtures variances and (0.01, 0.1, 1) for the epigenetic effects, age and sex. Four chains for each trait with different starting values were executed. We assessed the convergence of the hyperparameters $\sigma^2_\epsilon, \sigma^2_G, \sigma^2_\phi$ through the Geweke test [34] and the $\hat{R}$ criteria [35], with the help of the R package "ggmcmc" [36] (see **sec.**S2). As result, the algorithm yielded a set of samples over the posterior distribution of effects conditioned on the observed phenotype, the genetic and epigenetic probes and controlled by age and sex. We further scaled in each sample the hyperparameters $\sigma^2_\epsilon, \sigma^2_G$ and σ^2_ϕ by dividing each one by their sum $(\sigma^2_\epsilon + \sigma^2_G + \sigma^2_\phi)$. The posterior distribution is summarized in **table** S1 for BMI and **table** S2 for smoking. Posterior Inclusion Probabilities (IP) were computed by counting the times a probe is present in the model (in any of the mixtures) and divided by the total number of posterior samples.

5.5.2 Enrichment analysis

Probes were associated to their respective gene ENTREZ identifiers using the R packages "IlluminaHumanMethylation450kanno.ilmn12.hg19" [37] and "biomaRT" [38]. We provide a list of each gene with IP greater than >5% for BMI **table** S4, and for smoking **table** S5.

Then we associated the mapped genes with their respective terms in the Gene Onthology (GO) using the R package [39]. With these probe-terms associations we computed enrichment as defined by:

$$enrichment = \frac{p.PVE}{p.Term}$$

with $p.PVE$ being the proportion of variance explained by probes associated with the term, having β_{Term} being the effects associated with the term and being β_{Model} the effects in the model(that is, those which are not coming from the "spike" at zero) in the current sample, we have

$$p.PVE = \frac{\sum^{Term} \beta^2_{Term}}{\sum^{Model} \beta^2_{Model}}$$

and $p.Term$ being the proportion of probes mapping to the term among all the probes mapping to a term in the current sample. Having $\#probes_{Term}$ being the number of probes mapping to a term and $\#probes_{Model}$ the number of probes in the model in the current sample, we have

$$p.Term = \frac{\#probes_{Term}}{\#probes_{Model}}$$

We also computed the posterior inclusion probability (IP) for a term by counting the times a term appears in the model and dividing by the number of samples. Finally, given that we have a posterior distribution over enrichment values, we adopt the ROPE decision rule [21], for which we accept the hypothesis that a term is significantly over/under-enriched if 95% of the posterior mass for the enrichment value is outside the interval (0.5,1.5) and the term has an IP >95%. Significantly enriched GO terms are presented in **fig.**3**e** and **fig.**S15 for BMI; in **fig.**3**f** and **fig.**S16 for smoking.

We then repeated the entire enrichment process, mapping probes to genes in the top 99% and lowest 1% percentiles of gene expression in the GTEx consortium [23] and DEPICT [24] datasets. We show the enrichment results in **fig.**S17 for BMI, with the corresponding tables, **table** S8,**table** S9 for GTEx; with **table** S12,**table** S13 for DEPICT. For smoking the corresponding plots are shown in **fig.**S18 and summarized in tables **table** S10,**table** S11 for GTEx and **table** S14,**table** S15 for DEPICT.

5.5.3 Estimates for replication

For both BMI and smoking, the posterior samples over effects where averaged and associated to their respective probe and SNP identities. For each replication cohort a predictor was built by multiplying the

posterior mean effects by the corresponding centered and scaled genetic and epigenetic marker readings, and predictive ability measured over the scaled and centered cohort trait was measured using the R^2 statistic.

5.5.4 Lothian Birth Cohort 1936

The Lothian Birth Cohort 1936 is a longitudinal study of aging [40]. It follows 1,091 members of the 1947 Scottish Mental Survey, who were recontacted in later life, when they were living in the Edinburgh area of Scotland. The cohort members were all born in 1936 and have been assessed for a wide variety of health and lifestyle outcomes at ages 70, 73, 76, 79, and 82 years. DNA has been collected at each clinical visit. In the present study, we considered DNA methylation data (Illumina 450k array) from whole blood, taken at mean age 70, for analysis. Details of the collection and processing of the data have been reported previously [27]. Briefly, after quality control to remove poorly performing methylation sites, samples, and individuals with mismatching genotypes or predicted sex, a sample of 906 individuals was available for prediction analysis. The genotype and methylation matrices were processed as with GS, given that the posterior effect sizes for age and sex were equal to zero for both traits, they were not included.

5.5.5 Avon Longitudinal Study of Parents and Children

Samples were drawn from the Avon Longitudinal Study of Parents and Children [41], [42]. Blood from 1018 mother–child pairs (children at three time points and their mothers at two time points) were selected for analysis as part of the Accessible Resource for Integrative Epigenomic Studies (ARIES, http://www.ariesepigenomics.org.uk/) [43]. Following DNA extraction, samples were bisulphite converted using the Zymo EZ DNA Methylation^{TM} kit (Zymo, Irvine, CA, USA). Following conversion, genome-wide methylation was measured using the Illumina Infinium HumanMethylation450 (HM450) BeadChip. The arrays were scanned using an Illumina iScan, with initial quality review using GenomeStudio. ARIES was preprocessed and normalized using the meffil R package [44]. ARIES consists of 5469 DNA methylation profiles obtained from 1022 mother-child pairs measured at five time points (three time points for children: birth, childhood and adolescence; and two for mothers: during pregnancy and at middle age). Low quality profiles were removed from further processing, and the remaining 4593 profiles were normalized using the Functional Normalization algorithm [45] with the top 10 control probe principal components. Full details of the preprocessing and normalization of ARIES has been described previously [44].

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7 URLS

BayesRR implementation in `https://github.com/ctggroup/bayesRRcpp`. Simulation scripts and postprocessing scripts in `https://github.com/ctggroup/BEpigenetics`.

8 Author contributions

MRR, REM and DTB conceived and designed the experiments. DTB conducted the experiments, with oversight by MRR and RM, and assistance of DLM, TB and GH. DTB and MRR derived the equations and the algorithm, developed the software, and wrote the paper. RMW, QZ, DJP, CSH, AFM, NRW, PMV, AMM, KLE and IJD provided study oversight and contributed data to the analysis. All authors approved the final manuscript prior to submission.

9 Author competing interests

The authors declare no competing interests

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Marian Beekman, Joris Deelen, Diana van Heemst, Jan H. Veldink, Leonard H. van den Berg, Cornelia M. van Duijn, Bert A. Hofman, André G. Uitterlinden, P. Mila Jhamai, Michael Verbiest, H. Eka D. Suchiman, Marijn Verkerk, Ruud van der Breggen, Jeroen van Rooij, Nico Lakenberg, Hailiang Mei, Maarten van Iterson, Michiel van Galen, Jan Bot, Peter van 't Hof, Patrick Deelen, Irene Nooren, Matthijs Moed, Martijn Vermaat, Dasha V. Zhernakova, René Luijk, Marc Jan Bonder, Freerk van Dijk, Wibowo Arindrarto, Szymon M. Kielbasa, Morris A. Swertz, Erik W. van Zwet, Daniel Levy, Nicholas G. Martin, John M. Starr, Cisca Wijmenga, Naomi R. Wray, Jian Yang, Grant W. Montgomery, Lude Franke, Ian J. Deary, and Peter M. Visscher. Improving phenotypic prediction by combining genetic and epigenetic associations. *The American Journal of Human Genetics*, 97(1):75–85, Jul 2015.

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Supplemental Materials: Inference of genetic and epigenetic signatures of complex traits

S1 Simulation results

Figure S1. Simulation results with GWAS-like method included

Figure S2. Simulation results without GWAS-like method included

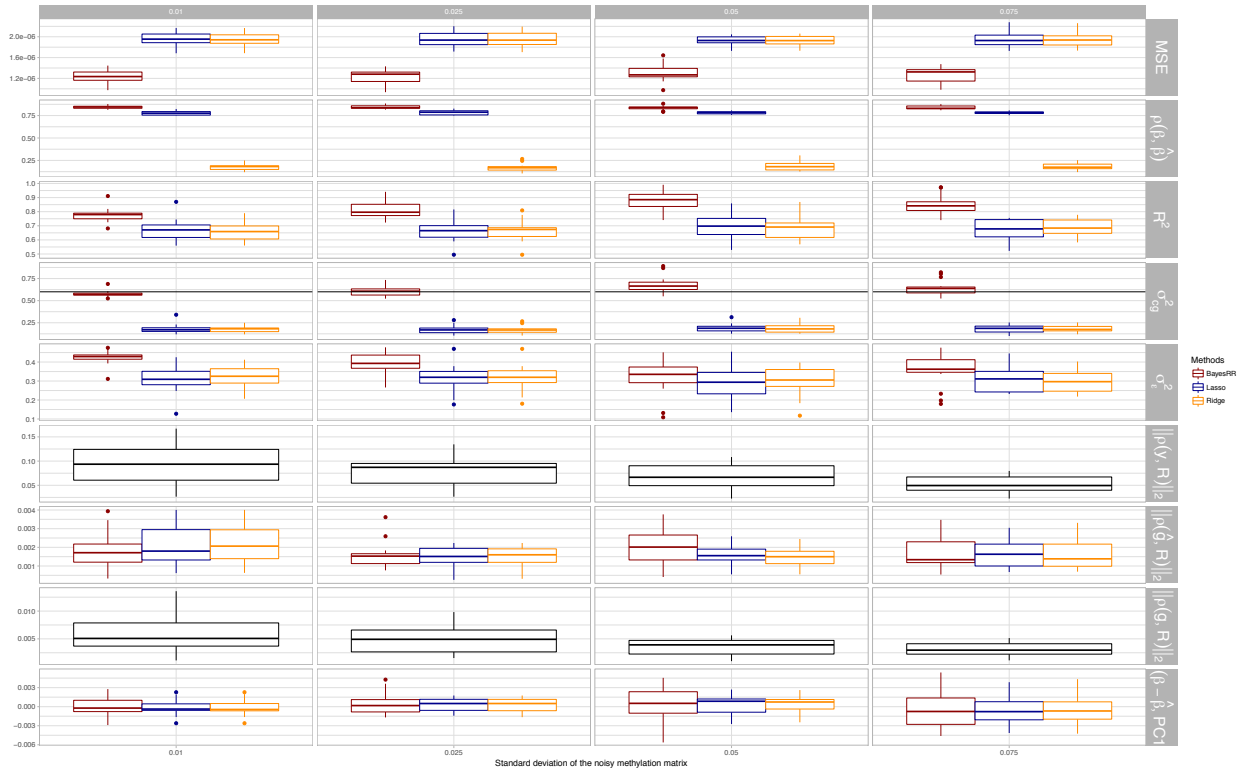

Figure S3. Simulation results without GWAS-like method included

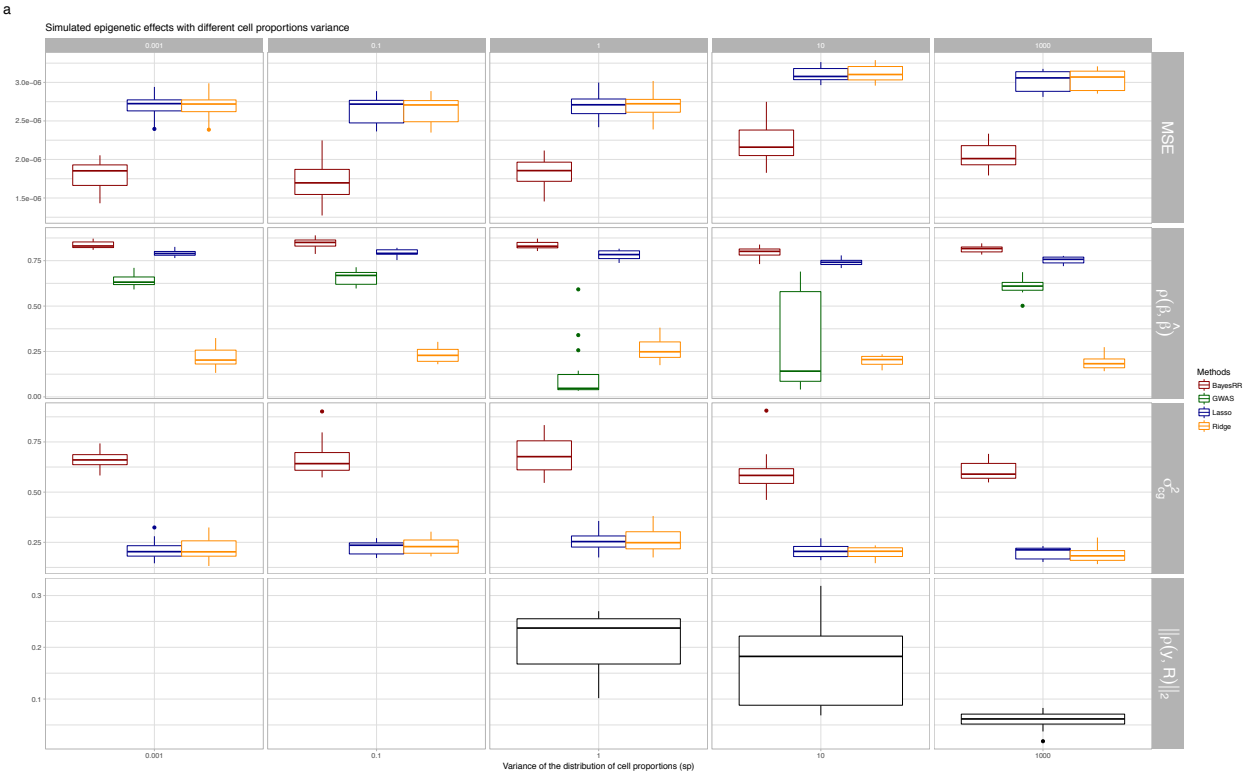

Figure S4. Simulation results for genetic and epigenetic markers included

S2 MCMC parameters and diagnostics

S2.1 BMI

Four chains for BMI were run first for 15000 samples with a burn-in of 10000 samples and thinning of 5 samples. After preliminary diagnostics it was decided to re-start the chains from the last sample, for another 15000 samples with a burn in of 10000 samples and a thinning of 10 samples. This resulted in 4 chains with 1000 samples each.

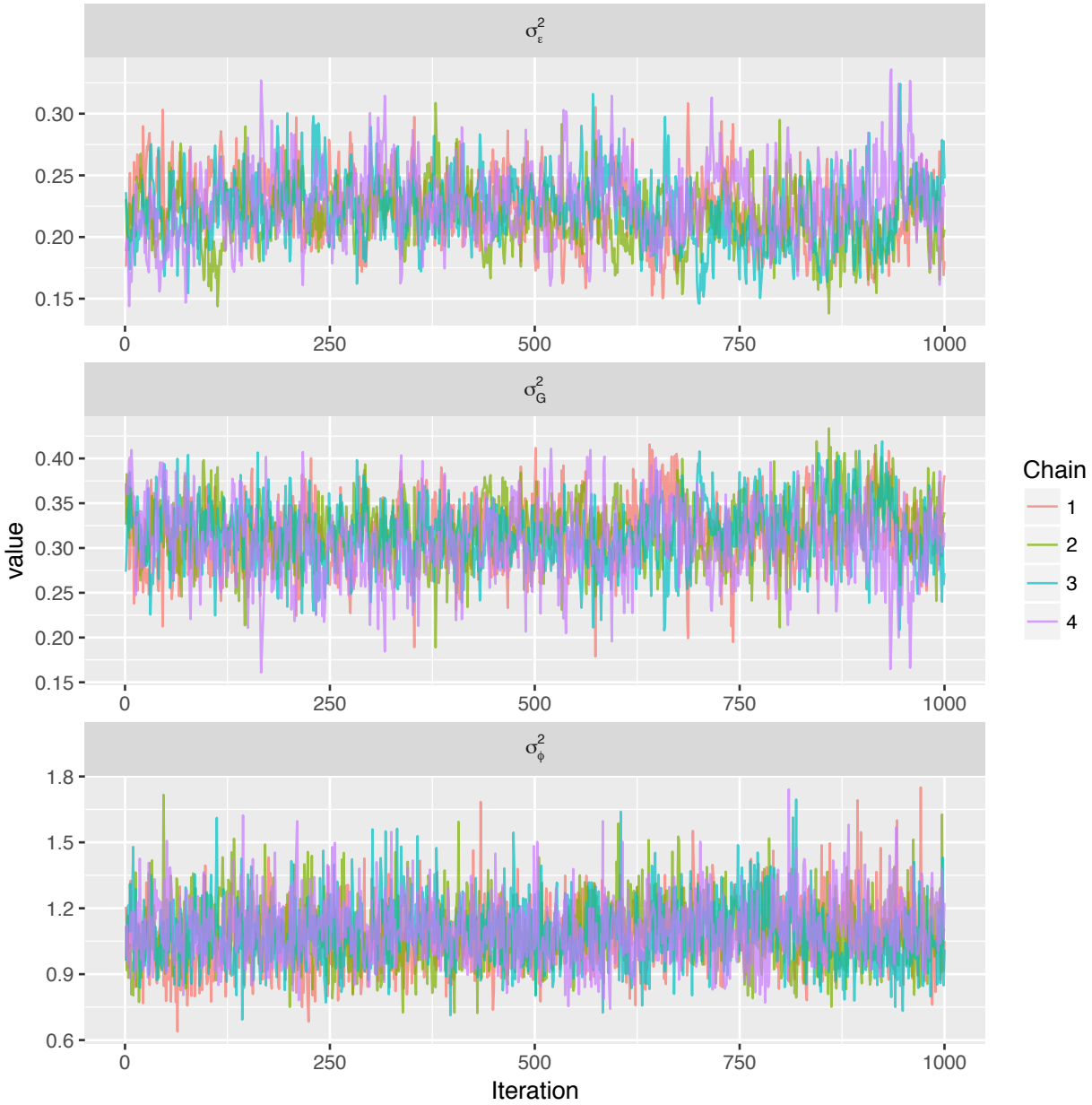

Figure S5. BMI: Traceplot for the hyper-parameters $\sigma^2_G, \sigma^2_\phi, \sigma^2_\epsilon$.

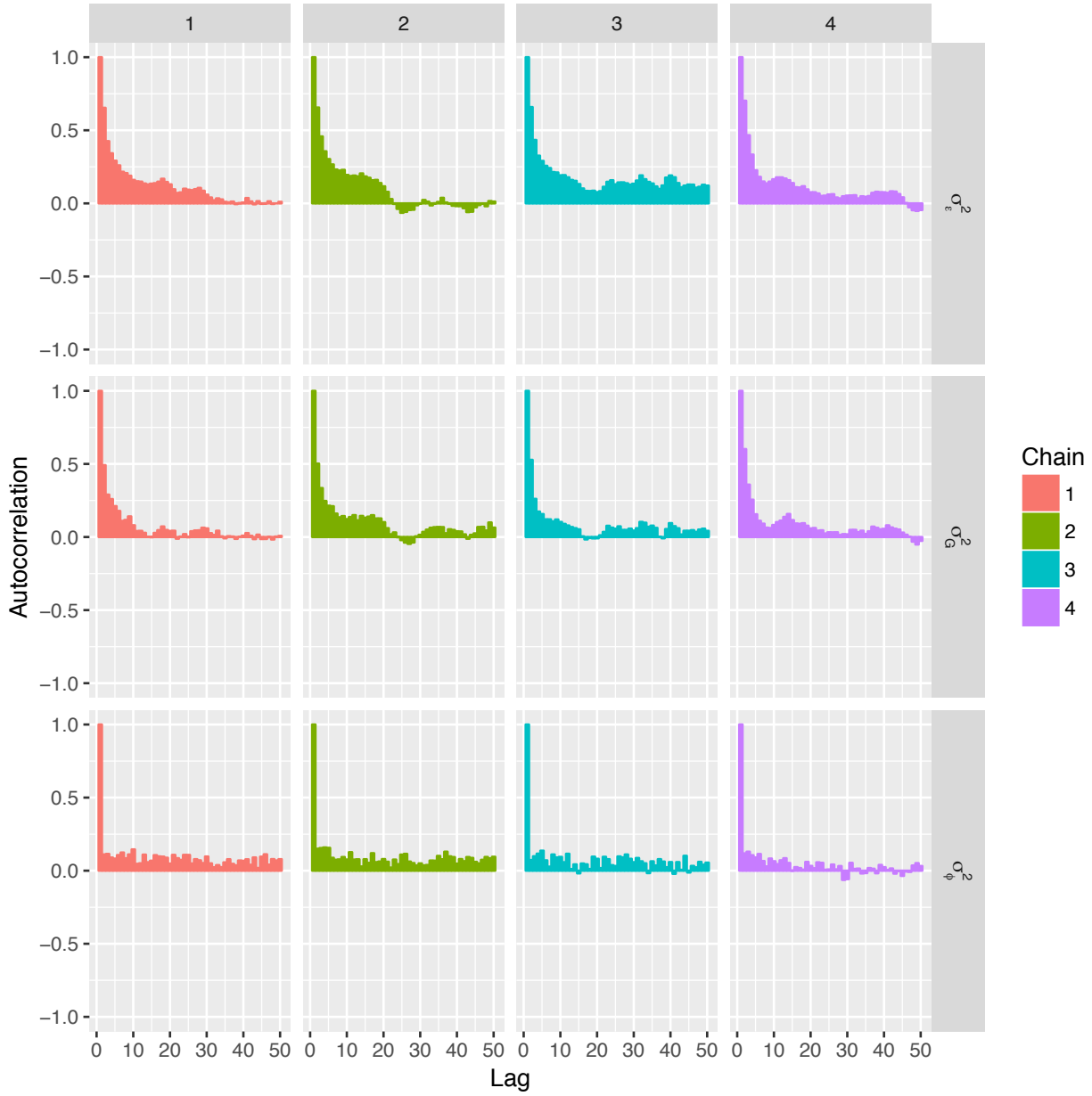

Figure S6. BMI: Autocorrelation (correlation of the chain with itself after a lag) plot for the four chains for the hyper-parameters $\sigma_G^2, \sigma_\phi^2, \sigma_\epsilon^2$.

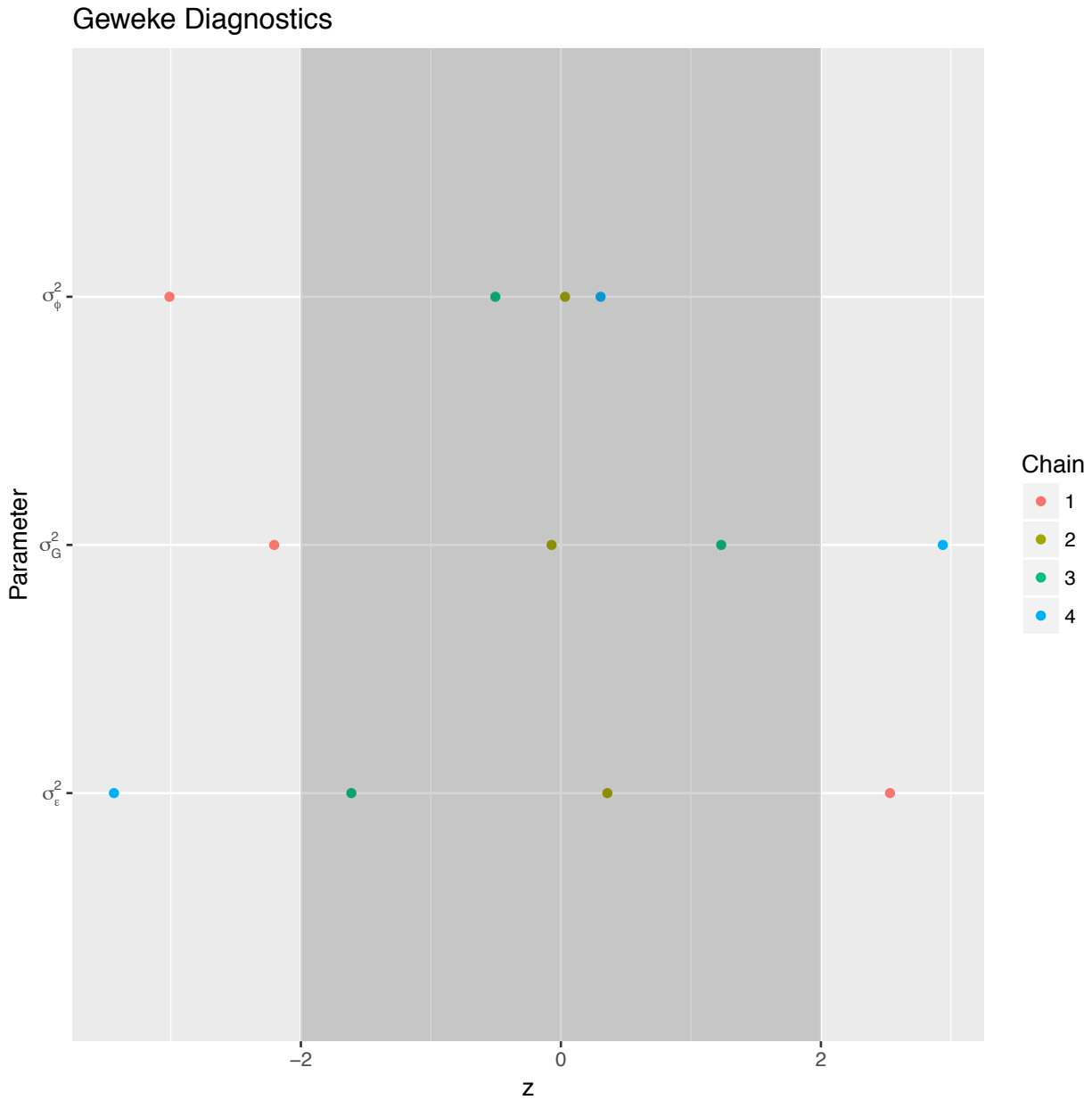

Figure S7. BMI: Geweke z-score diagnostic results for the four chains for the hyper-parameters $\sigma^2_G, \sigma^2_\phi, \sigma^2_\epsilon$, the acceptance interval(-2,2) is highlighted in dark gray.

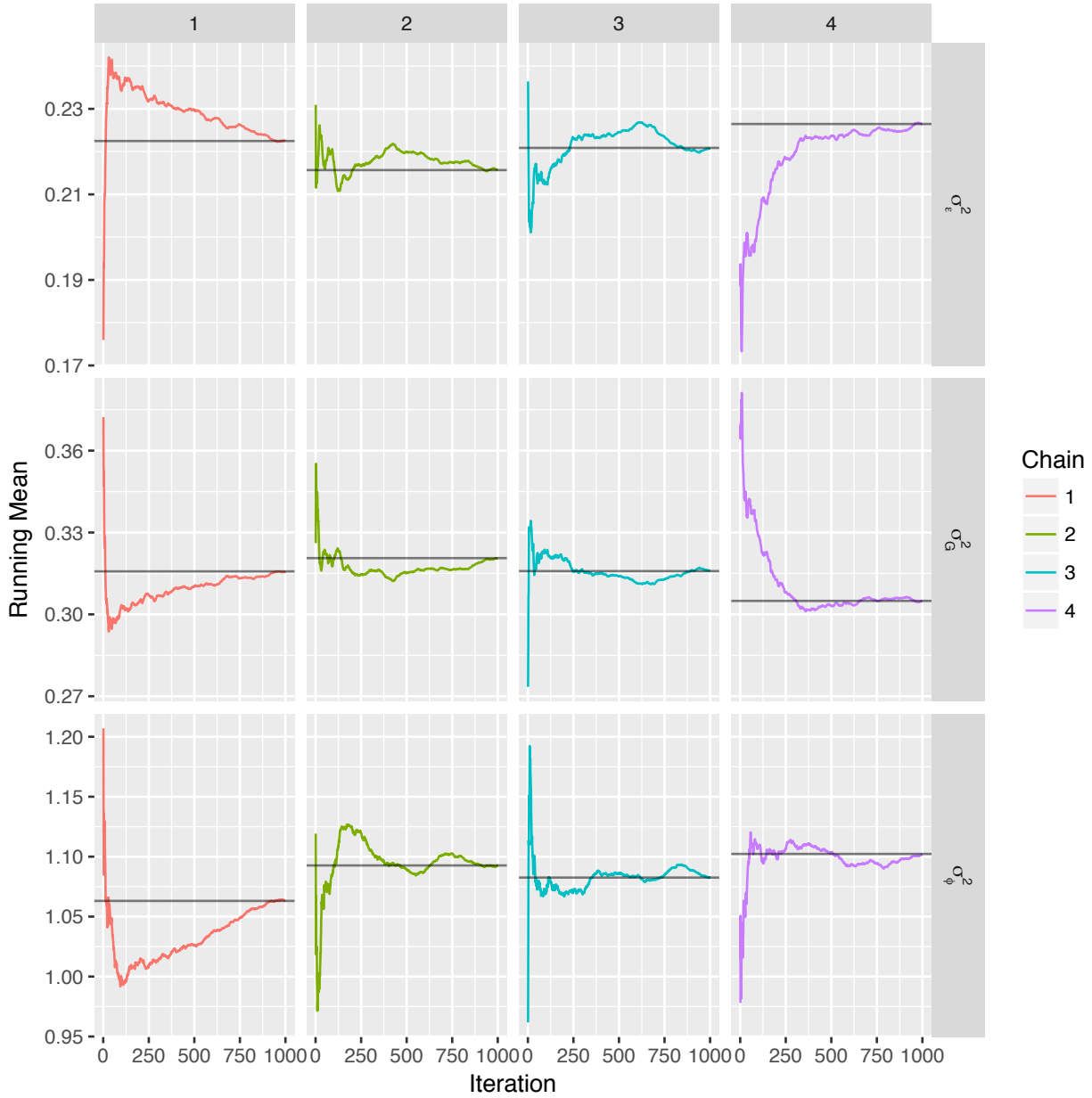

Figure S8. BMI: Running means plot for the hyper-parameters $\sigma_G^2, \sigma_\phi^2, \sigma_\epsilon^2$, the mean of the chain at each sample is compared against the chains mean(horizontal line).

Further thinning

The last 250 samples for each chain were selected as samples from the posterior distribution for the subsequent analysis.

S2.2 Smoking

Four chains for smoking were run for 15000 samples with a burn-in period of 10000 samples and thinning of 10 samples.

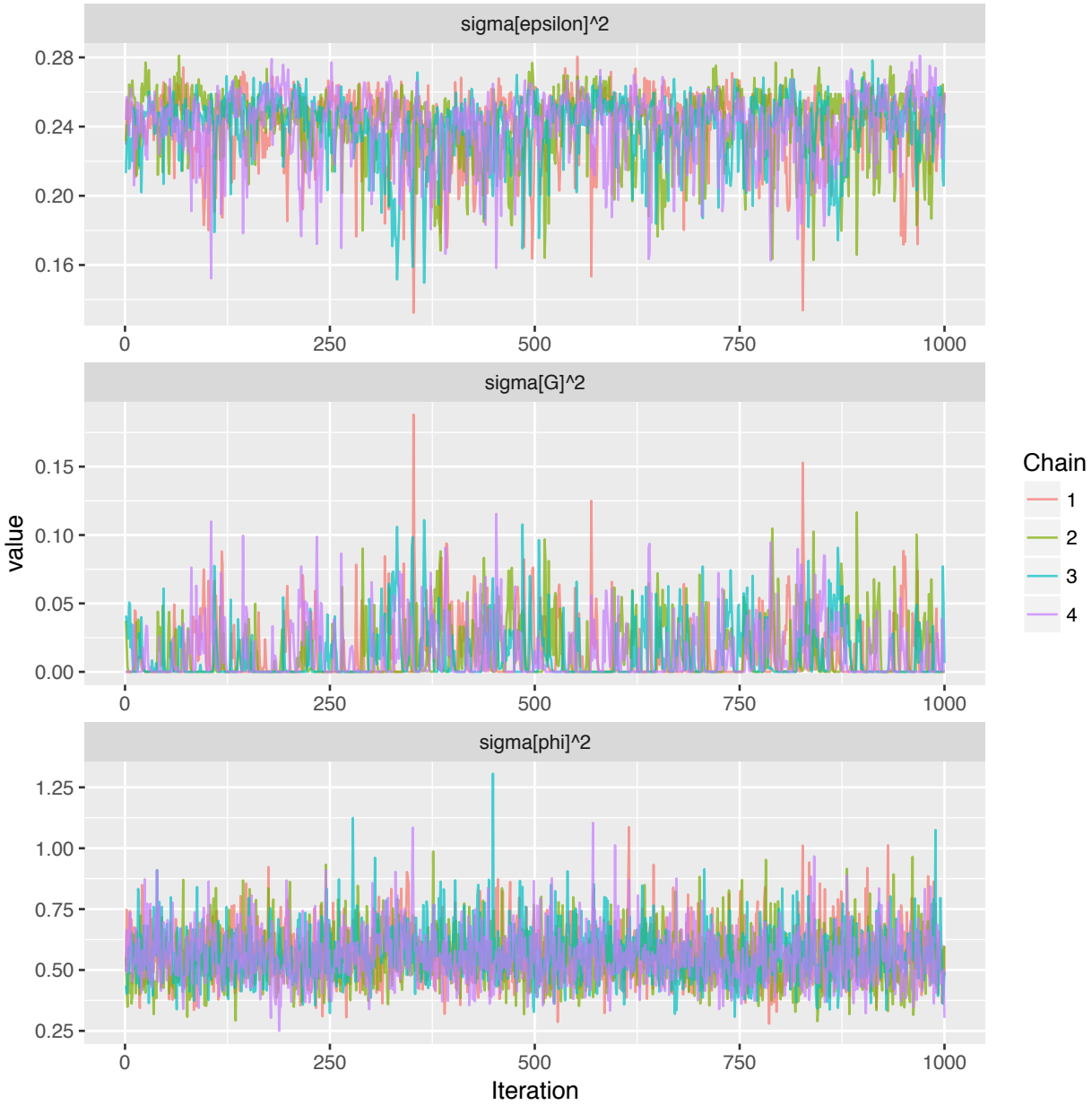

Figure S9. SMOKING: Traceplot for the hyper-parameters $\sigma_G^2, \sigma_\phi^2, \sigma_\epsilon^2$.

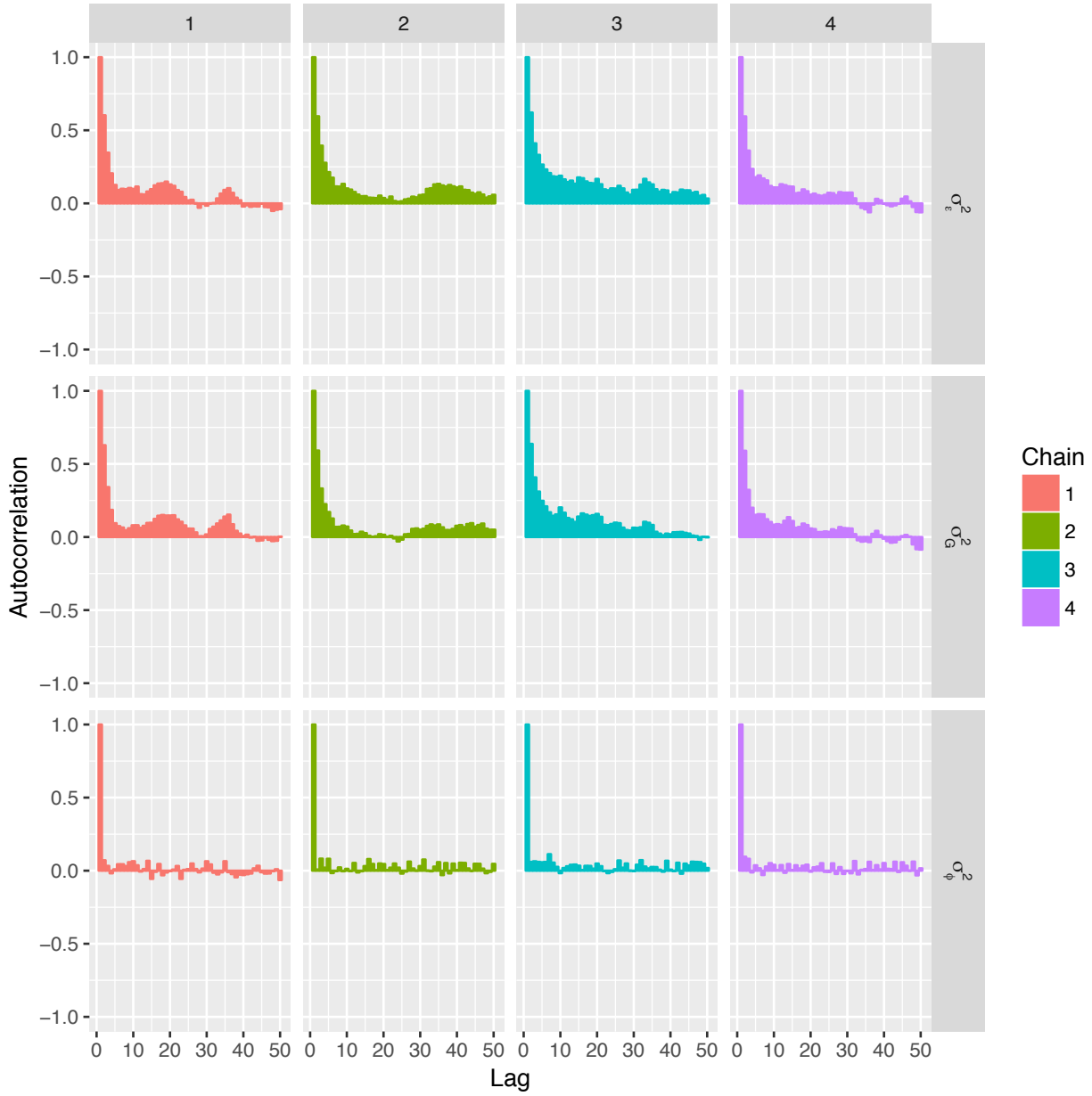

Figure S10. SMOKING: Autocorrelation (correlation of the chain with itself after a lag) plot for the four chains for the hyper-parameters $\sigma_G^2, \sigma_\phi^2, \sigma_\epsilon^2$.

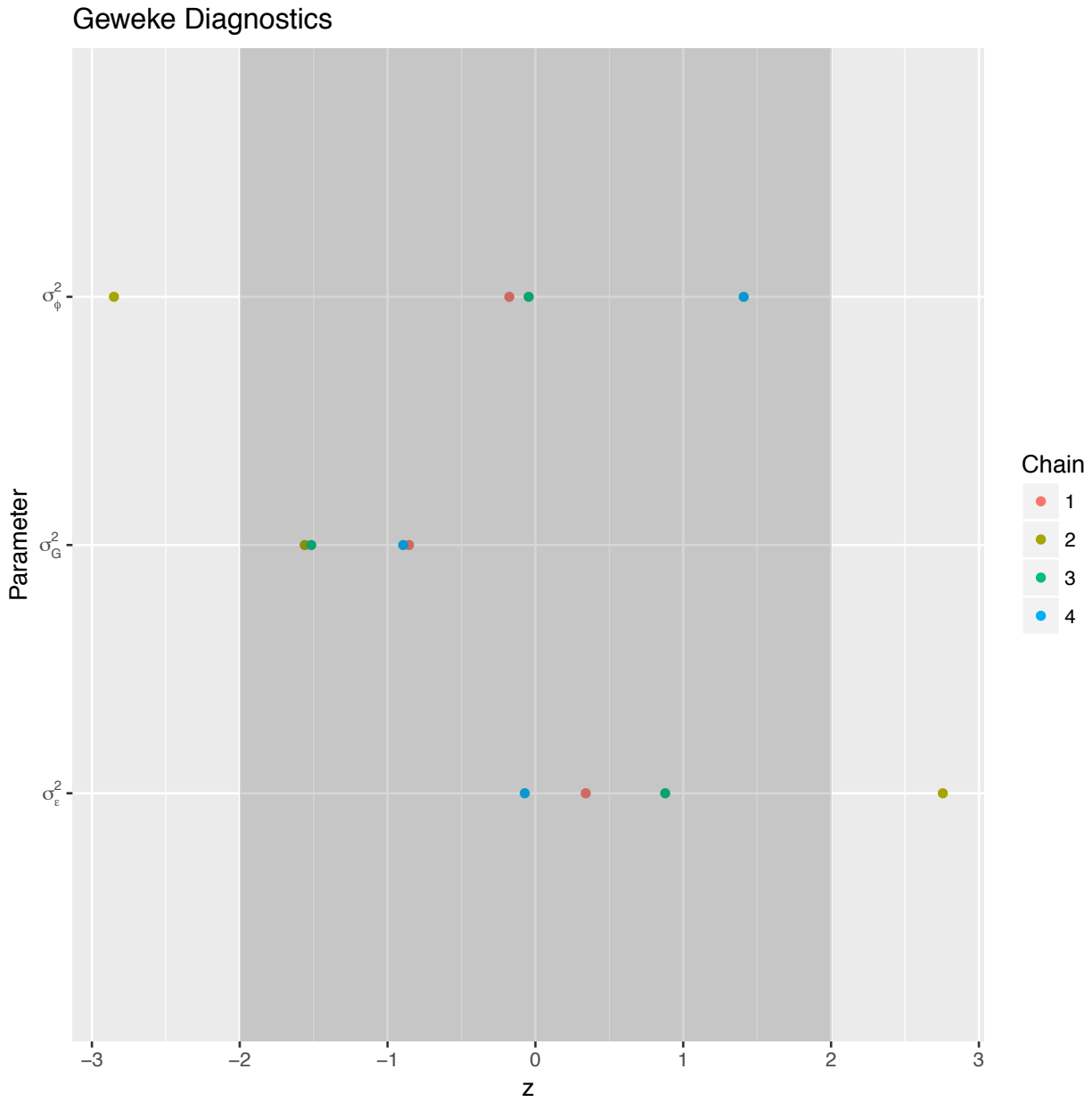

Figure S11. SMOKING: Geweke z-score diagnostic results for the four chains for the hyper-parameters $\sigma^2_G, \sigma^2_\phi, \sigma^2_\epsilon$, the acceptance interval(-2,2) is highlighted in dark gray.

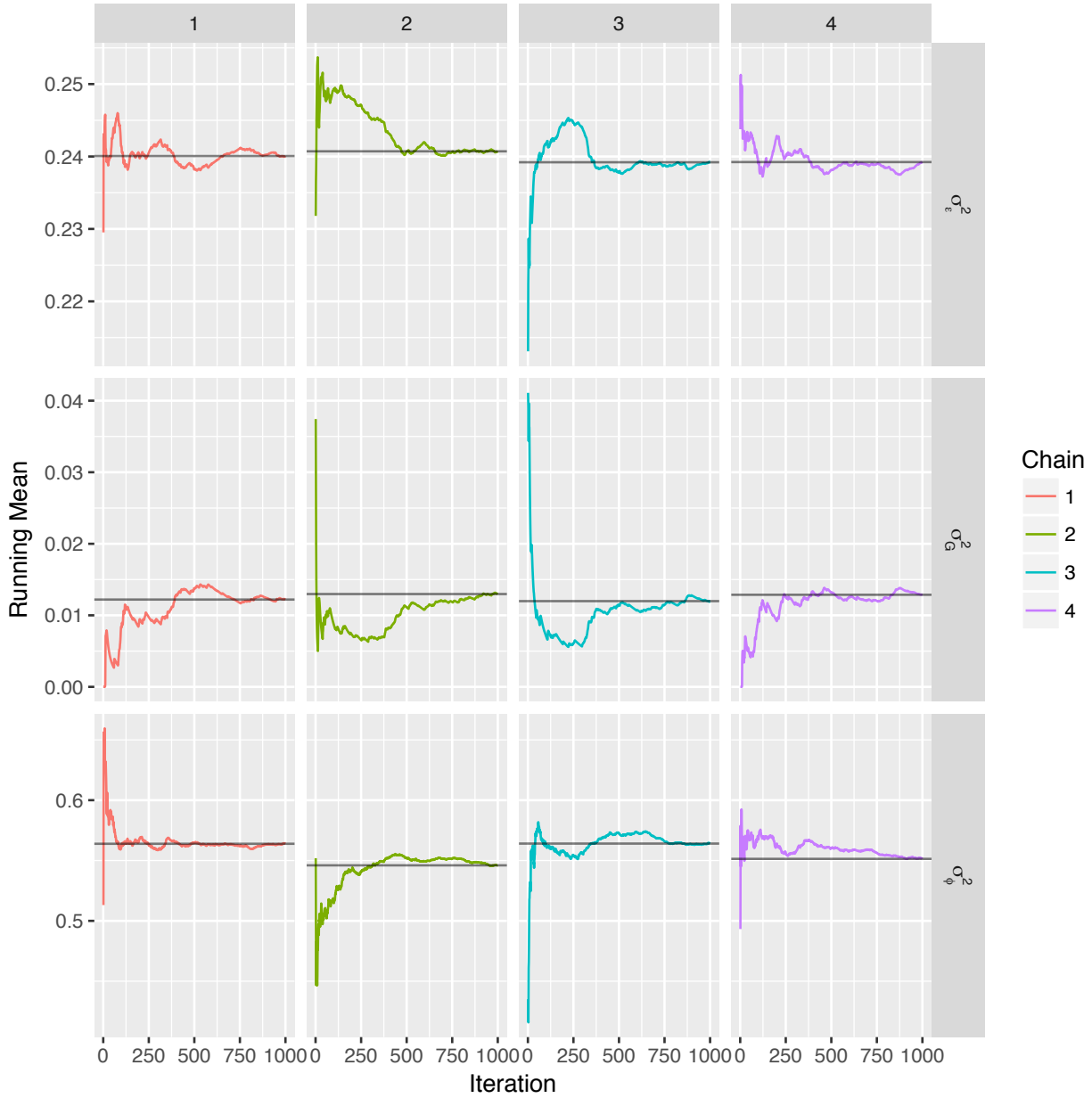

Figure S12. SMOKING: Running means plot for the hyper-parameters $\sigma^2_G, \sigma^2_\phi, \sigma^2_\epsilon$, the mean of the chain at each sample is compared against the chains mean(horizontal line).

Further thinning

The last 250 samples for each chain were selected as samples from the posterior distribution for the subsequent analysis.

S3 Figures

S3.1 Gene ontology enrichment

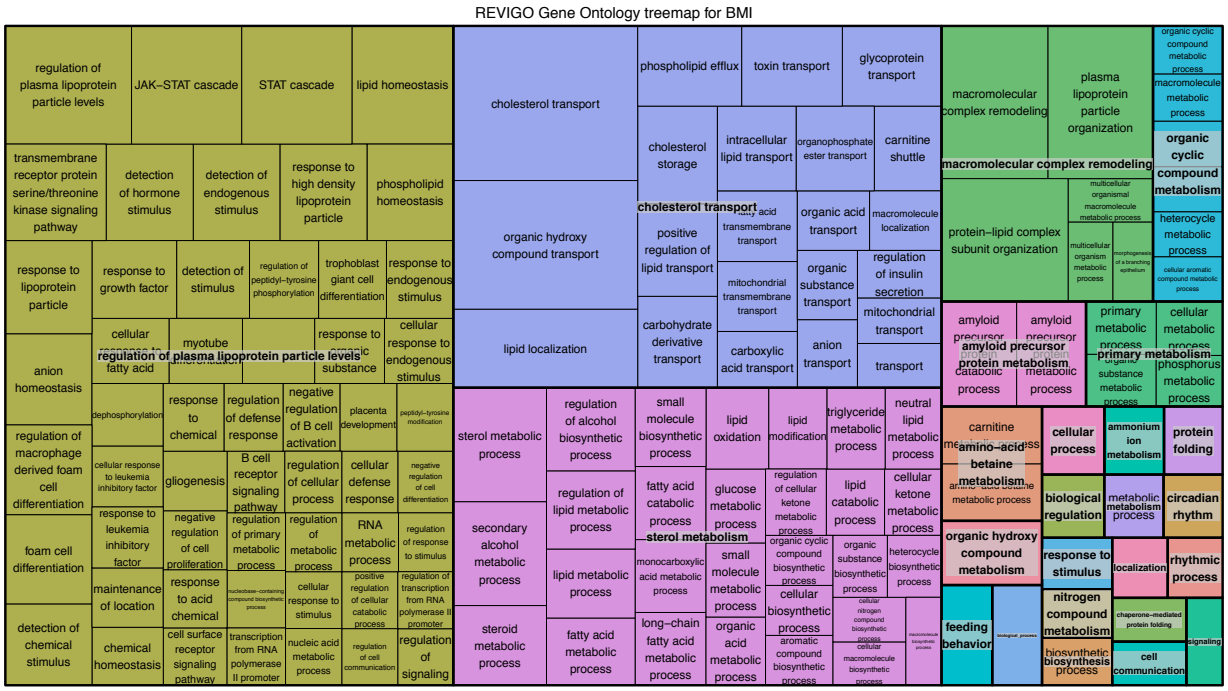

Figure S13. Treemap of the top GO enriched terms for BMI(enrichment>2.0 and PIP>95%). Plot generated with REVIGO

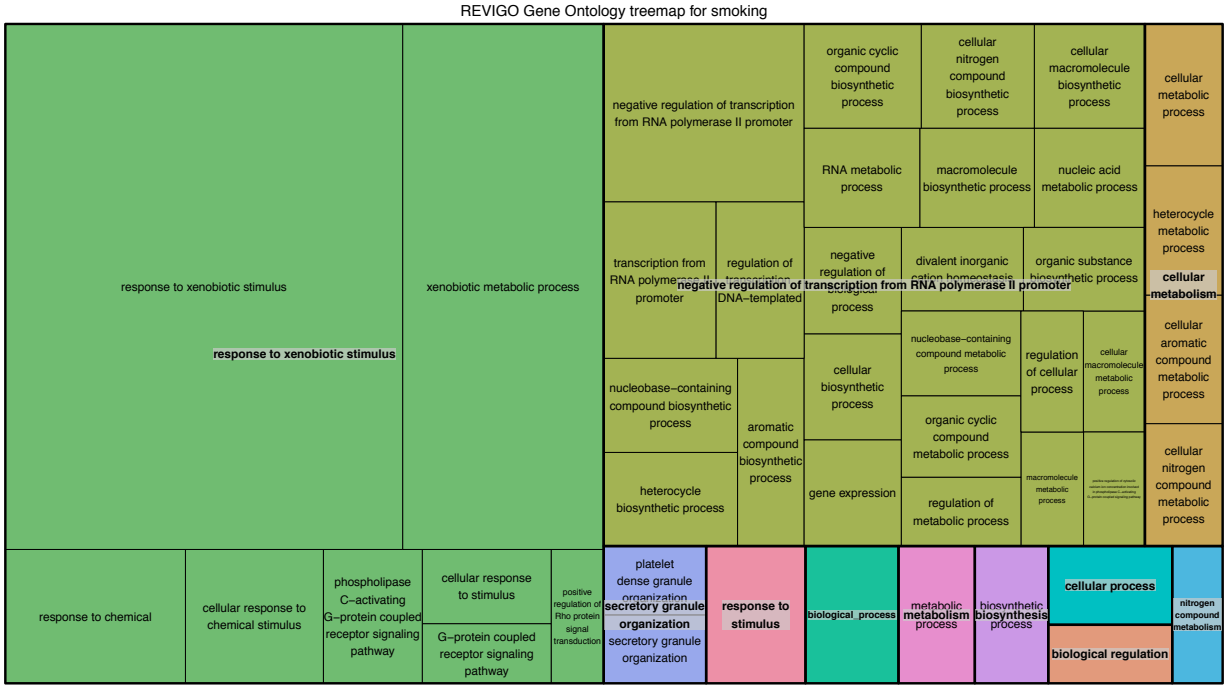

Figure S14. Treemap of the top GO enriched terms for smoking(enrichment>2.0 and PIP>95%). Plot generated with REVIGO

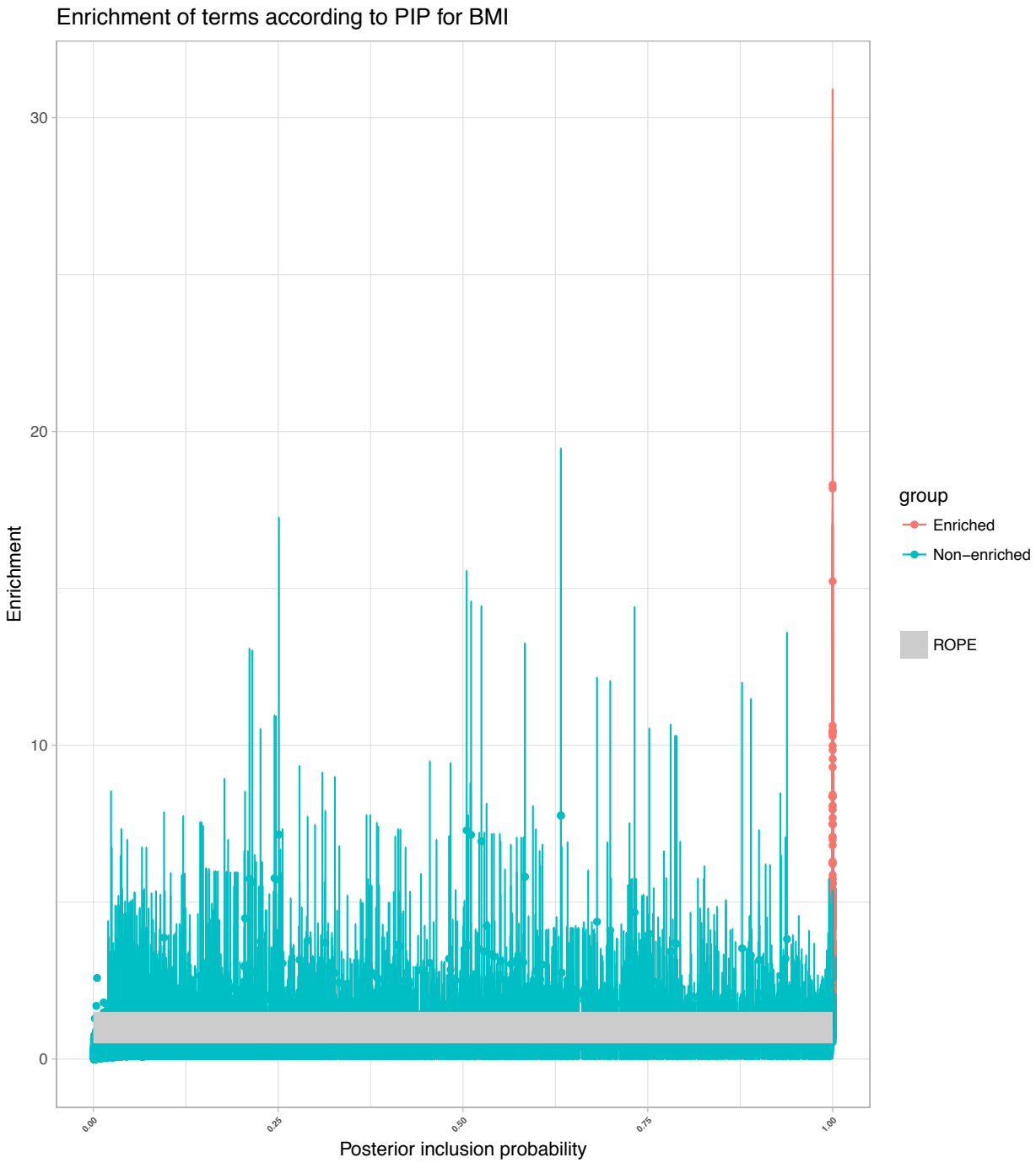

Figure S15. Enrichment of GO terms for BMI, plotted are the mean terms enrichment and the 95% highest posterior density intervals against the posterior inclusion probability of the term, on gray the rope area around enrichment 1.0(0.5-1.5).

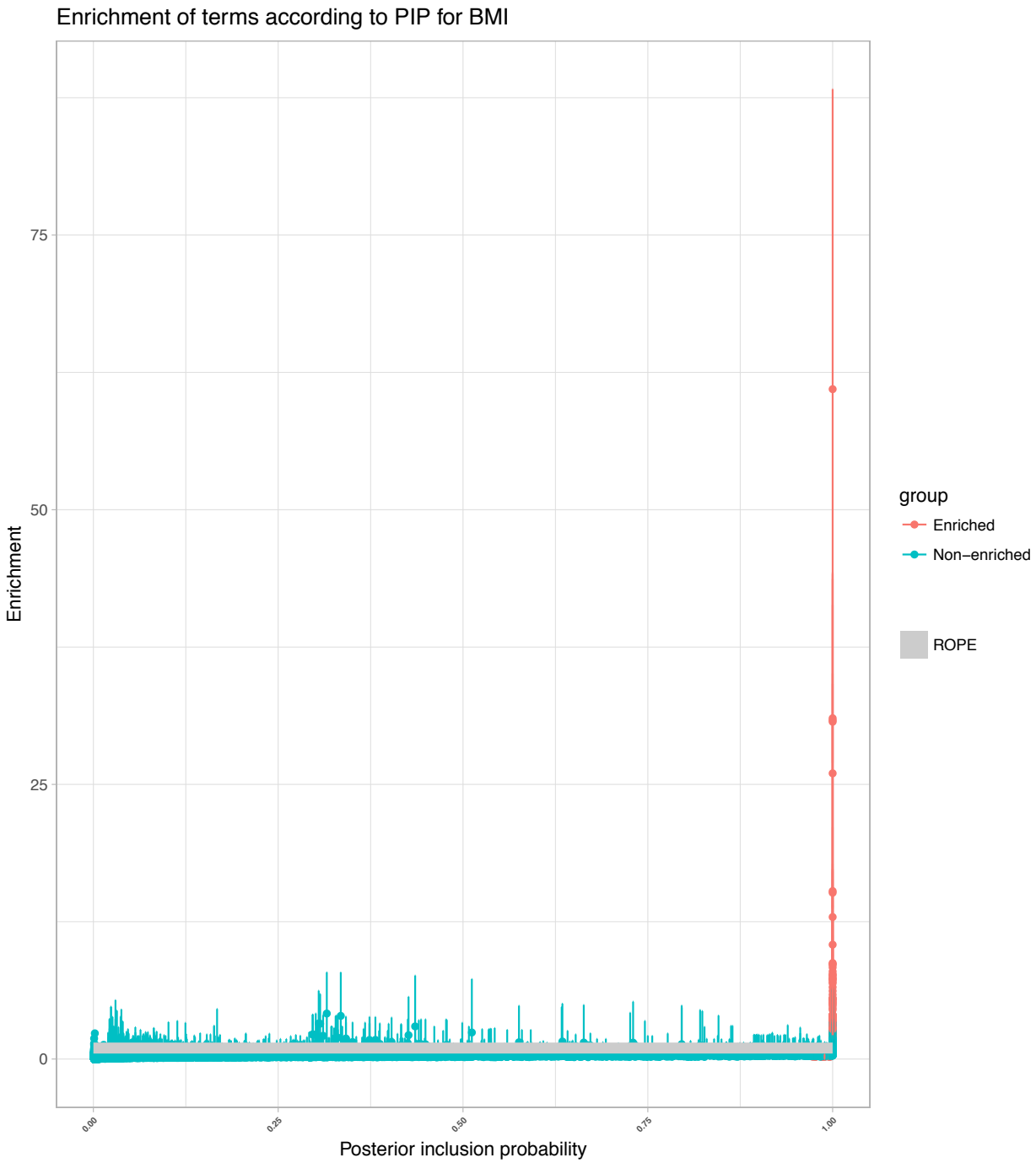

Figure S16. Enrichment of GO terms for smoking, plotted are the mean terms enrichment and the 95% highest posterior density intervals against the posterior inclusion probability of the term, on gray the rope area around enrichment 1.0(0.5-1.5).

S3.2 Tissue enrichment with GTEX and DEPICT

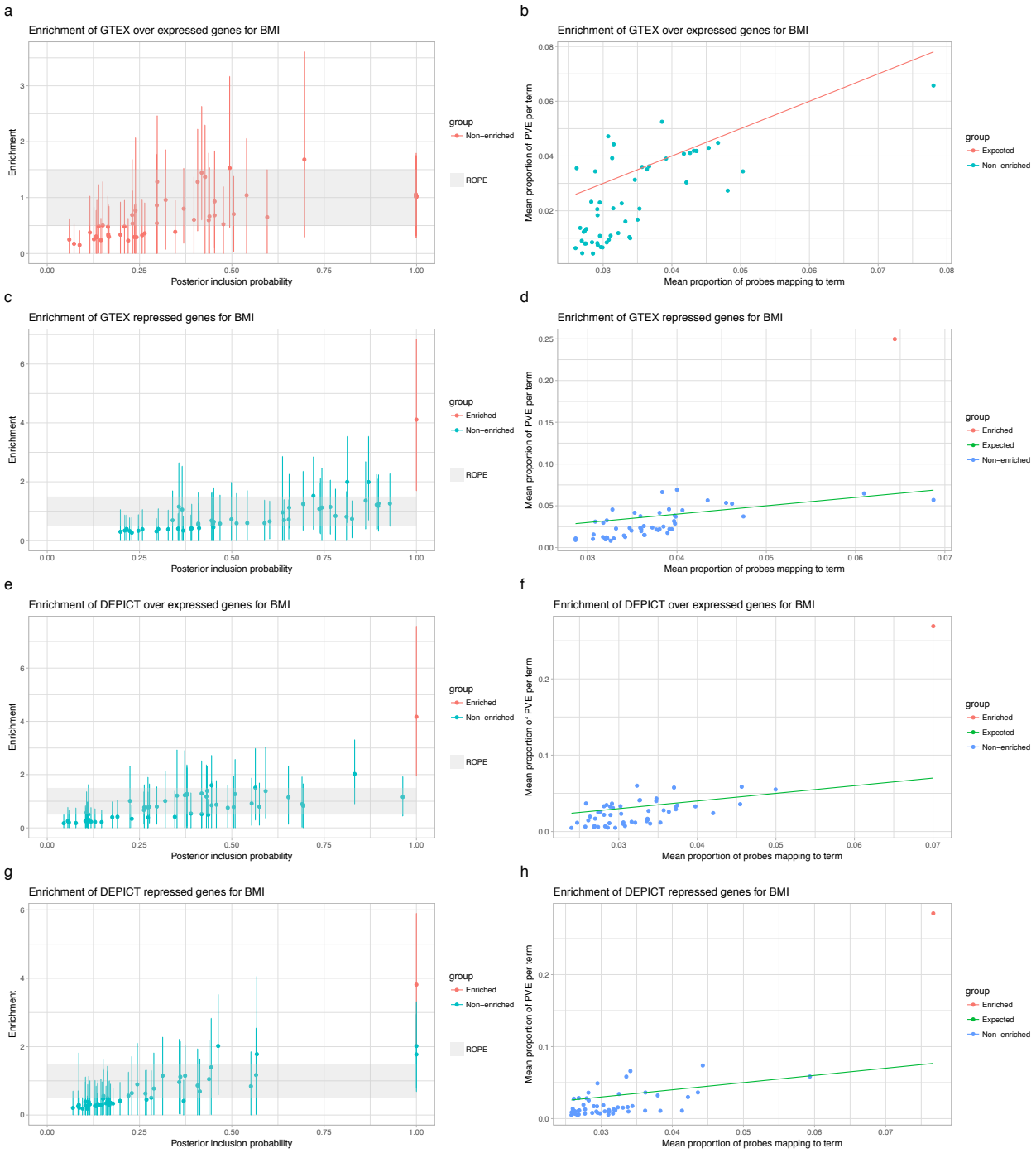

Figure S17. Enrichment analysis for BMI using over expressed(top 99% percentile) and repressed genes (lower 1% percentile) for GTEX and DEPICT

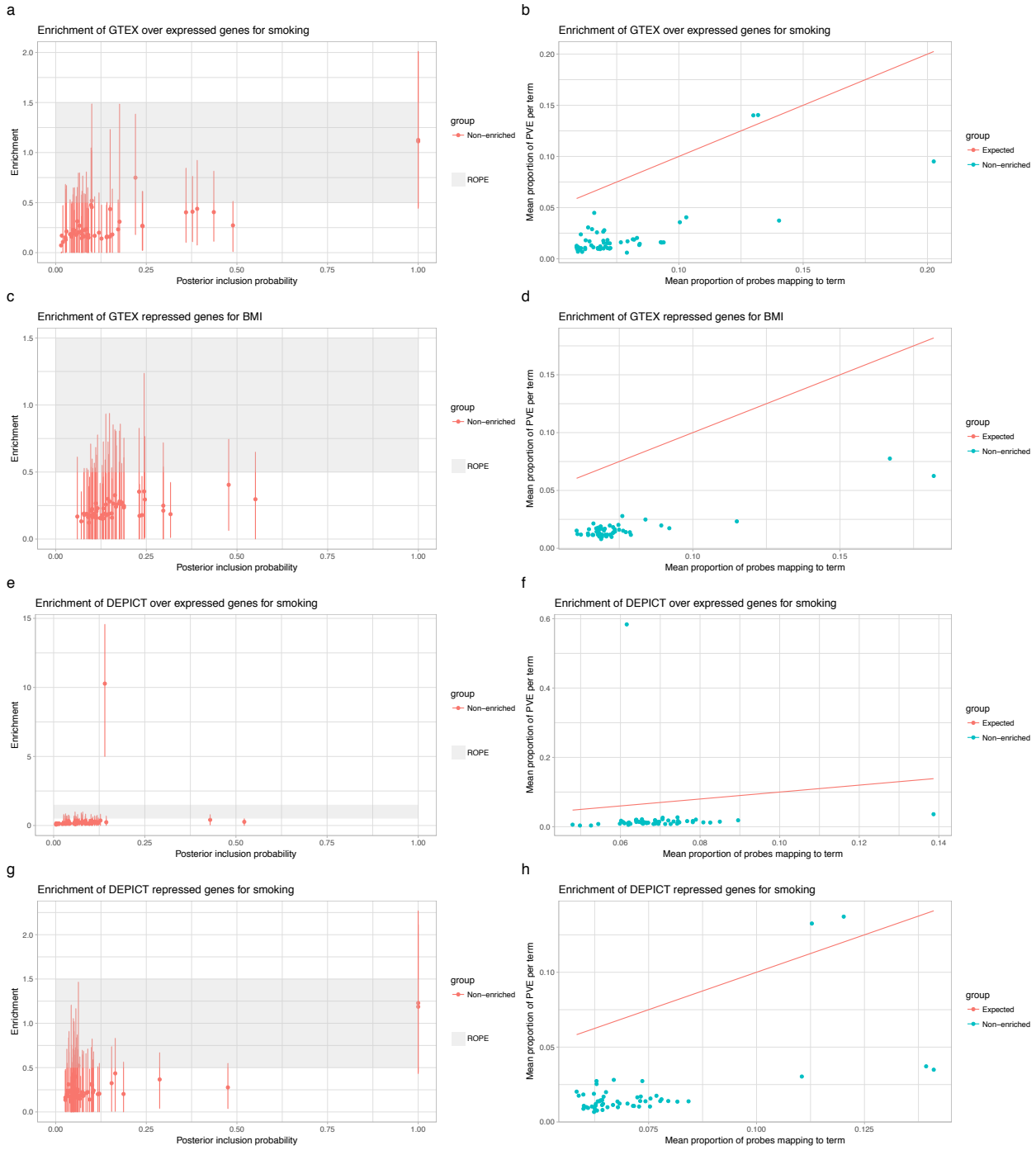

Figure S18. Enrichment analysis for smoking using over expressed(top 99% percentile) and repressed genes (lower 1% percentile) for GTEX and DEPICT

S4 Tables

	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	CI(l)	CI(h)
#Markers in model	5208.00	7869.50	8641.50	8554.57	9408.00	10568.00	6622.00	10231.00
#cpg probes in model	100.00	135.00	144.00	144.75	155.00	190.00	118.00	169.00
#SNP in model	5076.00	7728.50	8504.00	8409.55	9264.00	10418.00	6462.00	10084.00
#SNP in mixture 1	4529.00	7466.00	8326.00	8231.63	9178.75	10401.00	6000.00	9974.00
#SNP in mixture 2	0.00	72.00	161.00	175.68	254.25	698.00	0.00	385.00
#SNP in mixture 3	0.00	0.00	1.00	2.24	3.00	24.00	0.00	8.00
#cpg probes in mixture 1	100.00	134.00	143.00	143.66	153.00	190.00	116.00	168.00
#cpg probes in mixture 2	0.00	0.00	0.00	0.87	1.00	12.00	0.00	3.00
#cpg probes in mixture 3	0.00	0.00	0.00	0.22	0.00	3.00	0.00	1.00
VE(%) SNP	10.63	17.87	19.80	19.89	21.78	29.15	13.69	25.57
VE(%) SNP in mixture 1	6.82	13.96	16.24	16.39	18.68	27.92	9.80	23.01
VE(%) SNP in mixture 2	0.00	1.33	3.16	3.34	4.86	12.37	0.00	7.26
VE(%) SNP in mixture 3	0.00	0.00	0.00	0.13	0.20	1.44	0.00	0.59
VE(%) cpg	57.78	64.54	66.77	66.74	69.02	77.14	59.99	72.80
VE(%) cpg in mixture 1	48.74	61.52	65.68	65.47	69.27	82.40	53.75	77.28
VE(%) cpg in mixture 2	0.00	0.00	0.00	0.44	0.00	10.33	0.00	3.11
VE(%) cpg in mixture 3	0.00	0.00	0.00	0.05	0.00	7.69	0.00	0.00
VE(%) by probes with 95% IP	11.06	15.83	17.03	17.11	18.53	24.69	13.18	21.16
(%) genome	0.17	0.23	0.25	0.25	0.27	0.34	0.20	0.30

Table S1. BMI posterior summary

	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	CI(l)	CI(h)
#Markers in model	1741.00	3392.75	4256.50	4369.35	5312.75	7564.00	2084.00	6577.00
#cpg probes in model	32.00	51.00	59.00	59.05	66.00	99.00	37.00	78.00
#SNP in model	1690.00	3335.75	4197.00	4310.16	5253.75	7501.00	2018.00	6518.00
#SNP in mixture 1	1162.00	2946.25	3899.00	3983.11	5018.25	7312.00	1741.00	6321.00
#SNP in mixture 2	0.00	111.75	262.50	294.36	448.75	1118.00	0.00	660.00
#SNP in mixture 3	0.00	8.00	22.00	32.69	46.00	250.00	0.00	99.00
#cpg probes in mixture 1	27.00	48.00	56.00	56.31	64.00	91.00	35.00	77.00
#cpg probes in mixture 2	0.00	0.00	1.00	1.63	2.00	12.00	0.00	5.00
#cpg probes in mixture 3	0.00	1.00	1.00	1.12	2.00	6.00	0.00	3.00
VE(%) SNP	0.00	0.00	0.27	1.86	3.15	15.73	0.00	7.35
VE(%) SNP in mixture 1	0.00	0.00	0.10	0.81	1.17	8.68	0.00	3.58
VE(%) SNP in mixture 2	0.00	0.00	0.04	0.74	0.93	10.09	0.00	3.99
VE(%) SNP in mixture 3	0.00	0.00	0.02	0.31	0.33	5.47	0.00	1.57
VE(%) cpg	51.91	64.48	67.87	67.68	71.05	80.81	58.41	76.86
VE(%) cpg in mixture 1	11.85	22.36	26.34	26.30	29.98	44.97	15.27	37.10
VE(%) cpg in mixture 2	0.00	0.00	0.00	9.29	8.67	65.60	0.00	46.75
VE(%) cpg in mixture 3	0.00	0.00	0.00	9.39	12.88	69.23	0.00	49.44
VE(%) by probes with 95% IP	20.07	33.56	37.26	37.60	41.03	60.29	27.01	49.50
(%) genome	0.06	0.09	0.11	0.11	0.12	0.19	0.07	0.15

Table S2. Smoking posterior summary

	<5%	5%<50%	50%<95%	>95%
BMI	604180	605	29	10
smoking	587658	60	9	5

Table S3. Number of probes with posterior inclusion probabilities in ranges

	cpg	PIP	symbol	group	alias	entrezid
8123	cg00574958	1.00	CPT1A	5'UTR	CPT1A	1374
47302	cg03546163	1.00	FKBP5	5'UTR	FKBP5	2289
73244	cg05603985	1.00	SKI	1stExon	SKI	6497
83655	cg06500161	1.00	ABCG1	Body	ABCG1	9619
202317	cg16663980	1.00	MNDA	5'UTR	MNDA	4332
218488	cg18181703	1.00	SOCS3	Body	SOCS3	9021
311327	cg26950531	1.00	DPF1	Body	DPF1	8193
47249	cg03541746	0.78	CLSTN1	Body	CLSTN1	22883
164095	cg13478588	0.76	BAT2	Body	PRRC2A	7916
80188	cg06192883	0.75	MYO5C	Body	MYO5C	55930
85406	cg06644515	0.75	SNORD78	TSS200	SNORD78	692198
85407	cg06644515	0.75	SNORD80	TSS1500	SNORD80	26774
85408	cg06644515	0.75	GAS5	Body	GAS5	60674
85409	cg06644515	0.75	SNORD81	TSS1500	SNORD81	26769
85410	cg06644515	0.75	SNORD79	TSS1500	SNORD79	26770
85411	cg06644515	0.75	SNORD47	TSS1500	SNORD47	26802
182583	cg14870271	0.75	LGALS3BP	1stExon	LGALS3BP	3959
271841	cg23320499	0.75	DUSP16	Body	DUSP16	80824
52360	cg03940776	0.72	SYNJ2	Body	SYNJ2	8871
71624	cg05468843	0.69	IL10RA	Body	IL10RA	3587
155324	cg12648759	0.67	ATF6	Body	ATF6	22926
189751	cg15564619	0.64	SKI	Body	SKI	6497
296902	cg25648203	0.63	AHRR	Body	AHRR	57491
137501	cg11024682	0.60	SREBF1	Body	SREBF1	6720
117159	cg09238801	0.59	PNMA1	1stExon	PNMA1	9240
78192	cg06012428	0.58	ARID1B	Body	ARID1B	57492
27479	cg02043791	0.57	FGFR1	5'UTR	FGFR1	2260
280171	cg24088496	0.56	MAML2	Body	MAML2	84441
199041	cg16398761	0.55	C14orf43	5'UTR	ELMSAN1	91748
120843	cg09554443	0.53	CD247	1stExon	CD247	919
160053	cg13123009	0.51	LY6G6D	TSS1500	LY6G6D	58530
160054	cg13123009	0.51	LY6G6E	TSS200	LY6G6E	79136
36543	cg02714303	0.50	LMO7	TSS200	LMO7	4008
132625	cg10581837	0.50	LMO7	TSS200	LMO7	4008
193906	cg15939920	0.50	ACACA	Body	ACACA	31
228934	cg19169154	0.50	MFAP4	Body	MFAP4	4239
86902	cg06760830	0.50	MOBKL2C	Body	MOB3C	148932
189822	cg15571561	0.47	ARPP-21	5'UTR	ARPP21	10777
72893	cg05575921	0.46	AHRR	Body	AHRR	57491
112896	cg08857797	0.44	VPS25	Body	VPS25	84313
60070	cg04535521	0.43	GABRP	TSS1500	GABRP	2568
279229	cg24009074	0.39	NAPA	Body	NAPA	8775
60187	cg04546097	0.39	HGD	1stExon	HGD	3081
13418	cg00968616	0.39	CUEDC1	3'UTR	CUEDC1	404093
201062	cg16565294	0.38	TMX1	Body	TMX1	81542
141370	cg11376147	0.37	SLC43A1	Body	SLC43A1	8501
229229	cg19202384	0.36	PYCR1	Body	PYCR1	5831
77961	cg05991220	0.35	ITIH1	TSS200	ITIH1	3697
180130	cg14660446	0.34	NAPA	Body	NAPA	8775
21654	cg01593673	0.33	HOXB3	5'UTR	HOXB3	3213
278099	cg23919844	0.33	ARHGEF7	Body	ARHGEF7	8874

315271	cg27309702	0.33	KIFC3	3'UTR	KIFC3	3801
173873	cg14195216	0.31	ANKS1B	TSS1500	ANKS1B	56899
314105	cg27203924	0.31	ADAMTS9	Body	ADAMTS9	56999
286696	cg24687805	0.30	RAB27A	Body	RAB27A	5873
100757	cg07839457	0.29	NLRC5	TSS1500	NLRC5	84166
154363	cg12571570	0.29	ZEB2	Body	ZEB2	9839
289209	cg24910161	0.28	GSDMA	TSS200	GSDMA	284110
248992	cg21113478	0.28	DCLK3	TSS1500	DCLK3	85443
100596	cg07826387	0.28	CHRM3	Body	CHRM3	1131
267034	cg22884440	0.28	ASAP1	Body	ASAP1	50807
318020	cg27554156	0.27	GSG1	Body	GSG1	83445
176726	cg14410503	0.26	TNS3	Body	TNS3	64759
202290	cg16662477	0.26	RFFL	5'UTR	RFFL	117584
144815	cg11704631	0.25	RUNX1	Body	RUNX1	861
214557	cg17836177	0.25	PEBP4	Body	PEBP4	157310
215706	cg17942763	0.25	SKI	Body	SKI	6497
239464	cg20146909	0.25	LRRC8D	5'UTR	LRRC8D	55144
108086	cg08447387	0.25	ASAP1	Body	ASAP1	50807
49227	cg03691549	0.25	TENC1	5'UTR	TNS2	23371
48539	cg03636183	0.25	F2RL3	Body	F2RL3	9002
272572	cg23384027	0.24	NFE2	Body	NFE2	4778
252549	cg21468274	0.24	TMEM102	Body	TMEM102	284114
139862	cg11236746	0.23	GLB1	Body	GLB1	2720
169031	cg13844237	0.22	MAPKAP1	Body	MAPKAP1	79109
152051	cg12358527	0.21	BCAS3	Body	BCAS3	54828
49666	cg03725309	0.20	SARS	Body	SARS	6301
114965	cg09039672	0.20	ACVR1B	Body	ACVR1B	91
150676	cg12216054	0.20	ZBTB9	Body	ZBTB9	221504
4453	cg00318947	0.20	HOXA3	5'UTR	HOXA3	3200
166891	cg13680388	0.20	GNAS	Body	GNAS	2778
198683	cg16365807	0.19	BACE2	Body	BACE2	25825
252984	cg21507987	0.19	AMPD3	3'UTR	AMPD3	272
310978	cg26921611	0.19	EIF4EBP1	3'UTR	EIF4EBP1	1978
116024	cg09138671	0.18	TMCO4	5'UTR	TMCO4	255104
16575	cg01199327	0.18	CD82	Body	CD82	3732
37452	cg02780017	0.18	SLC22A20	TSS200	SLC22A20P	440044
132827	cg10596609	0.18	UGT1A8	TSS1500	UGT1A8	54576
53215	cg04006327	0.17	ATG16L2	Body	ATG16L2	89849
104312	cg08135379	0.17	AMIGO2	TSS1500	AMIGO2	347902
72799	cg05568797	0.16	BHLHE41	Body	BHLHE41	79365
108433	cg08472795	0.16	HS6ST1	Body	HS6ST1	9394
114151	cg08958168	0.16	SLC12A4	Body	SLC12A4	6560
303178	cg26253134	0.16	TGFA	Body	TGFA	7039
63986	cg04858631	0.15	DDIT4	3'UTR	DDIT4	54541
309971	cg26841040	0.15	GUK1	TSS200	GUK1	2987
24683	cg01831904	0.14	LRRC37B2	Body	LRRC37BP1	147172
313550	cg27153059	0.14	TMEM86A	TSS1500	TMEM86A	144110
200256	cg16500874	0.14	LETM1	Body	LETM1	3954
82942	cg06437430	0.14	NKD2	Body	NKD2	85409
130324	cg10381071	0.14	TLE3	TSS1500	TLE3	7090
216332	cg18004701	0.14	PTPRN2	Body	PTPRN2	5799
213527	cg17741339	0.14	ESR1	5'UTR	ESR1	2099

318414	cg27588321	0.13	CYLD	TSS1500	CYLD	1540
138174	cg11087049	0.13	NIN	5'UTR	NIN	51199
42461	cg03162314	0.13	CTU1	3'UTR	CTU1	90353
301103	cg26066277	0.13	DYSFIP1	1stExon	PPP1R27	116729
60942	cg04604050	0.12	SYNPO	Body	SYNPO	11346
175684	cg14323854	0.12	ZNF177	TSS1500	ZNF177	7730
40490	cg03010301	0.12	MIR125A	TSS1500	MIR125A	406910
40491	cg03010301	0.12	MIR99B	TSS1500	MIR99B	407056
40492	cg03010301	0.12	MIRLET7E	TSS1500	MIRLET7E	406887
40493	cg03010301	0.12	NCRNA00085	TSS1500	SPACA6	147650
206049	cg17024258	0.12	VANGL2	5'UTR	VANGL2	57216
86442	cg06728793	0.12	PRKAR1B	Body	PRKAR1B	5575
127850	cg10169539	0.12	NIN	5'UTR	NIN	51199
166132	cg13624385	0.12	PCDH7	TSS200	PCDH7	5099
268588	cg23032421	0.12	IL5RA	5'UTR	IL5RA	3568
73879	cg05655915	0.11	NARF	TSS1500	NARF	26502
299449	cg25919221	0.11	CA6	Body	CA6	765
126192	cg10028434	0.11	KLC1	Body	KLC1	3831
35143	cg02612927	0.11	DEFB124	TSS200	DEFB124	245937
253461	cg21550372	0.11	WDR25	Body	WDR25	79446
121198	cg09581649	0.11	C16orf5	5'UTR	CDIP1	29965
232335	cg19502457	0.11	GPX2	1stExon	GPX2	2877
153632	cg12499235	0.11	ASCL2	TSS1500	ASCL2	430
192769	cg15833940	0.11	DLGAP2	Body	DLGAP2	9228
111218	cg08711064	0.10	RASA1	1stExon	RASA1	5921
54750	cg04125273	0.10	ZG16	Body	ZG16	653808
134402	cg10738119	0.10	YWHAG	3'UTR	YWHAG	7532
44875	cg03358113	0.10	MAD1L1	Body	MAD1L1	8379
92999	cg07217499	0.10	CACNA1C	Body	CACNA1C	775
182945	cg14906103	0.10	TMEM33	TSS1500	TMEM33	55161
285220	cg24550026	0.10	BCL2L15	1stExon	BCL2L15	440603
290230	cg25006231	0.10	C10orf41	Body	ZNF503-AS2	100131213
226305	cg18896032	0.10	SSRP1	Body	SSRP1	6749
295293	cg25496297	0.10	MYO18A	Body	MYO18A	399687
88952	cg06914133	0.09	SAMD4A	Body	SAMD4A	23034
122791	cg09728393	0.09	KIF13A	Body	KIF13A	63971
232304	cg19499748	0.09	TRIL	5'UTR	TRIL	9865
243115	cg20525527	0.09	MPRIP	Body	MPRIP	23164
28966	cg02154448	0.09	OVGP1	Body	OVGP1	5016
117237	cg09245872	0.09	DOC2A	3'UTR	DOC2A	8448
117238	cg09245872	0.09	INO80E	3'UTR	INO80E	283899
224499	cg18734095	0.09	NOSIP	Body	NOSIP	51070
30290	cg02257517	0.09	SLC2A6	Body	SLC2A6	11182
49575	cg03719040	0.09	TMEM128	TSS1500	TMEM128	85013
30438	cg02268192	0.09	RIN3	Body	RIN3	79890
183696	cg14978174	0.09	TIPARP	TSS1500	TIPARP	25976
24805	cg01839993	0.09	DDIT4	Body	DDIT4	54541
179488	cg14609407	0.09	SLPI	1stExon	SLPI	6590
168842	cg13828047	0.09	MPI	TSS1500	MPI	4351
302185	cg26160945	0.09	STK38L	TSS1500	STK38L	23012
24042	cg01787285	0.08	SKI	Body	SKI	6497
238199	cg20018057	0.08	GNAS	3'UTR	GNAS	2778

291873	cg25158622	0.08	BRD2	Body	BRD2	6046
269400	cg23097139	0.08	SNUPN	TSS1500	SNUPN	10073
88447	cg06876354	0.08	RALB	5'UTR	RALB	5899
235263	cg19759478	0.08	C1orf183	Body	FAM212B	55924
14213	cg01024458	0.08	RERE	Body	RERE	473
144156	cg11649376	0.08	ACSS3	Body	ACSS3	79611
301889	cg26134737	0.08	DIP2C	Body	DIP2C	22982
247406	cg20961940	0.08	SLC44A4	Body	SLC44A4	80736
3975	cg00285294	0.08	C7orf50	Body	C7orf50	84310
130104	cg10363549	0.08	FAM190A	3'UTR	CCSER1	401145
215898	cg17961943	0.08	PLB1	Body	PLB1	151056
75682	cg05806375	0.08	ERAP1	TSS200	ERAP1	51752
5088	cg00363312	0.07	HIPK2	Body	HIPK2	28996
225627	cg18835596	0.07	MYB	3'UTR	MYB	4602
275765	cg23685712	0.07	CYP24A1	1stExon	CYP24A1	1591
275750	cg23684682	0.07	ZNF30	5'UTR	ZNF30	90075
247745	cg20991801	0.07	CDK13	1stExon	CDK13	8621
148173	cg11992736	0.07	IL12RB1	Body	IL12RB1	3594
178602	cg14547895	0.07	PKNOX2	5'UTR	PKNOX2	63876
46638	cg03498559	0.07	UGT2B4	1stExon	UGT2B4	7363
111408	cg08726900	0.07	ANKRD11	5'UTR	ANKRD11	29123
190687	cg15643574	0.07	PICALM	Body	PICALM	8301
207122	cg17124844	0.07	DLGAP2	Body	DLGAP2	9228
277975	cg23909013	0.07	KCNJ6	TSS1500	KCNJ6	3763
302267	cg26168117	0.07	MDN1	3'UTR	MDN1	23195
11170	cg00799631	0.06	TNRC18	Body	TNRC18	84629
283613	cg24410469	0.06	AGAP1	Body	AGAP1	116987
34922	cg02595681	0.06	ZNF215	TSS1500	ZNF215	7762
39636	cg02949469	0.06	PNKD	1stExon	PNKD	25953
39637	cg02949469	0.06	AAMP	TSS1500	AAMP	14
112938	cg08861449	0.06	CSMD2	3'UTR	CSMD2	114784
269770	cg23137881	0.06	C4orf45	Body	C4orf45	152940
84460	cg06568880	0.06	SMG6	Body	SMG6	23293
204181	cg16828491	0.06	SH3TC1	Body	SH3TC1	54436
297748	cg25736198	0.06	TPH2	Body	TPH2	121278
167343	cg13711063	0.06	KCNJ8	3'UTR	KCNJ8	3764
225593	cg18832247	0.06	JARID2	Body	JARID2	3720
203106	cg16725642	0.06	EPHB4	Body	EPHB4	2050
203751	cg16786297	0.06	SDCBP2	3'UTR	SDCBP2	27111
231754	cg19445335	0.06	ADAP1	Body	ADAP1	11033
74099	cg05670596	0.06	CCRL2	TSS1500	CCRL2	9034
126644	cg10069470	0.06	C5orf30	5'UTR	C5orf30	90355
198521	cg16352321	0.06	TP53INP2	3'UTR	TP53INP2	58476
9594	cg00684043	0.06	DNASE1L2	3'UTR	DNASE1L2	1775
13937	cg01004980	0.06	PRKAR2A	Body	PRKAR2A	5576
171719	cg14034270	0.06	MEG3	TSS1500	MEG3	55384
189013	cg15488009	0.06	FSTL3	Body	FSTL3	10272
96748	cg07525299	0.06	ASCL2	TSS1500	ASCL2	430
124924	cg09914675	0.06	SEPX1	1stExon	MSRB1	51734
182141	cg14836313	0.06	MRPL23	Body	MRPL23	6150
277356	cg23850913	0.06	JARID2	Body	JARID2	3720
245804	cg20784591	0.05	PILRA	Body	PILRA	29992

164629	cg13520520	0.05	ECSIT	3'UTR	ECSIT	51295
164630	cg13520520	0.05	ZNF653	TSS1500	ZNF653	115950
278162	cg23925173	0.05	RASAL1	3'UTR	RASAL1	8437
109487	cg08561775	0.05	UBE2O	Body	UBE2O	63893
286590	cg24681499	0.05	FOXJ3	Body	FOXJ3	22887
237319	cg19936912	0.05	FAM160A1	TSS1500	FAM160A1	729830
283498	cg24401026	0.05	MAP7	Body	MAP7	9053
314602	cg27253454	0.05	USP43	Body	USP43	124739

Table S4. Probes with IP $>$ 5% for BMI

	cpg	PIP	symbol	group	alias	entrezid
48539	cg03636183	1.00	F2RL3	Body	F2RL3	9002
72893	cg05575921	1.00	AHRR	Body	AHRR	57491
224710	cg18754985	1.00	CLDND1	Body	CLDND1	56650
129621	cg10321266	0.91	MBNL1	5'UTR	MBNL1	4154
140769	cg11321090	0.89	ZFYVE28	Body	ZFYVE28	57732
132514	cg10573386	0.84	CELSR3	TSS200	CELSR3	1951
139459	cg11207515	0.83	CNTNAP2	Body	CNTNAP2	26047
153879	cg12524061	0.67	SDR9C7	TSS1500	SDR9C7	121214
175434	cg14305420	0.65	NOXA1	Body	NOXA1	10811
192021	cg15763258	0.56	FLI1	TSS1500	FLI1	2313
155345	cg12651044	0.46	APH1A	TSS200	APH1A	51107
97753	cg07597069	0.45	PLEC1	Body	PLEC	5339
305460	cg26450010	0.45	ABHD8	Body	ABHD8	79575
117421	cg09256832	0.36	SPSB1	5'UTR	SPSB1	80176
68570	cg05218653	0.31	ABCA3	Body	ABCA3	21
244423	cg20661303	0.31	LEFTY2	TSS1500	LEFTY2	7044
49424	cg03707168	0.30	PPP1R15A	Body	PPP1R15A	23645
223203	cg18607609	0.23	IQGAP2	TSS1500	IQGAP2	10788
67319	cg05119988	0.21	SC4MOL	5'UTR	MSMO1	6307
229657	cg19246197	0.20	USP2	Body	USP2	9099
80786	cg06241380	0.19	CTCF	TSS1500	CTCF	10664
138134	cg11084015	0.16	OSBPL10	Body	OSBPL10	114884
143182	cg11560197	0.15	PCDHA3	1stExon	PCDHA3	56145
143183	cg11560197	0.15	PCDHA1	Body	PCDHA1	56147
143184	cg11560197	0.15	PCDHA2	Body	PCDHA2	56146
217745	cg18119192	0.15	GATA4	Body	GATA4	2626
199041	cg16398761	0.14	C14orf43	5'UTR	ELMSAN1	91748
95978	cg07468289	0.14	NCRNA00171	TSS1500	ZNRD1ASP	80862
95979	cg07468289	0.14	ZNRD1	Body	ZNRD1	30834
261719	cg22371743	0.13	MATN1	Body	MATN1	4146
135796	cg10861146	0.13	EFNA1	TSS1500	EFNA1	1942
281164	cg24169820	0.12	CAMKK2	Body	CAMKK2	10645
160873	cg13209613	0.11	WNT3	Body	WNT3	7473
173423	cg14163311	0.11	RASSF5	Body	RASSF5	83593
236825	cg19895882	0.10	KIAA0564	Body	VWA8	23078
223693	cg18654464	0.10	MIR1227	Body	MIR1227	100302283
223694	cg18654464	0.10	PLEKHJ1	Body	PLEKHJ1	55111
245612	cg20764780	0.09	PTPRN2	Body	PTPRN2	5799
95557	cg07435237	0.07	ARMC5	TSS1500	ARMC5	79798
185843	cg15164708	0.07	SLC17A7	Body	SLC17A7	57030
37002	cg02746869	0.07	VIM	Body	VIM	7431
176229	cg14371731	0.07	ZMIZ1	Body	ZMIZ1	57178
309591	cg26813561	0.07	ACAD10	Body	ACAD10	80724
18941	cg01389283	0.07	UBQLNL	TSS1500	UBQLNL	143630
108347	cg08466269	0.07	DHRS12	Body	DHRS12	79758
94457	cg07339236	0.06	ATP9A	Body	ATP9A	10079
147135	cg11897145	0.06	ETV1	5'UTR	ETV1	2115
196297	cg16163140	0.06	ADAMTS16	Body	ADAMTS16	170690
316610	cg27425996	0.06	COBL	Body	COBL	23242
170690	cg13967864	0.06	NCBP1	1stExon	NCBP1	4686
170691	cg13967864	0.06	TSTD2	TSS200	TSTD2	158427

192934	cg15847614	0.06	FAM64A	5'UTR	PIMREG	54478
211054	cg17480760	0.06	CA3	TSS200	CA3	761
100013	cg07782603	0.06	GALNT9	Body	GALNT9	50614
110477	cg08647039	0.06	NFIX	Body	NFIX	4784
200001	cg16476048	0.06	C10orf122	TSS1500	TEX36	387718
57912	cg04367503	0.05	NFIX	Body	NFIX	4784
65751	cg04992150	0.05	NUP210	Body	NUP210	23225
163182	cg13415795	0.05	SH2D7	3'UTR	SH2D7	646892
238783	cg20077343	0.05	MUC6	Body	MUC6	4588
243459	cg20560182	0.05	TAF7	TSS200	TAF7	6879

Table S5. Probes with IP $> 5\%$ for smoking

	Term	P.DE
GO:0032365	intracellular lipid transport	0.00
GO:0009720	detection of hormone stimulus	0.00
GO:0034437	glycoprotein transporter activity	0.00
GO:0034041	sterol-transporting ATPase activity	0.00
GO:1990698	positive regulation of cytosolic calcium ion...	0.00
GO:0055099	response to high density lipoprotein particle	0.00
GO:0034040	lipid-transporting ATPase activity	0.00
GO:0009726	detection of endogenous stimulus	0.00
GO:0046811	histone deacetylase inhibitor activity	0.00
GO:0045834	positive regulation of lipid metabolic process	0.00

Table S6. GO enrichment for the probes with 95%IP in BMI

	Term	P.DE
GO:0015057	thrombin-activated receptor activity	0.00
GO:0060155	platelet dense granule organization	0.00
GO:0070493	thrombin-activated receptor signaling pathway	0.00
GO:0035025	positive regulation of Rho protein signal transduction	0.00
GO:0051482	positive regulation of cytosolic calcium ...	0.00
GO:0033363	secretory granule organization	0.01
GO:0051281	positive regulation of release of ...	0.01
GO:0010524	positive regulation of calcium ion ...	0.01
GO:0046579	positive regulation of Ras protein signal transduction	0.01
GO:0001191	transcriptional repressor activity, RNA polymerase II ...	0.01

Table S7. GO enrichment for the probes with 95%IP in smoking

	tissue	mean_pprobes	mean_pve	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	CI(l)	CI(h)	ROPE	prob	group
1	Adipose_Subcutaneous	0.03	0.01	0.00	0.11	0.25	0.34	0.47	1.44	0.00	0.92	0.05	0.20	Non-enriched
2	Adipose_Visceral_.Omentum.	0.03	0.03	0.18	0.93	1.24	1.28	1.59	3.08	0.40	2.22	0.27	0.41	Non-enriched
3	Adrenal_Gland	0.03	0.05	0.14	1.00	1.53	1.68	2.18	4.96	0.30	3.61	0.30	0.70	Non-enriched
4	Artery_Aorta	0.03	0.02	0.00	0.33	0.65	0.68	0.96	2.44	0.00	1.49	0.26	0.45	Non-enriched
5	Artery_Coronary	0.03	0.02	0.01	0.41	0.66	0.70	0.96	1.89	0.04	1.38	0.31	0.50	Non-enriched
6	Artery_Tibial	0.03	0.01	0.00	0.17	0.32	0.39	0.56	1.54	0.00	0.95	0.11	0.35	Non-enriched
7	Bladder	0.03	0.01	0.00	0.33	0.50	0.54	0.70	1.32	0.00	1.12	0.12	0.23	Non-enriched
8	Brain_Amygdala	0.04	0.04	0.02	0.75	0.99	1.03	1.26	2.66	0.29	1.75	0.82	1.00	Non-enriched
9	Brain_Anterior_cingulate_cortex_.BA24.	0.04	0.04	0.02	0.74	0.97	1.02	1.26	2.52	0.32	1.75	0.82	1.00	Non-enriched
10	Brain_Caudate_.basal_ganglia.	0.04	0.04	0.17	0.80	1.02	1.06	1.29	2.86	0.33	1.75	0.82	1.00	Non-enriched
11	Brain_Cerebellar_Hemisphere	0.03	0.01	0.00	0.08	0.20	0.29	0.43	1.64	0.00	0.87	0.04	0.24	Non-enriched
12	Brain_Cerebellum	0.03	0.01	0.00	0.07	0.17	0.23	0.32	1.36	0.00	0.63	0.03	0.22	Non-enriched
13	Brain_Cortex	0.04	0.04	0.02	0.75	0.98	1.03	1.26	2.52	0.32	1.75	0.82	1.00	Non-enriched
14	Brain_Frontal_Cortex_.BA9.	0.04	0.04	0.02	0.75	0.97	1.02	1.26	2.52	0.33	1.75	0.82	1.00	Non-enriched
15	Brain_Hippocampus	0.05	0.04	0.02	0.73	0.97	1.01	1.25	2.52	0.32	1.75	0.82	1.00	Non-enriched
16	Brain_Hypothalamus	0.04	0.04	0.02	0.76	0.99	1.04	1.26	2.86	0.29	1.79	0.82	1.00	Non-enriched
17	Brain_Nucleus_accumbens_.basal_ganglia.	0.05	0.04	0.02	0.76	0.97	1.01	1.22	2.52	0.35	1.69	0.85	1.00	Non-enriched
18	Brain_Putamen_.basal_ganglia.	0.04	0.04	0.17	0.79	1.00	1.04	1.24	2.52	0.46	1.75	0.86	1.00	Non-enriched
19	Brain_Spinal_cord_.cervical_c.1.	0.04	0.04	0.00	0.63	0.99	1.04	1.41	3.00	0.00	2.06	0.33	0.54	Non-enriched
20	Brain_Substantia_nigra	0.03	0.02	0.00	0.33	0.59	0.66	0.94	2.47	0.00	1.53	0.23	0.44	Non-enriched
21	Breast_Mammary_Tissue	0.03	0.03	0.00	0.54	0.94	0.93	1.25	2.90	0.10	1.83	0.29	0.45	Non-enriched
22	Cells_EBV.transformed_lymphocytes	0.03	0.01	0.00	0.10	0.19	0.29	0.41	1.47	0.00	0.95	0.02	0.13	Non-enriched
23	Cells_Transformed_fibroblasts	0.03	0.01	0.00	0.10	0.21	0.29	0.40	1.21	0.00	0.89	0.04	0.24	Non-enriched
24	Cervix_Ectocervix	0.03	0.01	0.00	0.13	0.27	0.32	0.45	1.03	0.00	0.84	0.03	0.17	Non-enriched
25	Cervix_Endocervix	0.03	0.01	0.00	0.13	0.26	0.30	0.42	1.05	0.00	0.85	0.02	0.17	Non-enriched
26	Colon_Sigmoid	0.08	0.07	0.00	0.18	0.41	0.60	0.79	3.61	0.00	1.80	0.14	0.44	Non-enriched
27	Colon_Transverse	0.04	0.03	0.00	0.26	0.59	0.69	1.02	3.16	0.00	1.68	0.10	0.23	Non-enriched
28	Esophagus_Gastroesophageal_Junction	0.04	0.02	0.00	0.36	0.56	0.65	0.87	2.54	0.00	1.50	0.31	0.60	Non-enriched
29	Esophagus_Mucosa	0.03	0.00	0.00	0.06	0.14	0.17	0.26	0.64	0.00	0.53	0.00	0.07	Non-enriched
30	Esophagus_Muscularis	0.04	0.02	0.00	0.27	0.47	0.52	0.73	1.99	0.00	1.19	0.22	0.48	Non-enriched
31	Fallopian_Tube	0.03	0.04	0.33	1.04	1.34	1.44	1.75	3.98	0.60	2.63	0.25	0.42	Non-enriched
32	Heart_Atrial_Appendage	0.03	0.02	0.00	0.18	0.40	0.50	0.80	1.58	0.00	1.29	0.06	0.15	Non-enriched
33	Heart_Left_Ventricle	0.03	0.01	0.00	0.14	0.28	0.34	0.48	1.56	0.00	0.88	0.04	0.17	Non-enriched
34	Kidney_Cortex	0.03	0.00	0.00	0.05	0.11	0.15	0.23	0.69	0.00	0.41	0.00	0.09	Non-enriched
35	Liver	0.04	0.05	0.00	1.00	1.35	1.37	1.78	3.54	0.00	2.30	0.21	0.43	Non-enriched
36	Lung	0.03	0.02	0.00	0.25	0.58	0.77	1.11	2.86	0.00	2.07	0.09	0.24	Non-enriched
37	Minor_Salivary_Gland	0.04	0.04	0.01	0.62	0.90	0.96	1.28	2.90	0.07	1.85	0.22	0.32	Non-enriched
38	Muscle_Skeletal	0.03	0.01	0.00	0.12	0.24	0.33	0.46	1.81	0.00	0.96	0.05	0.26	Non-enriched
39	Nerve_Tibial	0.05	0.03	0.00	0.22	0.49	0.54	0.82	1.89	0.00	1.28	0.14	0.30	Non-enriched
40	Ovary	0.03	0.01	0.00	0.09	0.21	0.24	0.32	0.76	0.00	0.63	0.02	0.15	Non-enriched
41	Pancreas	0.03	0.02	0.00	0.52	0.82	0.86	1.16	2.46	0.01	1.77	0.20	0.30	Non-enriched
42	Pituitary	0.05	0.03	0.00	0.31	0.54	0.60	0.85	1.77	0.00	1.37	0.21	0.40	Non-enriched
43	Prostate	0.03	0.01	0.00	0.13	0.32	0.38	0.58	1.29	0.00	1.03	0.04	0.12	Non-enriched
44	Skin_Not_Sun_Exposed_.Suprapubic.	0.03	0.01	0.00	0.23	0.46	0.48	0.71	1.43	0.00	1.03	0.08	0.16	Non-enriched
45	Skin_Sun_Exposed_.Lower_leg.	0.03	0.01	0.00	0.27	0.46	0.48	0.67	1.43	0.00	0.95	0.09	0.21	Non-enriched
46	Small_Intestine_Terminal_Ileum	0.03	0.01	0.01	0.21	0.40	0.49	0.71	1.73	0.01	1.23	0.05	0.14	Non-enriched
47	Spleen	0.03	0.02	0.07	0.49	0.76	0.80	1.09	2.31	0.18	1.52	0.26	0.37	Non-enriched
48	Stomach	0.03	0.01	0.00	0.12	0.26	0.31	0.44	0.95	0.00	0.77	0.02	0.13	Non-enriched
49	Testis	0.03	0.04	0.00	0.84	1.24	1.28	1.76	3.48	0.00	2.46	0.14	0.30	Non-enriched
50	Thyroid	0.03	0.01	0.00	0.06	0.20	0.25	0.37	1.15	0.00	0.83	0.02	0.13	Non-enriched
51	Uterus	0.03	0.01	0.00	0.17	0.31	0.36	0.48	1.68	0.00	0.91	0.06	0.26	Non-enriched
52	Vagina	0.03	0.01	0.00	0.10	0.23	0.25	0.31	1.06	0.00	0.62	0.01	0.06	Non-enriched
53	Whole_Blood	0.03	0.04	0.24	0.92	1.38	1.53	2.01	3.96	0.47	3.17	0.26	0.49	Non-enriched

Table S8. Enrichment summary of over-expressed genes in GTEx for BMI

	tissue	mean_pprobes	mean_pve	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	CI(l)	CI(h)	ROPE	prob	group
1	Adipose_Subcutaneous	0.04	0.04	0.09	0.79	1.07	1.15	1.46	3.33	0.22	2.06	0.54	0.77	Non-enriched
2	Adipose_Visceral_.Omentum.	0.04	0.04	0.22	0.75	1.01	1.08	1.34	3.15	0.27	1.96	0.56	0.74	Non-enriched
3	Adrenal_Gland	0.05	0.04	0.00	0.50	0.76	0.81	1.07	2.82	0.00	1.67	0.55	0.81	Non-enriched
4	Artery_Aorta	0.03	0.01	0.00	0.20	0.37	0.41	0.58	1.22	0.00	0.92	0.12	0.35	Non-enriched
5	Artery_Coronary	0.04	0.04	0.00	0.34	0.66	0.96	1.35	5.05	0.00	2.86	0.27	0.64	Non-enriched
6	Artery_Tibial	0.03	0.01	0.00	0.14	0.30	0.34	0.49	1.11	0.00	0.84	0.09	0.37	Non-enriched
7	Bladder	0.04	0.04	0.28	0.85	1.13	1.18	1.44	3.19	0.40	2.10	0.69	0.90	Non-enriched
8	Brain_Amygdala	0.04	0.02	0.00	0.19	0.40	0.53	0.75	2.57	0.00	1.44	0.16	0.45	Non-enriched
9	Brain_Anterior_cingulate_cortex_.BA24.	0.04	0.02	0.00	0.21	0.45	0.58	0.81	2.67	0.00	1.55	0.19	0.47	Non-enriched
10	Brain_Caudate_.basal_ganglia.	0.03	0.01	0.00	0.16	0.37	0.43	0.63	1.94	0.00	1.02	0.15	0.41	Non-enriched
11	Brain_Cerebellar_Hemisphere	0.04	0.07	0.51	1.35	1.91	1.99	2.48	4.81	0.61	3.54	0.25	0.81	Non-enriched
12	Brain_Cerebellum	0.03	0.01	0.00	0.12	0.28	0.39	0.53	2.25	0.00	1.04	0.08	0.33	Non-enriched
13	Brain_Cortex	0.04	0.02	0.00	0.24	0.49	0.64	0.88	2.74	0.00	1.80	0.19	0.45	Non-enriched
14	Brain_Frontal_Cortex_.BA9.	0.04	0.02	0.00	0.24	0.47	0.59	0.81	2.74	0.00	1.60	0.21	0.51	Non-enriched
15	Brain_Hippocampus	0.04	0.02	0.00	0.30	0.51	0.59	0.81	2.57	0.00	1.38	0.28	0.59	Non-enriched
16	Brain_Hypothalamus	0.03	0.02	0.00	0.19	0.44	0.58	0.84	2.74	0.00	1.63	0.16	0.41	Non-enriched
17	Brain_Nucleus_accumbens_.basal_ganglia.	0.04	0.02	0.00	0.18	0.46	0.60	0.87	2.74	0.00	1.66	0.18	0.45	Non-enriched
18	Brain_Putamen_.basal_ganglia.	0.04	0.02	0.00	0.16	0.42	0.57	0.84	2.74	0.00	1.62	0.18	0.45	Non-enriched
19	Brain_Spinal_cord_.cervical_c.1.	0.04	0.07	0.58	1.39	1.88	1.99	2.50	4.81	0.70	3.54	0.27	0.87	Non-enriched
20	Brain_Substantia_nigra	0.04	0.02	0.00	0.45	0.64	0.70	0.92	2.57	0.00	1.39	0.41	0.64	Non-enriched
21	Breast_Mammary_Tissue	0.06	0.06	0.09	0.73	1.04	1.10	1.44	3.40	0.23	2.11	0.49	0.74	Non-enriched
22	Cells_EBV.transformed_lymphocytes	0.05	0.05	0.00	0.62	1.02	1.13	1.55	3.41	0.00	2.45	0.41	0.74	Non-enriched
23	Cells_Transformed_fibroblasts	0.06	0.25	1.17	3.16	3.91	4.11	4.80	11.26	1.70	6.85	0.00	1.00	Enriched
24	Cervix_Ectocervix	0.03	0.01	0.00	0.09	0.21	0.30	0.40	1.63	0.00	1.06	0.04	0.20	Non-enriched
25	Cervix_Endocervix	0.03	0.03	0.11	0.76	1.05	1.12	1.40	2.83	0.42	2.26	0.50	0.66	Non-enriched
26	Colon_Sigmoid	0.04	0.06	0.24	0.90	1.21	1.36	1.71	4.78	0.40	2.68	0.54	0.86	Non-enriched
27	Colon_Transverse	0.04	0.02	0.00	0.38	0.64	0.65	0.89	2.05	0.06	1.34	0.37	0.60	Non-enriched
28	Esophagus_Gastroesophageal_Junction	0.05	0.05	0.17	0.89	1.22	1.26	1.57	3.21	0.32	2.24	0.61	0.90	Non-enriched
29	Esophagus_Mucosa	0.03	0.01	0.00	0.13	0.30	0.39	0.54	1.87	0.00	1.06	0.07	0.26	Non-enriched
30	Esophagus_Muscularis	0.04	0.04	0.12	0.85	1.16	1.22	1.52	3.21	0.38	2.26	0.62	0.89	Non-enriched
31	Fallopian_Tube	0.04	0.05	0.17	0.84	1.19	1.25	1.58	3.51	0.35	2.36	0.45	0.69	Non-enriched
32	Heart_Atrial_Appendage	0.03	0.01	0.00	0.15	0.29	0.32	0.44	1.23	0.00	0.75	0.05	0.30	Non-enriched
33	Heart_Left_Ventricle	0.04	0.02	0.00	0.22	0.39	0.41	0.56	1.76	0.00	0.87	0.13	0.39	Non-enriched
34	Kidney_Cortex	0.04	0.02	0.00	0.15	0.36	0.45	0.66	2.08	0.00	1.20	0.17	0.45	Non-enriched
35	Liver	0.03	0.05	0.27	1.01	1.42	1.52	1.96	4.88	0.39	2.84	0.38	0.72	Non-enriched
36	Lung	0.03	0.01	0.00	0.18	0.41	0.40	0.57	1.42	0.00	0.87	0.07	0.22	Non-enriched
37	Minor_Salivary_Gland	0.04	0.03	0.07	0.51	0.68	0.74	0.92	1.96	0.10	1.36	0.59	0.83	Non-enriched
38	Muscle_Skeletal	0.03	0.01	0.00	0.13	0.30	0.33	0.46	1.61	0.00	0.78	0.04	0.22	Non-enriched
39	Nerve_Tibial	0.03	0.01	0.00	0.11	0.20	0.27	0.36	1.93	0.00	0.79	0.04	0.23	Non-enriched
40	Ovary	0.03	0.01	0.00	0.14	0.34	0.40	0.56	2.39	0.00	1.08	0.09	0.30	Non-enriched
41	Pancreas	0.03	0.01	0.00	0.11	0.27	0.34	0.50	1.60	0.00	0.88	0.06	0.25	Non-enriched
42	Pituitary	0.04	0.03	0.00	0.32	0.61	0.68	0.94	2.78	0.00	1.62	0.24	0.45	Non-enriched
43	Prostate	0.03	0.02	0.00	0.27	0.55	0.72	1.05	3.85	0.00	1.98	0.21	0.50	Non-enriched
44	Skin_Not_Sun_Exposed_.Suprapubic.	0.03	0.03	0.00	0.44	1.01	1.06	1.47	4.46	0.00	2.53	0.17	0.37	Non-enriched
45	Skin_Sun_Exposed_.Lower_leg.	0.03	0.03	0.00	0.49	1.06	1.16	1.59	5.72	0.00	2.65	0.16	0.36	Non-enriched
46	Small_Intestine_Terminal_Ileum	0.04	0.01	0.00	0.14	0.30	0.42	0.58	2.60	0.00	1.24	0.10	0.39	Non-enriched
47	Spleen	0.04	0.03	0.00	0.47	0.79	0.84	1.11	3.73	0.00	1.75	0.49	0.78	Non-enriched
48	Stomach	0.04	0.03	0.04	0.44	0.68	0.72	0.95	2.28	0.05	1.39	0.44	0.65	Non-enriched
49	Testis	0.03	0.02	0.00	0.25	0.48	0.54	0.74	2.10	0.00	1.27	0.19	0.41	Non-enriched
50	Thyroid	0.07	0.06	0.00	0.19	0.45	0.60	0.80	3.44	0.00	1.71	0.21	0.54	Non-enriched
51	Uterus	0.04	0.04	0.27	0.90	1.22	1.26	1.55	3.28	0.49	2.27	0.65	0.93	Non-enriched
52	Vagina	0.03	0.02	0.00	0.27	0.55	0.69	0.98	3.85	0.00	1.69	0.15	0.34	Non-enriched
53	Whole_Blood	0.03	0.01	0.00	0.13	0.28	0.34	0.50	1.41	0.00	0.87	0.05	0.21	Non-enriched

Table S9. Enrichment summary of repressed genes in GTEx for BMI

	tissue	mean_pprobes	mean_pve	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	CI(l)	CI(h)	ROPE	prob	group
1	Adipose_Subcutaneous	0.08	0.02	0.00	0.08	0.17	0.22	0.29	1.09	0.00	0.77	0.01	0.07	Non-enriched
2	Adipose_Visceral_.Omentum.	0.07	0.02	0.00	0.11	0.18	0.23	0.33	0.77	0.01	0.58	0.01	0.08	Non-enriched
3	Adrenal_Gland	0.07	0.01	0.00	0.08	0.12	0.18	0.26	0.75	0.00	0.62	0.01	0.07	Non-enriched
4	Artery_Aorta	0.06	0.01	0.00	0.05	0.13	0.17	0.24	0.70	0.00	0.56	0.00	0.11	Non-enriched
5	Artery_Coronary	0.07	0.03	0.00	0.28	0.38	0.41	0.51	1.28	0.11	0.76	0.10	0.38	Non-enriched
6	Artery_Tibial	0.07	0.03	0.00	0.28	0.38	0.41	0.50	1.04	0.11	0.81	0.11	0.44	Non-enriched
7	Bladder	0.07	0.02	0.00	0.11	0.18	0.21	0.28	0.59	0.00	0.58	0.00	0.07	Non-enriched
8	Brain_Amygdala	0.07	0.01	0.00	0.04	0.13	0.16	0.23	0.65	0.00	0.44	0.00	0.14	Non-enriched
9	Brain_Anterior_cingulate_cortex_.BA24.	0.07	0.01	0.00	0.04	0.14	0.16	0.22	0.65	0.00	0.48	0.00	0.14	Non-enriched
10	Brain_Caudate_.basal_ganglia.	0.07	0.01	0.00	0.03	0.10	0.16	0.24	0.65	0.00	0.50	0.00	0.09	Non-enriched
11	Brain_Cerebellar_Hemisphere	0.10	0.04	0.00	0.28	0.38	0.44	0.54	1.70	0.08	0.92	0.12	0.39	Non-enriched
12	Brain_Cerebellum	0.10	0.04	0.00	0.26	0.36	0.40	0.50	1.16	0.10	0.84	0.09	0.36	Non-enriched
13	Brain_Cortex	0.07	0.02	0.00	0.16	0.23	0.26	0.32	0.85	0.02	0.61	0.02	0.24	Non-enriched
14	Brain_Frontal_Cortex_.BA9.	0.07	0.02	0.00	0.16	0.23	0.27	0.32	0.90	0.02	0.61	0.02	0.24	Non-enriched
15	Brain_Hippocampus	0.07	0.01	0.00	0.04	0.13	0.16	0.23	0.65	0.00	0.47	0.00	0.15	Non-enriched
16	Brain_Hypothalamus	0.07	0.02	0.00	0.14	0.21	0.23	0.29	0.79	0.00	0.53	0.01	0.17	Non-enriched
17	Brain_Nucleus_accumbens_.basal_ganglia.	0.07	0.01	0.00	0.04	0.09	0.14	0.21	0.65	0.00	0.48	0.00	0.13	Non-enriched
18	Brain_Putamen_.basal_ganglia.	0.07	0.01	0.00	0.03	0.10	0.15	0.23	0.65	0.00	0.44	0.00	0.09	Non-enriched
19	Brain_Spinal_cord_.cervical_c.1.	0.13	0.14	0.24	0.81	1.05	1.11	1.35	2.64	0.46	2.01	0.79	1.00	Non-enriched
20	Brain_Substantia_nigra	0.13	0.14	0.18	0.81	1.07	1.13	1.36	3.17	0.44	2.01	0.78	1.00	Non-enriched
21	Breast_Mammary_Tissue	0.08	0.02	0.00	0.07	0.19	0.22	0.30	0.98	0.00	0.58	0.00	0.05	Non-enriched
22	Cells_EBV.transformed_lymphocytes	0.06	0.01	0.00	0.09	0.18	0.22	0.28	0.72	0.00	0.65	0.01	0.05	Non-enriched
23	Cells_Transformed_fibroblasts	0.08	0.01	0.00	0.06	0.12	0.16	0.24	0.60	0.00	0.59	0.00	0.08	Non-enriched
24	Cervix_Ectocervix	0.07	0.01	0.00	0.10	0.16	0.19	0.30	0.43	0.00	0.42	0.00	0.05	Non-enriched
25	Cervix_Endocervix	0.06	0.02	0.00	0.13	0.32	0.45	0.67	2.08	0.00	1.49	0.03	0.10	Non-enriched
26	Colon_Sigmoid	0.20	0.10	0.00	0.08	0.15	0.31	0.28	2.62	0.00	1.48	0.02	0.18	Non-enriched
27	Colon_Transverse	0.09	0.02	0.00	0.04	0.15	0.20	0.25	1.01	0.00	0.80	0.01	0.06	Non-enriched
28	Esophagus_Gastroesophageal_Junction	0.07	0.01	0.00	0.04	0.13	0.16	0.23	1.45	0.00	0.50	0.01	0.14	Non-enriched
29	Esophagus_Mucosa	0.06	0.01	0.00	0.06	0.13	0.16	0.22	0.63	0.00	0.49	0.00	0.04	Non-enriched
30	Esophagus_Muscularis	0.07	0.01	0.00	0.04	0.14	0.18	0.25	1.45	0.00	0.64	0.01	0.16	Non-enriched
31	Fallopian_Tube	0.06	0.01	0.00	0.06	0.14	0.18	0.25	0.57	0.00	0.53	0.00	0.04	Non-enriched
32	Heart_Atrial_Appendage	0.09	0.02	0.00	0.06	0.15	0.17	0.24	0.52	0.00	0.45	0.00	0.09	Non-enriched
33	Heart_Left_Ventricle	0.09	0.02	0.00	0.07	0.16	0.18	0.25	0.51	0.00	0.47	0.00	0.09	Non-enriched
34	Kidney_Cortex	0.06	0.01	0.00	0.06	0.11	0.15	0.19	0.68	0.00	0.68	0.00	0.03	Non-enriched
35	Liver	0.06	0.01	0.01	0.03	0.13	0.17	0.23	0.54	0.00	0.01	0.03	0.02	Non-enriched
36	Lung	0.07	0.04	0.15	0.53	0.70	0.75	0.96	1.78	0.18	1.38	0.17	0.22	Non-enriched
37	Minor_Salivary_Gland	0.06	0.01	0.00	0.04	0.18	0.23	0.37	0.69	0.00	0.65	0.01	0.05	Non-enriched
38	Muscle_Skeletal	0.08	0.02	0.00	0.04	0.13	0.20	0.31	1.03	0.00	0.60	0.01	0.12	Non-enriched
39	Nerve_Tibial	0.14	0.04	0.00	0.18	0.25	0.27	0.36	1.05	0.01	0.51	0.03	0.49	Non-enriched
40	Ovary	0.07	0.01	0.00	0.06	0.12	0.14	0.21	0.39	0.00	0.36	0.00	0.07	Non-enriched
41	Pancreas	0.06	0.01	0.00	0.02	0.09	0.11	0.12	0.47	0.00	0.47	0.00	0.02	Non-enriched
42	Pituitary	0.06	0.01	0.00	0.04	0.12	0.18	0.24	0.76	0.00	0.65	0.01	0.09	Non-enriched
43	Prostate	0.08	0.02	0.00	0.04	0.09	0.21	0.36	0.67	0.00	0.67	0.01	0.03	Non-enriched
44	Skin_Not_Sun_Exposed_.Suprapubic.	0.06	0.03	0.01	0.35	0.52	0.52	0.69	1.31	0.01	1.02	0.05	0.10	Non-enriched
45	Skin_Sun_Exposed_.Lower_leg.	0.07	0.03	0.01	0.31	0.44	0.48	0.64	1.31	0.01	1.05	0.04	0.10	Non-enriched
46	Small_Intestine_Terminal_Ileum	0.06	0.02	0.00	0.08	0.20	0.27	0.43	1.01	0.00	0.80	0.01	0.07	Non-enriched
47	Spleen	0.06	0.02	0.00	0.17	0.29	0.31	0.43	1.00	0.00	0.65	0.01	0.06	Non-enriched
48	Stomach	0.06	0.01	0.00	0.07	0.13	0.18	0.25	0.64	0.00	0.56	0.01	0.06	Non-enriched
49	Testis	0.08	0.01	0.00	0.03	0.06	0.07	0.09	0.35	0.00	0.00	0.03	0.01	Non-enriched
50	Thyroid	0.08	0.02	0.00	0.03	0.14	0.24	0.40	1.21	0.00	0.81	0.01	0.08	Non-enriched
51	Uterus	0.07	0.03	0.00	0.19	0.36	0.44	0.57	1.94	0.00	1.23	0.05	0.15	Non-enriched
52	Vagina	0.06	0.01	0.00	0.02	0.08	0.13	0.22	0.63	0.00	0.63	0.00	0.03	Non-enriched
53	Whole_Blood	0.08	0.01	0.00	0.04	0.13	0.18	0.28	0.86	0.00	0.51	0.00	0.04	Non-enriched

Table S10. Enrichment summary of over-expressed genes in GTEx for smoking

	tissue	mean_pprobes	mean_pve	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	CI(l)	CI(h)	ROPE	prob	group
1	Adipose_Subcutaneous	0.09	0.02	0.00	0.07	0.17	0.22	0.32	1.05	0.00	0.54	0.01	0.10	Non-enriched
2	Adipose_Visceral_.Omentum.	0.07	0.01	0.00	0.07	0.12	0.18	0.25	0.83	0.00	0.50	0.00	0.10	Non-enriched
3	Adrenal_Gland	0.07	0.02	0.00	0.16	0.25	0.30	0.40	0.94	0.01	0.77	0.03	0.25	Non-enriched
4	Artery_Aorta	0.07	0.02	0.00	0.11	0.20	0.25	0.32	0.99	0.00	0.72	0.04	0.30	Non-enriched
5	Artery_Coronary	0.07	0.01	0.00	0.10	0.16	0.19	0.24	1.05	0.01	0.42	0.01	0.32	Non-enriched
6	Artery_Tibial	0.07	0.01	0.00	0.10	0.17	0.21	0.29	0.77	0.00	0.54	0.02	0.30	Non-enriched
7	Bladder	0.07	0.02	0.00	0.17	0.33	0.35	0.48	1.05	0.00	0.83	0.05	0.23	Non-enriched
8	Brain_Amygdala	0.07	0.01	0.00	0.05	0.13	0.19	0.25	1.21	0.00	0.63	0.01	0.15	Non-enriched
9	Brain_Anterior_cingulate_cortex_.BA24.	0.08	0.01	0.00	0.04	0.11	0.18	0.24	1.21	0.00	0.49	0.01	0.14	Non-enriched
10	Brain_Caudate_.basal_ganglia.	0.07	0.01	0.00	0.05	0.12	0.18	0.25	0.87	0.00	0.55	0.01	0.13	Non-enriched
11	Brain_Cerebellar_Hemisphere	0.07	0.02	0.00	0.08	0.20	0.26	0.36	1.64	0.00	0.85	0.02	0.16	Non-enriched
12	Brain_Cerebellum	0.07	0.02	0.00	0.10	0.22	0.28	0.39	1.64	0.00	0.81	0.02	0.18	Non-enriched
13	Brain_Cortex	0.07	0.01	0.00	0.05	0.12	0.16	0.23	0.71	0.00	0.42	0.00	0.12	Non-enriched
14	Brain_Frontal_Cortex_.BA9.	0.08	0.02	0.00	0.06	0.14	0.19	0.26	1.21	0.00	0.53	0.01	0.15	Non-enriched
15	Brain_Hippocampus	0.07	0.02	0.00	0.06	0.18	0.25	0.35	1.64	0.00	0.75	0.02	0.19	Non-enriched
16	Brain_Hypothalamus	0.07	0.02	0.00	0.06	0.21	0.28	0.39	1.64	0.00	0.94	0.02	0.15	Non-enriched
17	Brain_Nucleus_accumbens_.basal_ganglia.	0.07	0.02	0.00	0.06	0.17	0.24	0.33	1.64	0.00	0.81	0.02	0.17	Non-enriched
18	Brain_Putamen_.basal_ganglia.	0.08	0.01	0.00	0.05	0.10	0.16	0.22	0.81	0.00	0.46	0.00	0.13	Non-enriched
19	Brain_Spinal_cord_.cervical_c.1.	0.07	0.02	0.00	0.06	0.20	0.26	0.36	1.37	0.00	0.86	0.02	0.18	Non-enriched
20	Brain_Substantia_nigra	0.07	0.02	0.00	0.09	0.19	0.24	0.34	1.30	0.00	0.61	0.02	0.19	Non-enriched
21	Breast_Mammary_Tissue	0.17	0.08	0.00	0.13	0.24	0.36	0.42	2.62	0.00	1.24	0.04	0.24	Non-enriched
22	Cells_EBV.transformed_lymphocytes	0.07	0.01	0.00	0.05	0.11	0.16	0.23	0.72	0.00	0.45	0.00	0.16	Non-enriched
23	Cells_Transformed_fibroblasts	0.07	0.02	0.00	0.16	0.23	0.27	0.37	1.07	0.00	0.57	0.02	0.18	Non-enriched
24	Cervix_Ectocervix	0.06	0.01	0.00	0.07	0.16	0.19	0.31	0.56	0.00	0.50	0.00	0.08	Non-enriched
25	Cervix_Endocervix	0.07	0.02	0.00	0.13	0.26	0.30	0.42	1.44	0.00	0.73	0.02	0.14	Non-enriched
26	Colon_Sigmoid	0.07	0.01	0.00	0.09	0.14	0.17	0.21	0.75	0.00	0.41	0.01	0.23	Non-enriched
27	Colon_Transverse	0.07	0.01	0.00	0.05	0.11	0.16	0.21	0.90	0.00	0.50	0.00	0.11	Non-enriched
28	Esophagus_Gastroesophageal_Junction	0.09	0.02	0.00	0.04	0.11	0.17	0.28	1.05	0.00	0.50	0.00	0.10	Non-enriched
29	Esophagus_Mucosa	0.07	0.01	0.00	0.06	0.14	0.19	0.28	0.98	0.00	0.57	0.00	0.11	Non-enriched
30	Esophagus_Muscularis	0.08	0.01	0.00	0.09	0.15	0.18	0.22	1.05	0.00	0.47	0.01	0.24	Non-enriched
31	Fallopian_Tube	0.08	0.02	0.00	0.16	0.28	0.33	0.42	1.17	0.00	0.82	0.03	0.16	Non-enriched
32	Heart_Atrial_Appendage	0.07	0.01	0.00	0.06	0.16	0.21	0.31	1.47	0.00	0.63	0.01	0.11	Non-enriched
33	Heart_Left_Ventricle	0.07	0.01	0.00	0.03	0.08	0.12	0.16	1.18	0.00	0.39	0.00	0.09	Non-enriched
34	Kidney_Cortex	0.08	0.03	0.00	0.27	0.39	0.40	0.52	1.37	0.06	0.74	0.13	0.48	Non-enriched
35	Liver	0.07	0.01	0.00	0.06	0.15	0.23	0.35	1.35	0.00	0.78	0.01	0.12	Non-enriched
36	Lung	0.11	0.02	0.00	0.05	0.14	0.18	0.27	0.73	0.00	0.46	0.00	0.09	Non-enriched
37	Minor_Salivary_Gland	0.06	0.01	0.00	0.06	0.14	0.19	0.28	0.92	0.00	0.59	0.01	0.14	Non-enriched
38	Muscle_Skeletal	0.07	0.01	0.00	0.03	0.12	0.17	0.19	1.18	0.00	0.61	0.00	0.06	Non-enriched
39	Nerve_Tibial	0.07	0.01	0.00	0.06	0.13	0.16	0.22	0.70	0.00	0.52	0.00	0.09	Non-enriched
40	Ovary	0.06	0.01	0.00	0.07	0.18	0.22	0.32	1.16	0.00	0.60	0.01	0.10	Non-enriched
41	Pancreas	0.07	0.02	0.00	0.06	0.18	0.26	0.38	1.37	0.00	0.93	0.02	0.14	Non-enriched
42	Pituitary	0.07	0.01	0.00	0.03	0.11	0.16	0.25	0.71	0.00	0.53	0.01	0.10	Non-enriched
43	Prostate	0.07	0.02	0.00	0.09	0.22	0.26	0.36	1.21	0.00	0.70	0.02	0.17	Non-enriched
44	Skin_Not_Sun_Exposed_.Suprapubic.	0.07	0.01	0.00	0.05	0.15	0.19	0.28	0.83	0.00	0.53	0.00	0.09	Non-enriched
45	Skin_Sun_Exposed_.Lower_leg.	0.07	0.01	0.00	0.04	0.13	0.18	0.29	0.83	0.00	0.53	0.00	0.08	Non-enriched
46	Small_Intestine_Terminal_Ileum	0.07	0.01	0.00	0.06	0.11	0.15	0.20	0.70	0.00	0.41	0.00	0.13	Non-enriched
47	Spleen	0.06	0.02	0.00	0.14	0.24	0.27	0.37	0.90	0.00	0.58	0.01	0.18	Non-enriched
48	Stomach	0.07	0.01	0.00	0.08	0.17	0.23	0.33	0.89	0.00	0.73	0.02	0.13	Non-enriched
49	Testis	0.07	0.01	0.00	0.05	0.14	0.18	0.24	1.16	0.00	0.53	0.01	0.11	Non-enriched
50	Thyroid	0.18	0.06	0.00	0.17	0.24	0.30	0.35	2.17	0.00	0.65	0.04	0.55	Non-enriched
51	Uterus	0.06	0.02	0.00	0.11	0.22	0.27	0.37	0.99	0.00	0.68	0.02	0.11	Non-enriched
52	Vagina	0.06	0.01	0.00	0.07	0.15	0.21	0.29	0.85	0.00	0.71	0.01	0.10	Non-enriched
53	Whole_Blood	0.07	0.01	0.00	0.05	0.10	0.13	0.18	0.65	0.00	0.35	0.00	0.07	Non-enriched

Table S11. Enrichment summary of over-expressed genes in GTEx for smoking

	tissue	p.probes	p.pve	Min.	1stQu.	Median	Mean	3rdQu.	Max.	CI(l)	CI(h)	ROPE	prob	group
1	KEGG_ABC_TRANSPORTERS	0.07	0.27	1.71	3.05	3.73	4.17	4.90	10.47	1.96	7.57	0.00	1.00	Enriched
2	KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY	0.03	0.03	0.00	0.52	0.80	0.87	1.16	2.74	0.00	1.78	0.31	0.46	Non-enriched
3	KEGG_ALDOSTERONE_REGULATED_SODIUM_REABSORPTION	0.03	0.01	0.00	0.23	0.37	0.42	0.55	1.27	0.00	1.04	0.05	0.19	Non-enriched
4	KEGG_AMINOACYL_TRNA_BIOSYNTHESIS	0.03	0.03	0.13	0.70	1.06	1.15	1.47	3.40	0.13	2.32	0.43	0.65	Non-enriched
5	KEGG_ASCORBATE_AND_ALDARATE_METABOLISM	0.02	0.01	0.00	0.16	0.38	0.51	0.72	2.10	0.00	1.62	0.03	0.11	Non-enriched
6	KEGG_ASTHMA	0.05	0.06	0.28	1.01	1.38	1.39	1.71	3.32	0.47	2.31	0.26	0.43	Non-enriched
7	KEGG_AXON_GUIDANCE	0.04	0.03	0.00	0.52	0.78	0.83	1.09	2.46	0.00	1.66	0.48	0.69	Non-enriched
8	KEGG_BASAL_CELL_CARCINOMA	0.04	0.03	0.00	0.49	0.81	0.89	1.24	3.01	0.03	1.91	0.42	0.69	Non-enriched
9	KEGG_BASAL_TRANSCRIPTION_FACTORS	0.03	0.01	0.00	0.04	0.13	0.18	0.26	0.91	0.00	0.75	0.00	0.08	Non-enriched
10	KEGG_CALCIUM_SIGNALING_PATHWAY	0.03	0.02	0.00	0.23	0.46	0.49	0.68	1.42	0.00	1.08	0.20	0.44	Non-enriched
11	KEGG_CELL_ADHESION_MOLECULES_CAMS	0.03	0.02	0.09	0.46	0.74	0.80	1.12	2.90	0.13	1.54	0.20	0.30	Non-enriched
12	KEGG_CYSTEINE_AND_METHIONINE_METABOLISM	0.03	0.03	0.00	0.78	1.25	1.29	1.71	3.81	0.00	2.52	0.21	0.42	Non-enriched
13	KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	0.03	0.01	0.00	0.23	0.52	0.58	0.82	1.86	0.01	1.36	0.05	0.11	Non-enriched
14	KEGG_DNA_REPLICATION	0.03	0.01	0.00	0.06	0.16	0.23	0.31	1.19	0.00	0.76	0.02	0.12	Non-enriched
15	KEGG_DORSO_VENTRAL_AXIS_FORMATION	0.04	0.03	0.00	0.41	0.79	0.85	1.14	3.31	0.00	1.74	0.27	0.45	Non-enriched
16	KEGG_DRUG_METABOLISM_CYTOCHROME_P450	0.03	0.04	0.01	0.86	1.27	1.28	1.62	3.66	0.01	2.36	0.22	0.38	Non-enriched
17	KEGG_DRUG_METABOLISM_OTHER_ENZYMES	0.03	0.04	0.00	0.87	1.24	1.24	1.58	3.51	0.07	2.29	0.23	0.38	Non-enriched
18	KEGG_ECM_RECEPTOR_INTERACTION	0.03	0.01	0.00	0.12	0.27	0.34	0.51	1.49	0.00	0.88	0.06	0.23	Non-enriched
19	KEGG_FOCAL_ADHESION	0.03	0.01	0.00	0.14	0.28	0.41	0.53	3.44	0.00	1.39	0.08	0.35	Non-enriched
20	KEGG_GALACTOSE_METABOLISM	0.03	0.03	0.00	0.67	1.10	1.18	1.63	3.40	0.00	2.36	0.23	0.43	Non-enriched
21	KEGG_GAP_JUNCTION	0.04	0.02	0.00	0.23	0.45	0.54	0.75	1.92	0.00	1.31	0.17	0.39	Non-enriched
22	KEGG_GLUTATHIONE_METABOLISM	0.03	0.03	0.00	0.50	1.00	1.01	1.41	3.41	0.00	2.15	0.17	0.32	Non-enriched
23	KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS_GANGLIO_SERIES	0.03	0.03	0.00	0.40	1.08	1.21	1.87	4.05	0.00	2.93	0.12	0.35	Non-enriched
24	KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS_GLOBO_SERIES	0.03	0.03	0.00	0.50	1.04	1.23	1.87	4.34	0.00	2.91	0.15	0.37	Non-enriched
25	KEGG_HUNTINGTONS_DISEASE	0.03	0.01	0.00	0.10	0.26	0.31	0.42	1.46	0.00	0.98	0.02	0.11	Non-enriched
26	KEGG_INSULIN_SIGNALING_PATHWAY	0.03	0.04	0.00	0.76	1.17	1.27	1.68	4.05	0.00	2.57	0.28	0.51	Non-enriched
27	KEGG_LEISHMANIA_INFECTION	0.03	0.06	0.50	1.59	2.02	2.02	2.41	4.41	0.90	3.31	0.17	0.83	Non-enriched
28	KEGG_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION	0.03	0.01	0.00	0.08	0.15	0.21	0.27	0.97	0.00	0.67	0.02	0.15	Non-enriched
29	KEGG_LONG_TERM_POTENTIATION	0.03	0.02	0.00	0.24	0.48	0.52	0.71	1.94	0.00	1.14	0.19	0.42	Non-enriched
30	KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	0.03	0.01	0.00	0.10	0.22	0.39	0.50	2.04	0.00	1.35	0.06	0.27	Non-enriched
31	KEGG_NON_HOMOLOGOUS_END_JOINING	0.03	0.01	0.00	0.11	0.23	0.31	0.47	1.19	0.00	0.83	0.03	0.11	Non-enriched
32	KEGG_NON_SMALL_CELL_LUNG_CANCER	0.05	0.04	0.00	0.41	0.68	0.76	1.04	3.24	0.01	1.61	0.29	0.49	Non-enriched
33	KEGG_O_GLYCAN_BIOSYNTHESIS	0.03	0.02	0.00	0.35	0.71	0.77	1.06	2.59	0.00	1.90	0.15	0.27	Non-enriched
34	KEGG_OTHER_GLYCAN_DEGRADATION	0.03	0.04	0.15	0.84	1.24	1.38	1.74	4.34	0.37	3.02	0.36	0.59	Non-enriched
35	KEGG_OXIDATIVE_PHOSPHORYLATION	0.04	0.01	0.00	0.05	0.15	0.26	0.34	1.46	0.00	0.98	0.02	0.11	Non-enriched
36	KEGG_PANTOTHENATE_AND_COA_BIOSYNTHESIS	0.03	0.03	0.00	0.48	0.94	1.01	1.49	3.20	0.00	2.31	0.11	0.22	Non-enriched
37	KEGG_PENTOSE_AND_GLUCURONATE_INTERCONVERSIONS	0.03	0.01	0.00	0.07	0.22	0.25	0.36	0.77	0.00	0.77	0.01	0.06	Non-enriched
38	KEGG_PEROXISOME	0.03	0.01	0.00	0.08	0.24	0.28	0.38	1.33	0.00	0.76	0.02	0.10	Non-enriched
39	KEGG_PRION_DISEASES	0.04	0.06	0.33	1.20	1.52	1.60	1.91	3.90	0.55	2.72	0.20	0.45	Non-enriched
40	KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	0.04	0.03	0.00	0.32	0.68	0.78	1.08	3.31	0.00	1.93	0.26	0.50	Non-enriched
41	KEGG_PROSTATE_CANCER	0.04	0.03	0.00	0.57	0.88	0.92	1.22	3.04	0.09	1.87	0.38	0.55	Non-enriched
42	KEGG_PROXIMAL_TUBULE_BICARBONATE_RECLAMATION	0.03	0.01	0.00	0.06	0.16	0.25	0.35	1.33	0.00	0.83	0.02	0.10	Non-enriched
43	KEGG_RIBOFLAVIN_METABOLISM	0.03	0.02	0.00	0.37	0.77	0.77	1.09	2.12	0.00	1.62	0.16	0.26	Non-enriched
44	KEGG_RIBOSOME	0.03	0.00	0.00	0.05	0.12	0.17	0.24	1.19	0.00	0.49	0.00	0.04	Non-enriched
45	KEGG_SMALL_CELL_LUNG_CANCER	0.04	0.03	0.02	0.47	0.72	0.80	1.04	2.69	0.10	1.69	0.38	0.57	Non-enriched
46	KEGG_STEROID_HORMONE_BIOSYNTHESIS	0.03	0.04	0.00	0.84	1.25	1.25	1.62	3.51	0.00	2.24	0.22	0.38	Non-enriched
47	KEGG_TASTE_TRANSDUCTION	0.02	0.00	0.00	0.07	0.15	0.21	0.30	0.85	0.00	0.66	0.00	0.06	Non-enriched
48	KEGG_TRYPTOPHAN_METABOLISM	0.03	0.04	0.01	1.02	1.42	1.51	1.96	3.74	0.29	2.98	0.26	0.56	Non-enriched
49	KEGG_TYPE_I_DIABETES_MELLITUS	0.03	0.02	0.02	0.48	0.70	0.80	1.09	2.54	0.18	1.65	0.18	0.28	Non-enriched
50	KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	0.03	0.01	0.00	0.05	0.15	0.22	0.34	0.95	0.00	0.72	0.02	0.13	Non-enriched
51	KEGG_VIBRIO_CHOLERAE_INFECTION	0.03	0.01	0.00	0.23	0.36	0.40	0.55	1.48	0.00	0.98	0.05	0.18	Non-enriched
52	KEGG_VIRAL_MYOCARDITIS	0.03	0.02	0.01	0.45	0.60	0.67	0.85	2.00	0.14	1.35	0.17	0.26	Non-enriched
53	KEGG_WNT_SIGNALING_PATHWAY	0.05	0.06	0.31	0.89	1.12	1.16	1.39	2.80	0.44	1.92	0.76	0.96	Non-enriched

Table S12. Enrichment summary of over-expressed genes in DEPICT for BMI

	tissue	p.probes	p.pve	Min.	1stQu.	Median	Mean	3rdQu.	Max.	CI(l)	CI(h)	ROPE	prob	group
1	KEGG_ABC_TRANSPORTERS	0.03	0.02	0.01	0.40	0.69	0.77	1.01	2.45	0.01	1.82	0.16	0.29	Non-enriched
2	KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY	0.03	0.01	0.00	0.08	0.16	0.19	0.26	0.70	0.00	0.51	0.00	0.10	Non-enriched
3	KEGG_ALDOSTERONE_REGULATED_SODIUM_REABSORPTION	0.04	0.01	0.00	0.10	0.24	0.27	0.38	1.10	0.00	0.64	0.02	0.14	Non-enriched
4	KEGG_AMINOACYL_TRNA_BIOSYNTHESIS	0.03	0.02	0.00	0.14	0.39	0.50	0.73	1.96	0.00	1.43	0.06	0.16	Non-enriched
5	KEGG_ASCORBATE_AND_ALDARATE_METABOLISM	0.03	0.02	0.00	0.32	0.50	0.57	0.68	2.55	0.00	1.26	0.10	0.22	Non-enriched
6	KEGG_ASTHMA	0.03	0.02	0.00	0.13	0.34	0.45	0.66	1.76	0.00	1.31	0.09	0.27	Non-enriched
7	KEGG_AXON_GUIDANCE	0.03	0.01	0.00	0.14	0.31	0.34	0.48	1.18	0.00	0.85	0.04	0.16	Non-enriched
8	KEGG_BASAL_CELL_CARCINOMA	0.04	0.07	0.49	1.33	1.68	1.77	2.12	4.21	0.69	2.95	0.37	1.00	Non-enriched
9	KEGG_BASAL_TRANSCRIPTION_FACTORS	0.03	0.05	0.00	1.02	1.57	1.78	2.27	7.62	0.00	4.06	0.22	0.57	Non-enriched
10	KEGG_CALCIUM_SIGNALING_PATHWAY	0.03	0.02	0.00	0.12	0.30	0.48	0.73	2.25	0.00	1.62	0.05	0.15	Non-enriched
11	KEGG_CELL_ADHESION_MOLECULES_CAMS	0.03	0.01	0.00	0.07	0.21	0.26	0.37	1.67	0.00	0.85	0.02	0.13	Non-enriched
12	KEGG_CYSTEINE_AND_METHIONINE_METABOLISM	0.03	0.01	0.01	0.07	0.19	0.21	0.34	0.68	0.01	0.52	0.00	0.09	Non-enriched
13	KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	0.04	0.03	0.00	0.30	0.62	0.69	0.98	2.38	0.00	1.64	0.22	0.41	Non-enriched
14	KEGG_DNA_REPLICATION	0.03	0.03	0.00	0.47	0.82	0.96	1.36	3.20	0.03	2.22	0.19	0.36	Non-enriched
15	KEGG_DORSO_VENTRAL_AXIS_FORMATION	0.03	0.01	0.00	0.04	0.16	0.30	0.30	2.92	0.00	1.82	0.00	0.09	Non-enriched
16	KEGG_DRUG_METABOLISM_CYTOCHROME_P450	0.04	0.04	0.00	0.67	1.00	1.05	1.36	3.39	0.00	2.20	0.29	0.44	Non-enriched
17	KEGG_DRUG_METABOLISM_OTHER_ENZYMES	0.03	0.01	0.00	0.09	0.22	0.35	0.50	1.51	0.00	1.25	0.04	0.16	Non-enriched
18	KEGG_ECM_RECEPTOR_INTERACTION	0.03	0.01	0.00	0.06	0.21	0.26	0.35	1.08	0.00	0.71	0.01	0.08	Non-enriched
19	KEGG_FOCAL_ADHESION	0.03	0.00	0.00	0.05	0.13	0.21	0.31	0.85	0.00	0.70	0.01	0.07	Non-enriched
20	KEGG_GALACTOSE_METABOLISM	0.03	0.02	0.00	0.14	0.28	0.41	0.53	2.44	0.00	1.29	0.04	0.16	Non-enriched
21	KEGG_GAP_JUNCTION	0.03	0.01	0.01	0.31	0.50	0.56	0.76	1.78	0.01	1.32	0.07	0.15	Non-enriched
22	KEGG_GLUTATHIONE_METABOLISM	0.03	0.01	0.00	0.16	0.38	0.51	0.78	2.61	0.00	1.30	0.11	0.28	Non-enriched
23	KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS_GANGLIO_SERIES	0.03	0.01	0.00	0.14	0.31	0.36	0.54	1.09	0.00	0.91	0.05	0.17	Non-enriched
24	KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS_GLOBO_SERIES	0.04	0.04	0.00	0.43	0.78	0.84	1.15	3.31	0.00	1.85	0.33	0.55	Non-enriched
25	KEGG_HUNTINGTONS_DISEASE	0.03	0.01	0.00	0.08	0.23	0.32	0.44	1.37	0.00	1.02	0.03	0.14	Non-enriched
26	KEGG_INSULIN_SIGNALING_PATHWAY	0.03	0.01	0.00	0.08	0.19	0.28	0.41	1.08	0.00	0.89	0.02	0.11	Non-enriched
27	KEGG_LEISHMANIA_INFECTION	0.03	0.01	0.00	0.10	0.19	0.29	0.40	1.39	0.00	1.00	0.03	0.17	Non-enriched
28	KEGG_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION	0.03	0.01	0.00	0.07	0.18	0.29	0.38	1.63	0.00	1.04	0.02	0.15	Non-enriched
29	KEGG_LONG_TERM_POTENTIATION	0.03	0.03	0.00	0.74	1.06	1.12	1.49	2.90	0.03	2.15	0.23	0.36	Non-enriched
30	KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	0.03	0.03	0.00	0.63	1.10	1.15	1.58	3.43	0.00	2.28	0.17	0.31	Non-enriched
31	KEGG_NON_HOMOLOGOUS_END_JOINING	0.03	0.03	0.29	0.84	1.11	1.15	1.44	2.65	0.40	2.03	0.28	0.37	Non-enriched
32	KEGG_NON_SMALL_CELL_LUNG_CANCER	0.03	0.01	0.00	0.15	0.40	0.48	0.74	1.78	0.01	1.38	0.06	0.15	Non-enriched
33	KEGG_O_GLYCAN_BIOSYNTHESIS	0.03	0.04	0.01	0.88	1.33	1.40	1.88	4.41	0.01	2.83	0.20	0.44	Non-enriched
34	KEGG_OTHER_GLYCAN_DEGRADATION	0.03	0.01	0.00	0.07	0.26	0.32	0.50	1.19	0.00	0.91	0.03	0.14	Non-enriched
35	KEGG_OXIDATIVE_PHOSPHORYLATION	0.04	0.01	0.00	0.03	0.15	0.27	0.39	1.37	0.00	1.01	0.02	0.13	Non-enriched
36	KEGG_PANTOTHENATE_AND_COA_BIOSYNTHESIS	0.03	0.01	0.00	0.24	0.39	0.41	0.55	1.53	0.00	0.96	0.06	0.20	Non-enriched
37	KEGG_PENTOSE_AND_GLUCURONATE_INTERCONVERSIONS	0.03	0.02	0.00	0.34	0.58	0.63	0.88	1.80	0.00	1.31	0.15	0.27	Non-enriched
38	KEGG_PEROXISOME	0.03	0.02	0.00	0.26	0.54	0.64	0.92	2.83	0.00	1.72	0.10	0.23	Non-enriched
39	KEGG_PRION_DISEASES	0.03	0.01	0.01	0.16	0.31	0.34	0.45	1.60	0.01	0.80	0.03	0.18	Non-enriched
40	KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	0.04	0.01	0.00	0.08	0.20	0.28	0.37	1.14	0.00	0.97	0.02	0.10	Non-enriched
41	KEGG_PROSTATE_CANCER	0.03	0.01	0.00	0.11	0.29	0.39	0.62	1.87	0.00	1.11	0.03	0.10	Non-enriched
42	KEGG_PROXIMAL_TUBULE_BICARBONATE_RECLAMATION	0.06	0.06	0.00	0.50	0.84	0.90	1.27	2.56	0.00	2.10	0.15	0.24	Non-enriched
43	KEGG_RIBOFLAVIN_METABOLISM	0.03	0.01	0.00	0.09	0.24	0.31	0.48	1.18	0.00	1.00	0.03	0.12	Non-enriched
44	KEGG_RIBOSOME	0.03	0.01	0.00	0.08	0.28	0.38	0.55	1.48	0.00	1.14	0.03	0.11	Non-enriched
45	KEGG_SMALL_CELL_LUNG_CANCER	0.03	0.01	0.00	0.16	0.36	0.41	0.59	2.09	0.00	1.02	0.12	0.37	Non-enriched
46	KEGG_STEROID_HORMONE_BIOSYNTHESIS	0.03	0.03	0.01	0.73	1.05	1.17	1.50	3.82	0.02	2.54	0.35	0.57	Non-enriched
47	KEGG_TASTE_TRANSDUCTION	0.04	0.03	0.00	0.44	0.79	0.86	1.20	3.26	0.00	1.94	0.24	0.41	Non-enriched
48	KEGG_TRYPTOPHAN_METABOLISM	0.08	0.29	1.60	3.03	3.67	3.81	4.44	7.54	2.06	5.90	0.00	1.00	Enriched
49	KEGG_TYPE_I_DIABETES_MELLITUS	0.03	0.06	0.46	1.40	1.98	2.02	2.54	4.59	0.58	3.53	0.13	0.46	Non-enriched
50	KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	0.03	0.01	0.00	0.25	0.40	0.44	0.59	1.69	0.00	0.99	0.06	0.17	Non-enriched
51	KEGG_VIBRIO_CHOLERAE_INFECTION	0.03	0.01	0.00	0.08	0.23	0.30	0.42	1.71	0.00	0.97	0.02	0.15	Non-enriched
52	KEGG_VIRAL_MYOCARDITIS	0.03	0.07	0.32	1.56	1.94	2.02	2.41	4.36	0.79	3.31	0.21	1.00	Non-enriched
53	KEGG_WNT_SIGNALING_PATHWAY	0.03	0.00	0.00	0.04	0.13	0.18	0.27	1.17	0.00	0.56	0.01	0.11	Non-enriched

Table S13. Enrichment summary of repressed genes in DEPICT for BMI

	tissue	p.probes	p.pve	Min.	1stQu.	Median	Mean	3rdQu.	Max.	CI(l)	CI(h)	ROPE	prob	group
1	KEGG_ABC_TRANSPORTERS	0.07	0.01	0.00	0.05	0.10	0.14	0.13	0.65	0.00	0.65	0.00	0.03	Non-enriched
2	KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY	0.07	0.01	0.00	0.04	0.11	0.15	0.20	1.16	0.00	0.52	0.00	0.09	Non-enriched
3	KEGG_ALDOSTERONE_REGULATED_SODIUM_REABSORPTION	0.07	0.03	0.00	0.20	0.33	0.37	0.50	1.22	0.00	0.82	0.03	0.13	Non-enriched
4	KEGG_AMINOACYL_TRNA_BIOSYNTHESIS	0.07	0.01	0.00	0.09	0.18	0.22	0.30	0.69	0.00	0.66	0.00	0.08	Non-enriched
5	KEGG_ASCORBATE_AND_ALDARATE_METABOLISM	0.05	0.01	0.00	0.01	0.05	0.13	0.27	0.39	0.00	0.00	0.01	0.01	Non-enriched
6	KEGG_ASTHMA	0.07	0.01	0.00	0.03	0.07	0.13	0.15	0.71	0.00	0.71	0.00	0.03	Non-enriched
7	KEGG_AXON_GUIDANCE	0.09	0.02	0.00	0.09	0.21	0.25	0.33	0.88	0.00	0.74	0.01	0.12	Non-enriched
8	KEGG_BASAL_CELL_CARCINOMA	0.08	0.01	0.00	0.05	0.14	0.17	0.24	0.57	0.00	0.41	0.00	0.10	Non-enriched
9	KEGG_BASAL_TRANSCRIPTION_FACTORS	0.07	0.02	0.00	0.16	0.24	0.30	0.37	1.37	0.00	0.98	0.01	0.06	Non-enriched
10	KEGG_CALCIUM_SIGNALING_PATHWAY	0.08	0.02	0.00	0.06	0.18	0.24	0.37	1.21	0.00	0.69	0.01	0.14	Non-enriched
11	KEGG_CELL_ADHESION_MOLECULES_CAMS	0.08	0.01	0.00	0.03	0.09	0.16	0.25	0.79	0.00	0.58	0.00	0.06	Non-enriched
12	KEGG_CYSTEINE_AND_METHIONINE_METABOLISM	0.07	0.01	0.00	0.06	0.13	0.19	0.25	0.81	0.00	0.81	0.00	0.03	Non-enriched
13	KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	0.06	0.01	0.00	0.02	0.11	0.15	0.17	0.74	0.00	0.74	0.00	0.03	Non-enriched
14	KEGG_DNA_REPLICATION	0.07	0.01	0.00	0.03	0.09	0.16	0.21	0.75	0.00	0.73	0.00	0.04	Non-enriched
15	KEGG_DORSO_VENTRAL_AXIS_FORMATION	0.07	0.02	0.00	0.07	0.26	0.31	0.42	1.34	0.00	0.98	0.02	0.08	Non-enriched
16	KEGG_DRUG_METABOLISM_CYTOCHROME_P450	0.05	0.00	0.01	0.02	0.07	0.07	0.12	0.16	0.00	0.01	0.02	0.01	Non-enriched
17	KEGG_DRUG_METABOLISM_OTHER_ENZYMES	0.05	0.00	0.01	0.02	0.04	0.07	0.11	0.23	0.00	0.01	0.02	0.01	Non-enriched
18	KEGG_ECM_RECEPTOR_INTERACTION	0.07	0.01	0.00	0.09	0.16	0.20	0.25	0.94	0.00	0.61	0.00	0.11	Non-enriched
19	KEGG_FOCAL_ADHESION	0.14	0.04	0.00	0.18	0.25	0.27	0.34	1.45	0.00	0.50	0.02	0.52	Non-enriched
20	KEGG_GALACTOSE_METABOLISM	0.07	0.01	0.00	0.07	0.15	0.23	0.33	1.37	0.00	0.72	0.01	0.06	Non-enriched
21	KEGG_GAP_JUNCTION	0.08	0.01	0.00	0.06	0.14	0.19	0.28	1.10	0.00	0.56	0.01	0.12	Non-enriched
22	KEGG_GLUTATHIONE_METABOLISM	0.07	0.02	0.00	0.08	0.19	0.21	0.26	1.12	0.00	0.52	0.00	0.07	Non-enriched
23	KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS_GANGLIO_SERIES	0.06	0.01	0.00	0.03	0.07	0.10	0.13	0.64	0.00	0.30	0.00	0.06	Non-enriched
24	KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS_GLOBO_SERIES	0.07	0.02	0.00	0.06	0.18	0.22	0.30	0.91	0.00	0.84	0.01	0.08	Non-enriched
25	KEGG_HUNTINGTONS_DISEASE	0.06	0.01	0.00	0.07	0.13	0.17	0.26	0.69	0.00	0.69	0.00	0.04	Non-enriched
26	KEGG_INSULIN_SIGNALING_PATHWAY	0.08	0.01	0.00	0.03	0.14	0.18	0.23	0.89	0.00	0.69	0.01	0.09	Non-enriched
27	KEGG_LEISHMANIA_INFECTION	0.06	0.02	0.00	0.11	0.32	0.35	0.53	0.86	0.00	0.80	0.02	0.07	Non-enriched
28	KEGG_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION	0.07	0.02	0.00	0.18	0.31	0.33	0.45	1.21	0.00	0.81	0.02	0.10	Non-enriched
29	KEGG_LONG_TERM_POTENTIATION	0.07	0.03	0.03	0.27	0.38	0.41	0.52	1.26	0.04	0.79	0.12	0.43	Non-enriched
30	KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	0.07	0.01	0.00	0.03	0.12	0.16	0.22	0.75	0.00	0.47	0.00	0.10	Non-enriched
31	KEGG_NON_HOMOLOGOUS_END_JOINING	0.06	0.02	0.00	0.10	0.28	0.33	0.53	1.08	0.00	0.83	0.02	0.09	Non-enriched
32	KEGG_NON_SMALL_CELL_LUNG_CANCER	0.07	0.02	0.00	0.14	0.23	0.27	0.40	0.81	0.00	0.63	0.01	0.11	Non-enriched
33	KEGG_O_GLYCAN_BIOSYNTHESIS	0.06	0.01	0.00	0.10	0.17	0.23	0.34	0.80	0.00	0.65	0.01	0.06	Non-enriched
34	KEGG_OTHER_GLYCAN_DEGRADATION	0.07	0.01	0.00	0.04	0.10	0.19	0.26	1.37	0.00	0.66	0.00	0.06	Non-enriched
35	KEGG_OXIDATIVE_PHOSPHORYLATION	0.07	0.01	0.00	0.05	0.09	0.15	0.22	0.69	0.00	0.42	0.00	0.04	Non-enriched
36	KEGG_PANTOTHENATE_AND_COA_BIOSYNTHESIS	0.08	0.02	0.00	0.04	0.12	0.18	0.26	0.73	0.00	0.68	0.00	0.04	Non-enriched
37	KEGG_PENTOSE_AND_GLUCURONATE_INTERCONVERSIONS	0.05	0.01	0.01	0.05	0.13	0.15	0.25	0.33	0.00	0.01	0.05	0.01	Non-enriched
38	KEGG_PEROXISOME	0.06	0.01	0.00	0.12	0.16	0.22	0.31	0.81	0.00	0.54	0.00	0.07	Non-enriched
39	KEGG_PRION_DISEASES	0.06	0.02	0.00	0.10	0.28	0.32	0.49	0.78	0.00	0.76	0.01	0.04	Non-enriched
40	KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	0.07	0.01	0.00	0.04	0.12	0.18	0.29	0.71	0.00	0.47	0.00	0.09	Non-enriched
41	KEGG_PROSTATE_CANCER	0.07	0.01	0.00	0.12	0.21	0.23	0.33	0.67	0.00	0.53	0.01	0.10	Non-enriched
42	KEGG_PROXIMAL_TUBULE_BICARBONATE_RECLAMATION	0.06	0.01	0.00	0.04	0.10	0.15	0.17	0.85	0.00	0.68	0.00	0.06	Non-enriched
43	KEGG_RIBOFLAVIN_METABOLISM	0.06	0.01	0.01	0.04	0.13	0.19	0.28	0.85	0.01	0.85	0.00	0.03	Non-enriched
44	KEGG_RIBOSOME	0.07	0.01	0.00	0.03	0.09	0.11	0.17	0.33	0.00	0.33	0.00	0.02	Non-enriched
45	KEGG_SMALL_CELL_LUNG_CANCER	0.06	0.01	0.00	0.05	0.16	0.23	0.37	0.85	0.00	0.68	0.01	0.12	Non-enriched
46	KEGG_STEROID_HORMONE_BIOSYNTHESIS	0.06	0.01	0.02	0.03	0.06	0.14	0.17	0.54	0.00	0.02	0.03	0.01	Non-enriched
47	KEGG_TASTE_TRANSDUCTION	0.07	0.01	0.00	0.05	0.13	0.14	0.23	0.39	0.00	0.00	0.05	0.01	Non-enriched
48	KEGG_TRYPTOPHAN_METABOLISM	0.06	0.58	3.99	8.32	10.13	10.28	12.23	17.12	5.00	14.56	0.00	0.14	Non-enriched
49	KEGG_TYPE_I_DIABETES_MELLITUS	0.07	0.01	0.00	0.05	0.09	0.18	0.19	0.69	0.00	0.69	0.00	0.03	Non-enriched
50	KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	0.06	0.02	0.00	0.13	0.27	0.29	0.42	0.99	0.00	0.71	0.02	0.11	Non-enriched
51	KEGG_VIBRIO_CHOLERAE_INFECTION	0.07	0.01	0.00	0.04	0.11	0.20	0.25	1.17	0.00	0.76	0.01	0.08	Non-enriched
52	KEGG_VIRAL_MYOCARDITIS	0.08	0.02	0.00	0.06	0.13	0.23	0.36	1.24	0.00	0.92	0.01	0.08	Non-enriched
53	KEGG_WNT_SIGNALING_PATHWAY	0.07	0.01	0.00	0.04	0.08	0.13	0.20	0.61	0.00	0.43	0.00	0.10	Non-enriched

Table S14. Enrichment summary of over-expressed genes in DEPICT for smoking

	tissue	p.probes	p.pve	Min.	1stQu.	Median	Mean	3rdQu.	Max.	CI(l)	CI(h)	ROPE	prob	group
1	KEGG_ABC_TRANSPORTERS	0.06	0.02	0.00	0.07	0.19	0.27	0.36	1.35	0.00	1.02	0.01	0.05	Non-enriched
2	KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY	0.06	0.01	0.00	0.05	0.14	0.26	0.36	1.05	0.00	0.87	0.01	0.06	Non-enriched
3	KEGG_ALDOSTERONE_REGULATED_SODIUM_REABSORPTION	0.11	0.03	0.00	0.07	0.13	0.23	0.33	1.21	0.00	0.70	0.01	0.06	Non-enriched
4	KEGG_AMINOACYL_TRNA_BIOSYNTHESIS	0.12	0.14	0.20	0.87	1.13	1.19	1.44	3.02	0.45	2.11	0.75	1.00	Non-enriched
5	KEGG_ASCORBATE_AND_ALDARATE_METABOLISM	0.07	0.03	0.00	0.13	0.36	0.40	0.58	1.34	0.00	1.17	0.02	0.06	Non-enriched
6	KEGG_ASTHMA	0.07	0.01	0.00	0.06	0.13	0.18	0.21	0.89	0.00	0.68	0.01	0.08	Non-enriched
7	KEGG_AXON_GUIDANCE	0.06	0.03	0.00	0.20	0.37	0.52	0.77	2.31	0.00	1.47	0.02	0.06	Non-enriched
8	KEGG_BASAL_CELL_CARCINOMA	0.07	0.01	0.00	0.04	0.13	0.17	0.21	0.72	0.00	0.55	0.00	0.05	Non-enriched
9	KEGG_BASAL_TRANSCRIPTION_FACTORS	0.07	0.02	0.00	0.18	0.29	0.32	0.45	1.14	0.00	0.74	0.03	0.15	Non-enriched
10	KEGG_CALCIUM_SIGNALING_PATHWAY	0.07	0.03	0.00	0.12	0.29	0.35	0.49	1.21	0.00	1.05	0.01	0.05	Non-enriched
11	KEGG_CELL_ADHESION_MOLECULES_CAMS	0.07	0.02	0.00	0.03	0.15	0.20	0.32	0.73	0.00	0.70	0.01	0.05	Non-enriched
12	KEGG_CYSTEINE_AND_METHIONINE_METABOLISM	0.06	0.02	0.01	0.14	0.29	0.31	0.40	0.84	0.01	0.84	0.00	0.04	Non-enriched
13	KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	0.08	0.02	0.00	0.05	0.15	0.24	0.38	0.87	0.00	0.68	0.02	0.10	Non-enriched
14	KEGG_DNA_REPLICATION	0.08	0.01	0.00	0.05	0.09	0.15	0.18	0.66	0.00	0.62	0.00	0.07	Non-enriched
15	KEGG_DORSO_VENTRAL_AXIS_FORMATION	0.06	0.01	0.00	0.04	0.12	0.25	0.26	1.35	0.00	1.21	0.01	0.04	Non-enriched
16	KEGG_DRUG_METABOLISM_CYTOCHROME_P450	0.08	0.01	0.00	0.04	0.11	0.19	0.29	0.85	0.00	0.84	0.01	0.06	Non-enriched
17	KEGG_DRUG_METABOLISM_OTHER_ENZYMES	0.06	0.01	0.00	0.05	0.12	0.15	0.23	0.49	0.00	0.41	0.00	0.04	Non-enriched
18	KEGG_ECM_RECEPTOR_INTERACTION	0.06	0.02	0.00	0.14	0.27	0.31	0.43	1.40	0.00	0.73	0.02	0.10	Non-enriched
19	KEGG_FOCAL_ADHESION	0.07	0.01	0.00	0.06	0.13	0.20	0.28	0.71	0.00	0.71	0.00	0.03	Non-enriched
20	KEGG_GALACTOSE_METABOLISM	0.06	0.01	0.00	0.08	0.12	0.15	0.20	0.49	0.00	0.44	0.00	0.05	Non-enriched
21	KEGG_GAP_JUNCTION	0.06	0.01	0.00	0.05	0.10	0.14	0.17	0.47	0.00	0.47	0.00	0.03	Non-enriched
22	KEGG_GLUTATHIONE_METABOLISM	0.06	0.01	0.00	0.07	0.16	0.21	0.28	0.76	0.00	0.55	0.01	0.12	Non-enriched
23	KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS_GANGLIO_SERIES	0.07	0.01	0.00	0.07	0.15	0.21	0.32	0.79	0.00	0.66	0.01	0.08	Non-enriched
24	KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS_GLOBO_SERIES	0.07	0.01	0.00	0.05	0.10	0.14	0.17	0.59	0.00	0.49	0.00	0.09	Non-enriched
25	KEGG_HUNTINGTONS_DISEASE	0.06	0.01	0.00	0.07	0.18	0.24	0.35	1.18	0.00	0.73	0.01	0.05	Non-enriched
26	KEGG_INSULIN_SIGNALING_PATHWAY	0.07	0.01	0.01	0.05	0.19	0.22	0.29	0.68	0.01	0.68	0.00	0.04	Non-enriched
27	KEGG_LEISHMANIA_INFECTION	0.06	0.01	0.00	0.01	0.06	0.13	0.18	0.60	0.00	0.49	0.00	0.04	Non-enriched
28	KEGG_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION	0.07	0.01	0.00	0.03	0.08	0.16	0.26	0.77	0.00	0.52	0.00	0.06	Non-enriched
29	KEGG_LONG_TERM_POTENTIATION	0.07	0.01	0.00	0.04	0.11	0.15	0.19	0.73	0.00	0.54	0.00	0.04	Non-enriched
30	KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	0.06	0.01	0.00	0.03	0.11	0.18	0.26	0.80	0.00	0.75	0.00	0.04	Non-enriched
31	KEGG_NON_HOMOLOGOUS_END_JOINING	0.11	0.13	0.24	0.89	1.16	1.23	1.50	3.53	0.43	2.27	0.72	1.00	Non-enriched
32	KEGG_NON_SMALL_CELL_LUNG_CANCER	0.06	0.01	0.00	0.05	0.12	0.16	0.22	0.48	0.00	0.48	0.00	0.03	Non-enriched
33	KEGG_O_GLYCAN_BIOSYNTHESIS	0.06	0.01	0.00	0.03	0.13	0.18	0.26	0.78	0.00	0.71	0.00	0.05	Non-enriched
34	KEGG_OTHER_GLYCAN_DEGRADATION	0.06	0.01	0.00	0.04	0.15	0.18	0.26	1.45	0.00	0.65	0.00	0.07	Non-enriched
35	KEGG_OXIDATIVE_PHOSPHORYLATION	0.08	0.02	0.00	0.06	0.18	0.22	0.36	0.73	0.00	0.70	0.01	0.07	Non-enriched
36	KEGG_PANTOTHENATE_AND_COA_BIOSYNTHESIS	0.06	0.01	0.00	0.08	0.16	0.22	0.29	0.91	0.00	0.59	0.01	0.10	Non-enriched
37	KEGG_PENTOSE_AND_GLUCURONATE_INTERCONVERSIONS	0.06	0.01	0.00	0.07	0.16	0.23	0.33	1.00	0.00	0.91	0.00	0.05	Non-enriched
38	KEGG_PEROXISOME	0.06	0.03	0.01	0.28	0.43	0.44	0.58	1.06	0.01	0.83	0.06	0.16	Non-enriched
39	KEGG_PRION_DISEASES	0.06	0.01	0.00	0.03	0.08	0.12	0.19	0.40	0.00	0.40	0.00	0.04	Non-enriched
40	KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	0.14	0.03	0.00	0.13	0.26	0.24	0.33	0.55	0.00	0.55	0.00	0.03	Non-enriched
41	KEGG_PROSTATE_CANCER	0.06	0.02	0.00	0.25	0.35	0.37	0.47	1.07	0.04	0.67	0.06	0.29	Non-enriched
42	KEGG_PROXIMAL_TUBULE_BICARBONATE_RECLAMATION	0.07	0.01	0.00	0.02	0.08	0.17	0.30	0.84	0.00	0.64	0.00	0.05	Non-enriched
43	KEGG_RIBOFLAVIN_METABOLISM	0.08	0.02	0.00	0.08	0.15	0.19	0.25	0.65	0.00	0.62	0.00	0.04	Non-enriched
44	KEGG_RIBOSOME	0.08	0.01	0.00	0.06	0.13	0.16	0.25	0.59	0.00	0.47	0.00	0.05	Non-enriched
45	KEGG_SMALL_CELL_LUNG_CANCER	0.07	0.01	0.00	0.08	0.19	0.20	0.27	1.10	0.00	0.56	0.01	0.19	Non-enriched
46	KEGG_STEROID_HORMONE_BIOSYNTHESIS	0.07	0.02	0.00	0.05	0.16	0.22	0.32	0.88	0.00	0.71	0.01	0.09	Non-enriched
47	KEGG_TASTE_TRANSDUCTION	0.06	0.02	0.00	0.09	0.22	0.30	0.49	1.05	0.00	0.82	0.02	0.10	Non-enriched
48	KEGG_TRYPTOPHAN_METABOLISM	0.07	0.01	0.00	0.05	0.16	0.19	0.29	0.91	0.00	0.56	0.00	0.06	Non-enriched
49	KEGG_TYPE_I_DIABETES_MELLITUS	0.08	0.01	0.00	0.08	0.16	0.20	0.29	0.97	0.00	0.51	0.01	0.12	Non-enriched
50	KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	0.06	0.01	0.00	0.06	0.16	0.18	0.25	0.63	0.00	0.56	0.00	0.04	Non-enriched
51	KEGG_VIBRIO_CHOLERAE_INFECTION	0.14	0.04	0.00	0.19	0.25	0.28	0.35	1.05	0.04	0.55	0.03	0.48	Non-enriched
52	KEGG_VIRAL_MYOCARDITIS	0.08	0.01	0.00	0.04	0.11	0.18	0.21	0.91	0.00	0.91	0.00	0.04	Non-enriched
53	KEGG_WNT_SIGNALING_PATHWAY	0.06	0.01	0.05	0.11	0.17	0.19	0.25	0.46	0.05	0.40	0.00	0.07	Non-enriched

Table S15. Enrichment summary of repressed genes in DEPICT for smoking