Supplementary Information

Co-occurring expression and methylation QTLs allow detection of common causal variants and shared biological mechanisms

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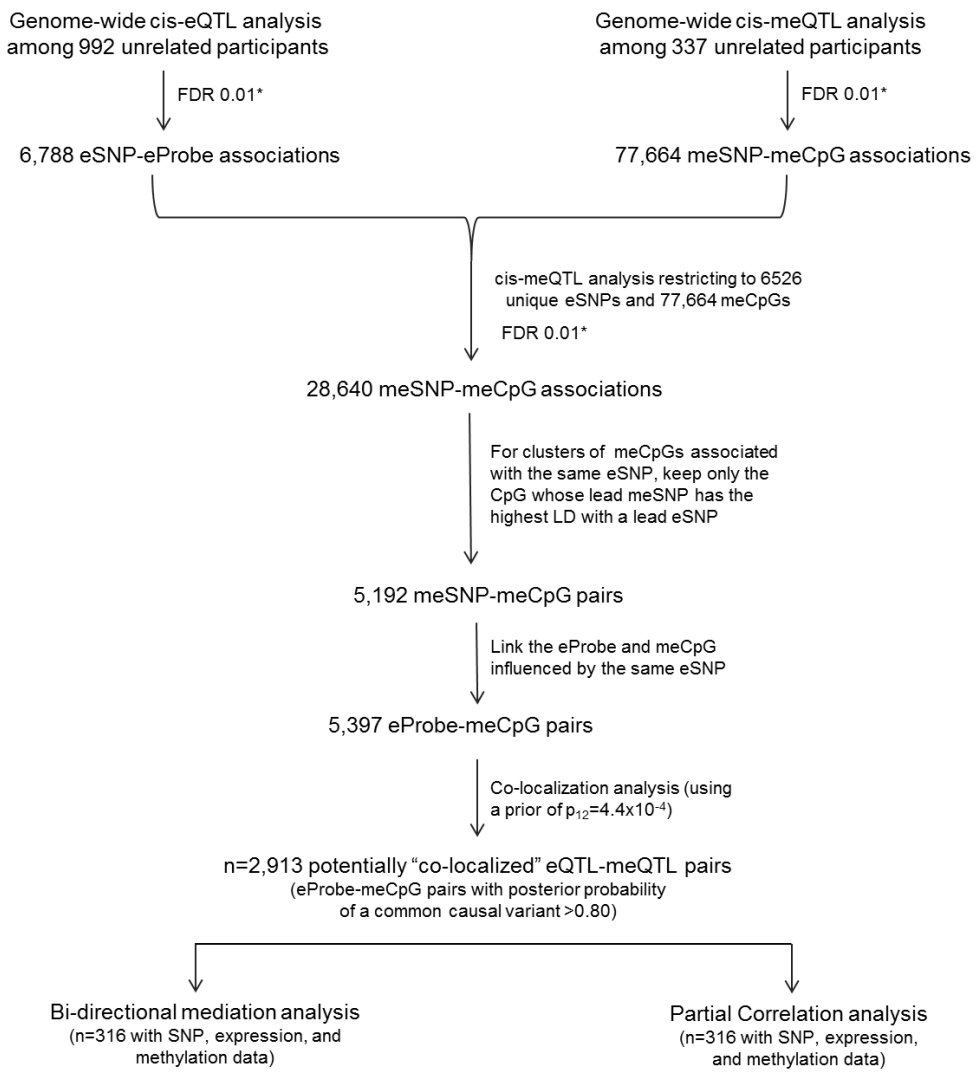
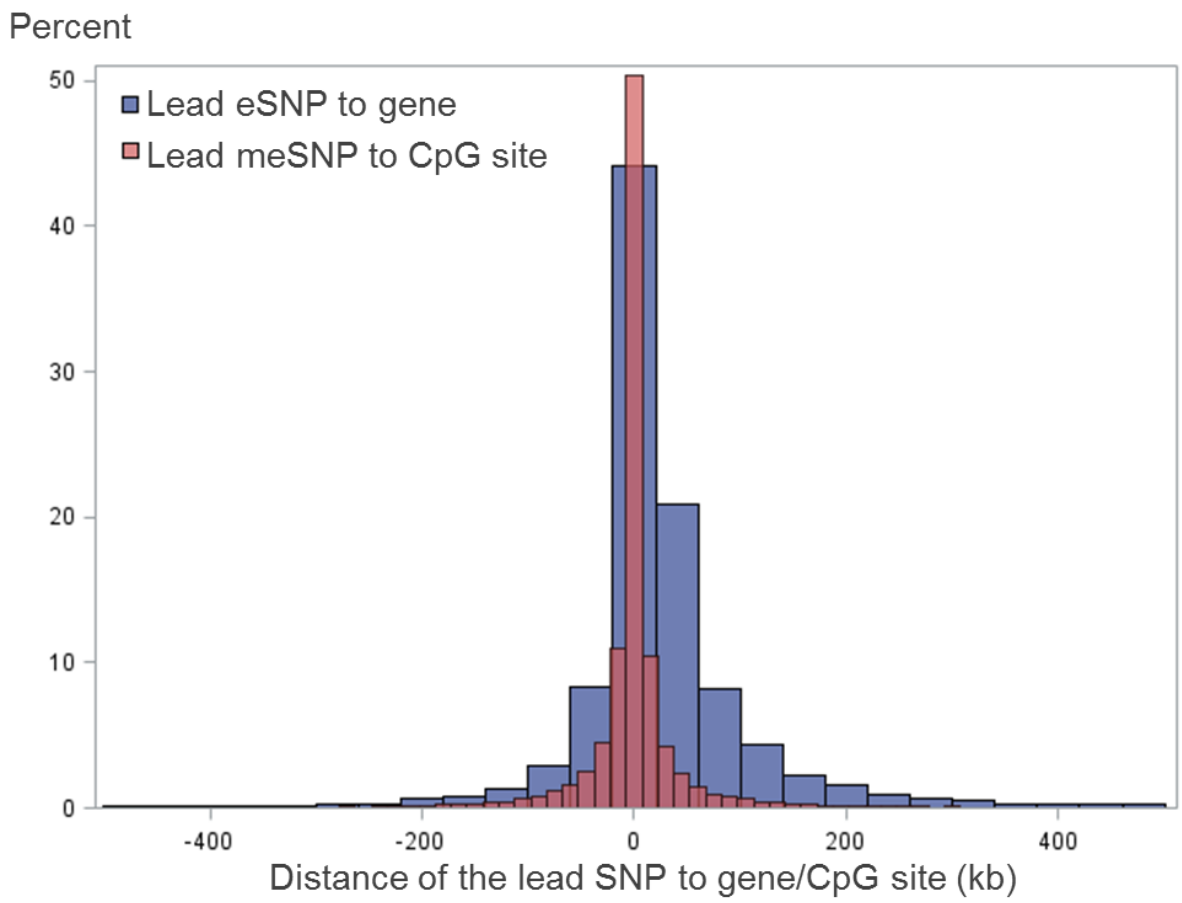
Supplementary Table 1. Logistic regression of Sobel P (SME) <0.05, Sobel P (SEM) <0.05, and Partial correlation P<0.05 on eQTL/meQTL P-values

Predictors	Outcome					
	Sobel P (SME) <0.05		Sobel P (SEM) <0.05		Corr. P<0.05	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
cis-eQTL P-value quartiles						
Quartile 1 (largest P-value)	1	Ref	1	Ref	1	Ref
Quartile 2	1.63 (1.10, 2.42)	0.02	3.38 (1.84, 6.22)	<.0001	1.32 (0.95, 1.82)	0.1
Quartile 3	2.61 (1.80, 3.77)	<.0001	7.56 (4.27, 13.40)	<.0001	1.86 (1.36, 2.53)	<.0001
Quartile 4 (smallest P-value)	2.91 (2.02, 4.19)	<.0001	9.86 (5.61, 17.33)	<.0001	2.21 (1.64, 3.00)	<.0001
cis-meQTL P-value quartiles						
Quartile 1 (largest P-value)	1	Ref	1	Ref	1	Ref
Quartile 2	1.41 (0.95, 2.08)	0.09	1.38 (0.90, 2.11)	0.14	1.15 (0.84, 1.58)	0.39
Quartile 3	2.02 (1.40, 2.92)	0.0002	1.99 (1.33, 2.96)	0.0008	1.45 (1.07, 1.97)	0.02
Quartile 4 (smallest P-value)	3.04 (2.14, 4.31)	<.0001	2.65 (1.80, 3.90)	<.0001	2.06 (1.54, 2.77)	<.0001

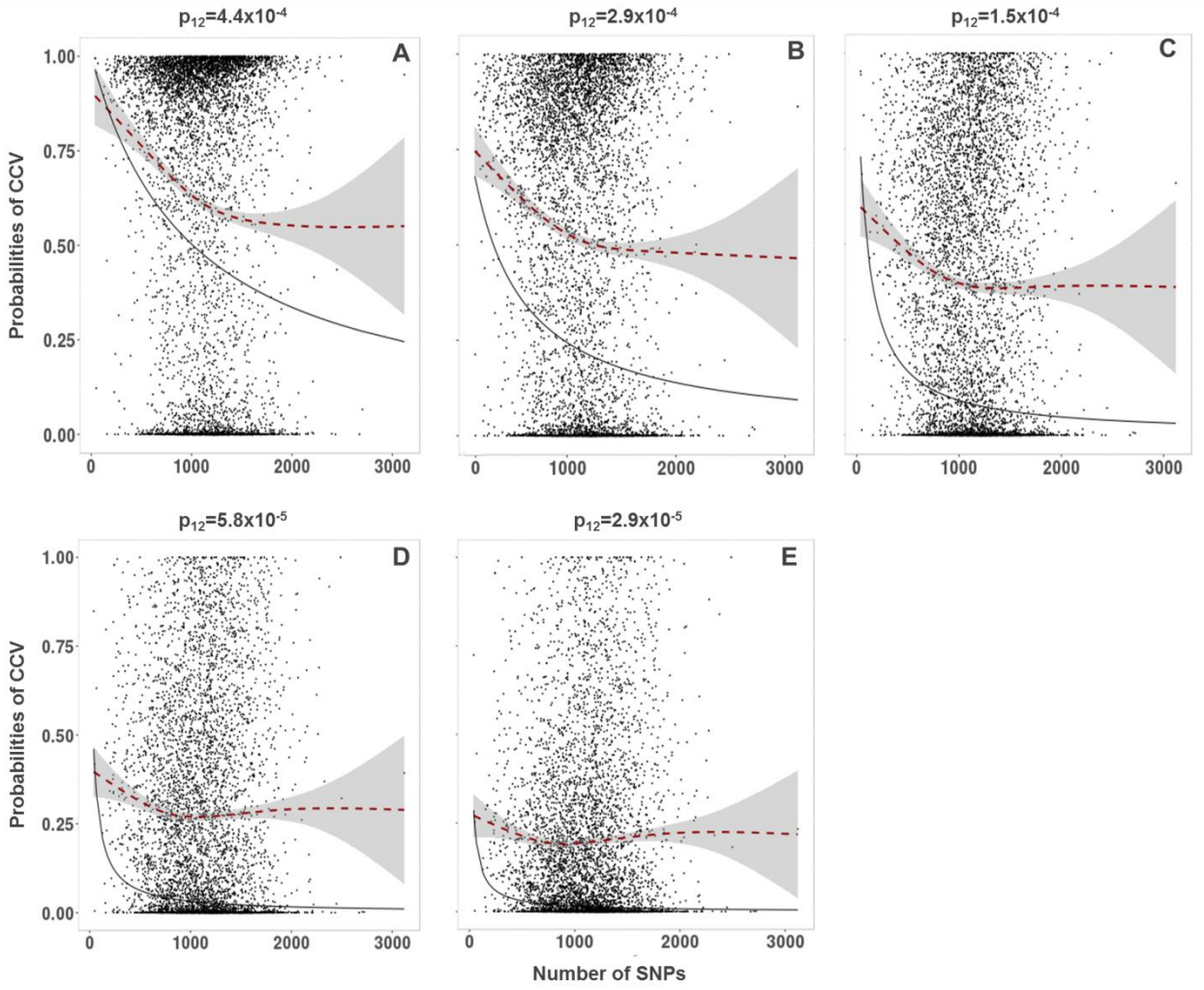
The sample size consists of 2,913 gene expression probe-SNP-CpG trios with posterior probability of one common causal variant >0.80.



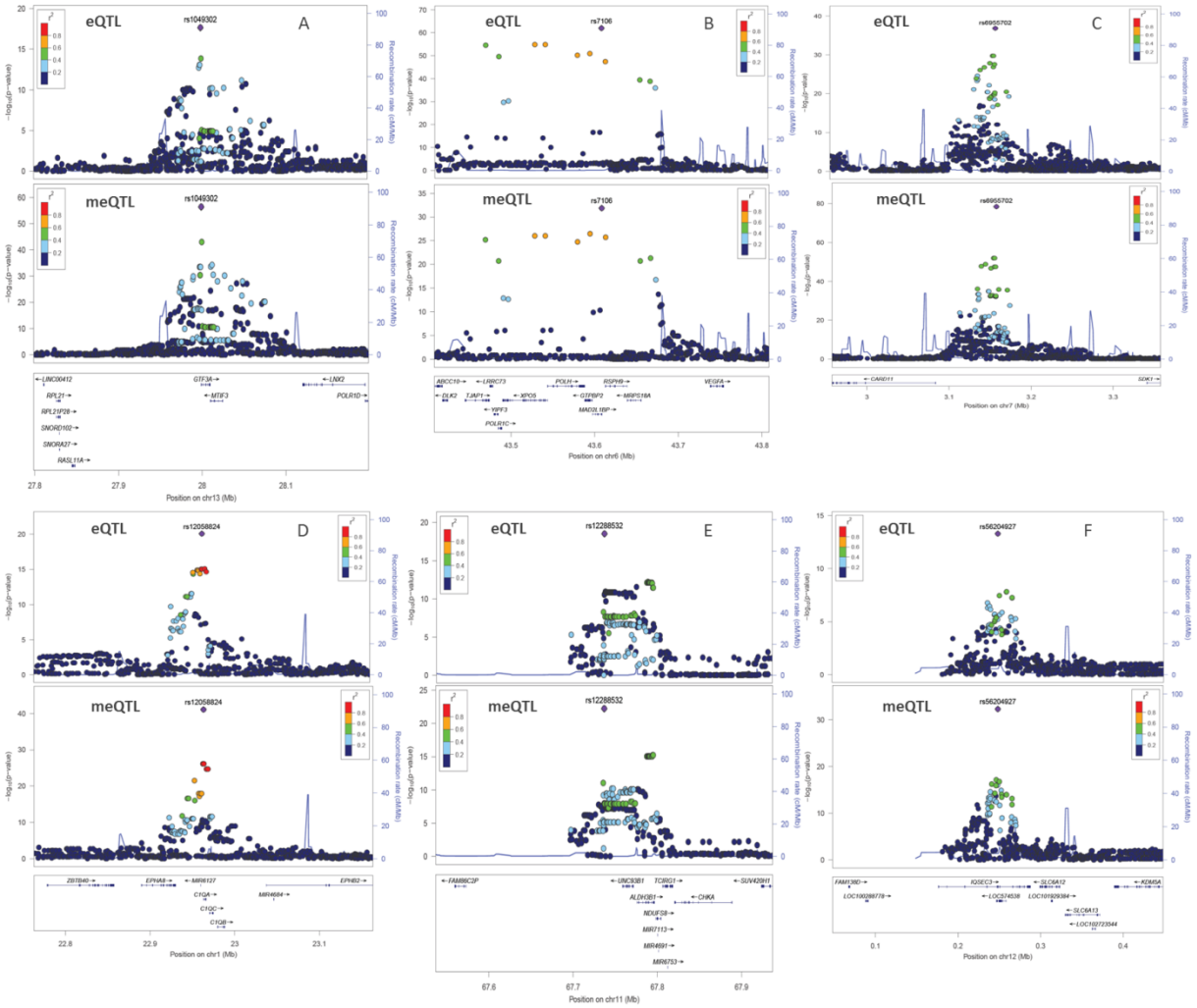
Supplementary Figure 1. Workflow for identifying eQTLs, meQTLs, and co-localized eQTL-meQTL pairs. *Beta distribution-adjusted empirical p-values from FastQTL were used to calculate q-values (Storey & Tibshirani, PNAS, 2003), and a false discovery rate (FDR) threshold of <0.01 was applied at the probe level to identify eProbes/meCpGs with a significant eQTL/meQTL.



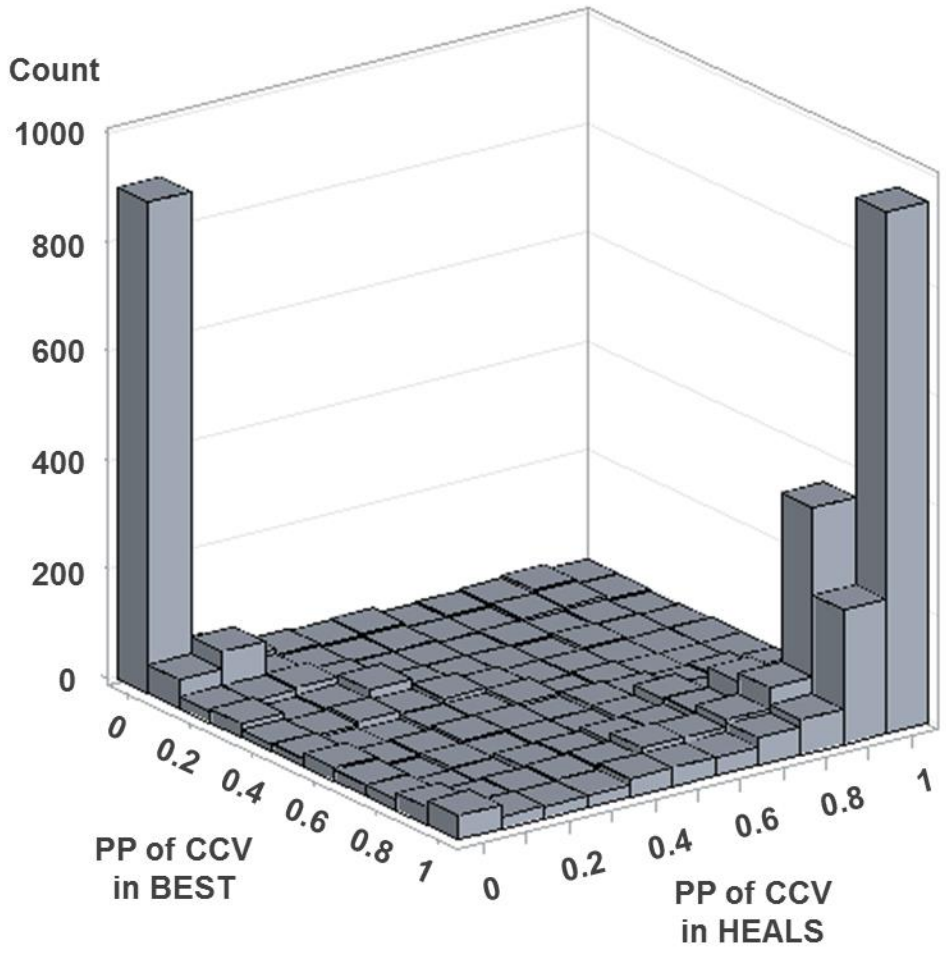
Supplementary Figure 2. Distance of the lead eSNP to the transcript start site of the target gene (n=6,788) and the distance of the lead meSNP to the affected CpG site (n=77,664).



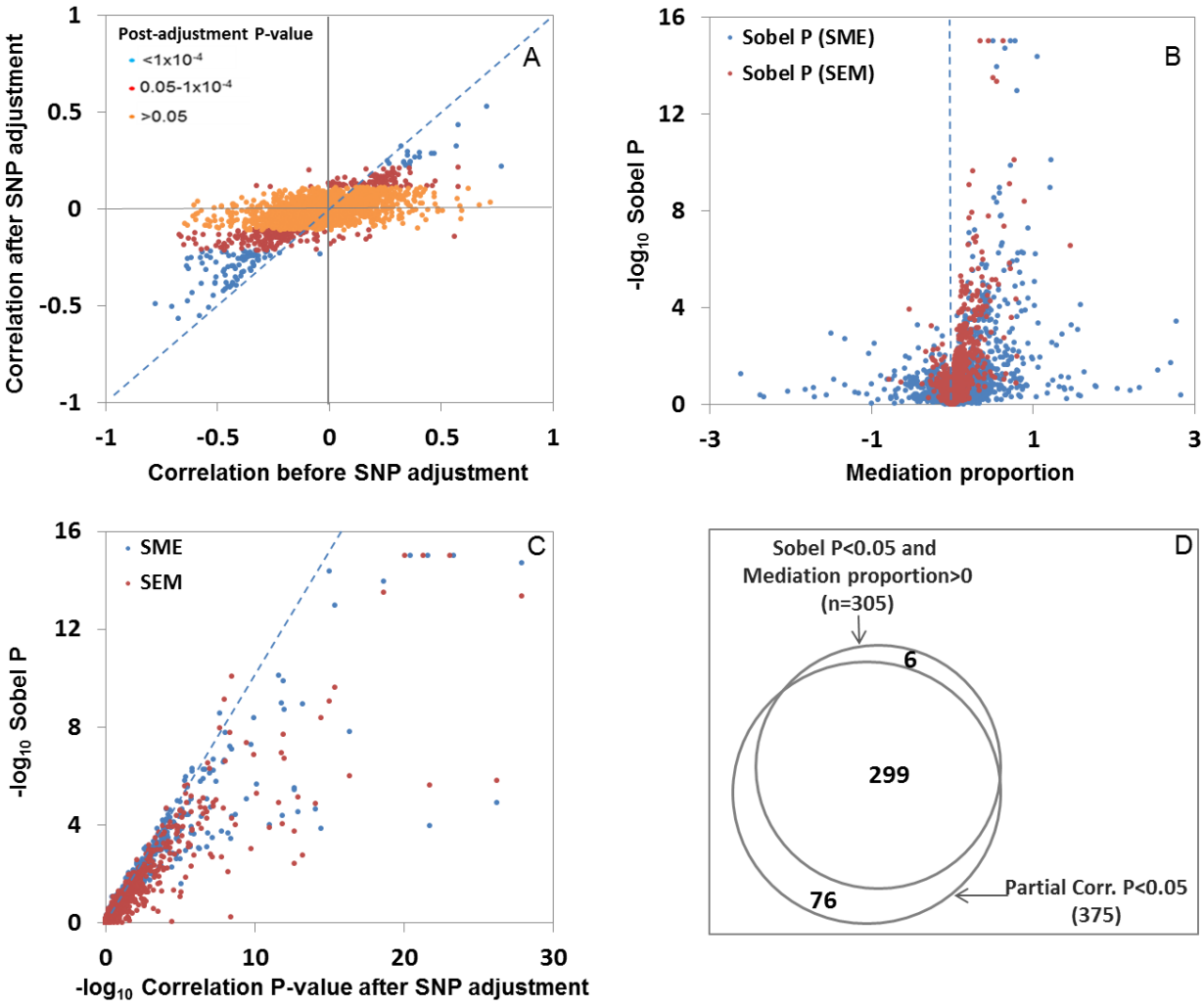
Supplementary Figure 3. Effect of choice of prior probability (p_{12}) of common causal variant (CCV) on the posterior probability of a CCV. For each eQTL-meQTL pair undergoing co-localization analyses, we plotted the relative posterior support for a CCV (as opposed to distinct causal variants, DCV) for each co-localization test, defined by PP of CCV/(PP of DCV + PP of CCV), against the number of SNPs used for each co-localization test . The red dotted line is the Loess smoothing curve of these points. The black solid line is the relative prior support for a CCV, based on the values selected the priors (p_1, p_2, and p_{12}), calculated using the equation provided by Guo *et al*.[22] This data is restricted to co-localization tests with a posterior probability of two distinct causal variants (PP of DCV) + posterior probability of common causal variant (PP of CCV) > 0.8 (100 out of 5397 tests excluded).



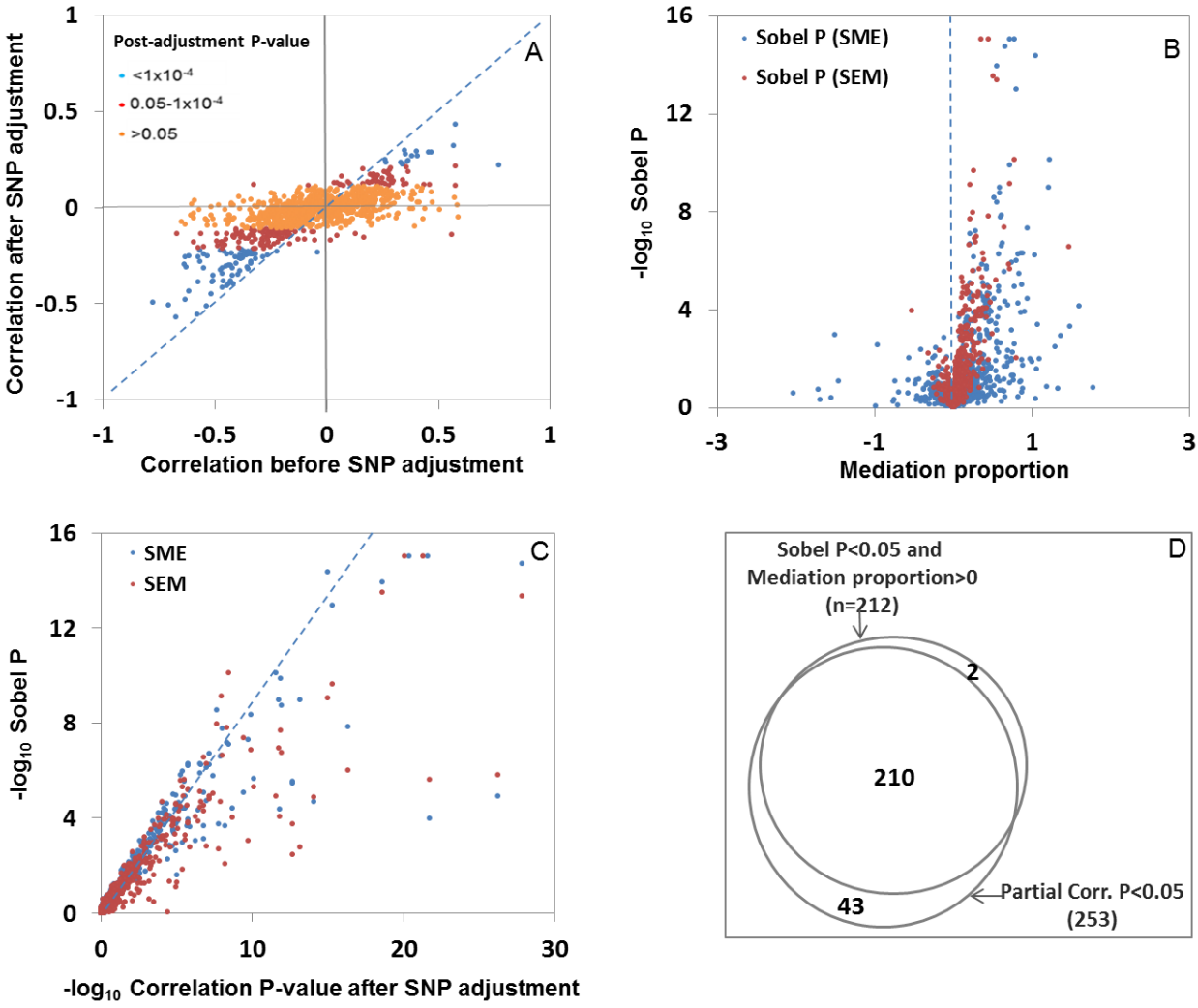
Supplementary Figure 4. Locus zoom plots for 6 examples of co-localized eQTL-meQTL pairs in Figure 3. The color of the dots in the eQTL plots reflects the LD r^2 level to the lead meSNP for the corresponding CpG site and the color of the dots in the meQTL plots reflects the LD r^2 level to the lead eSNP for the corresponding gene.



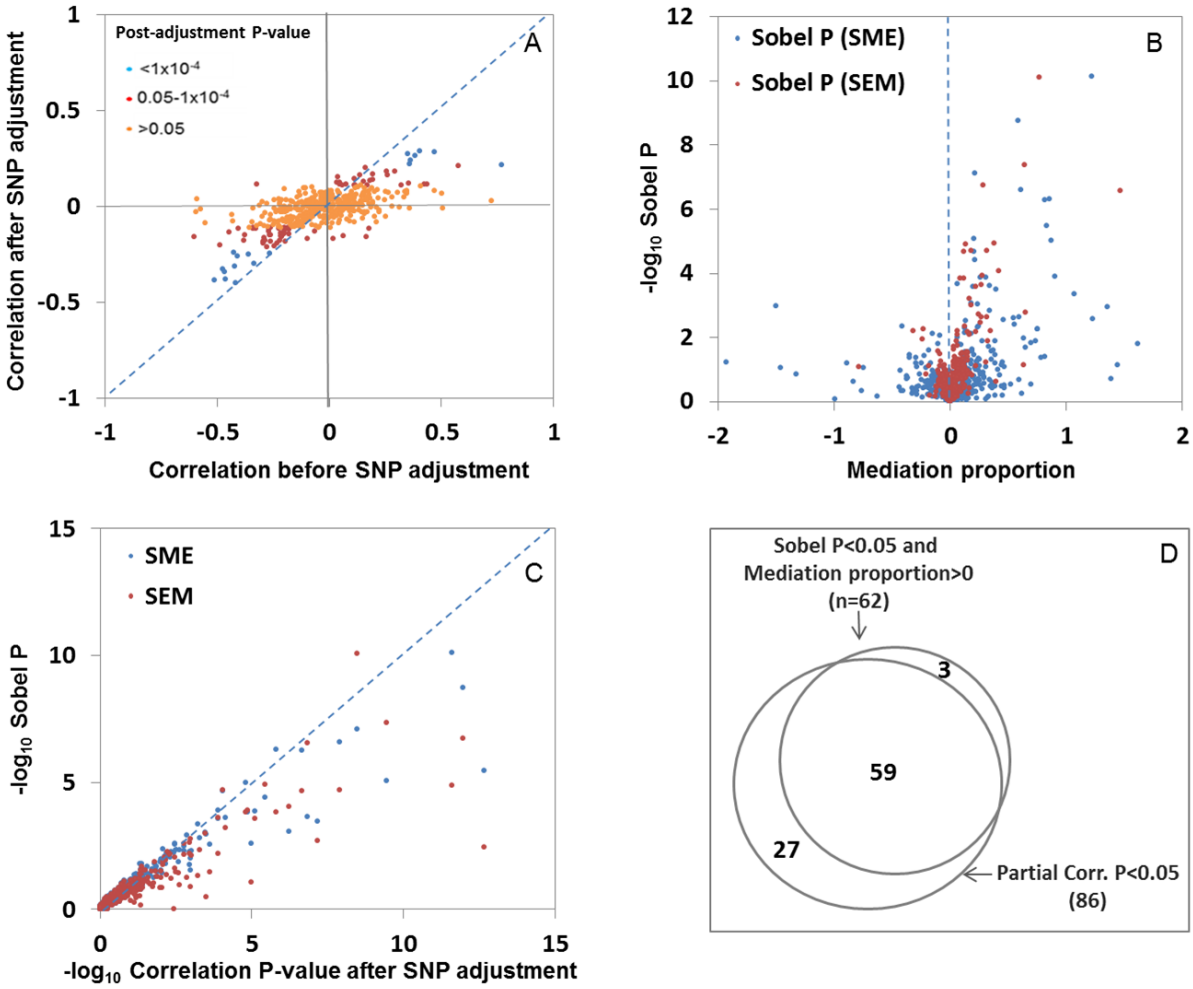
Supplementary Figure 5. Results of replication of co-localization analyses for 4,875 eQTL-meQTL pairs. The histogram compares the posterior probability (PP) of a common causal variant (CCV) based on BEST methylation data (450K array) to PP of CCV based on HEALS methylation data (EPIC array). Both analyses use a p_{12} value of 4.4×10^{-4}.



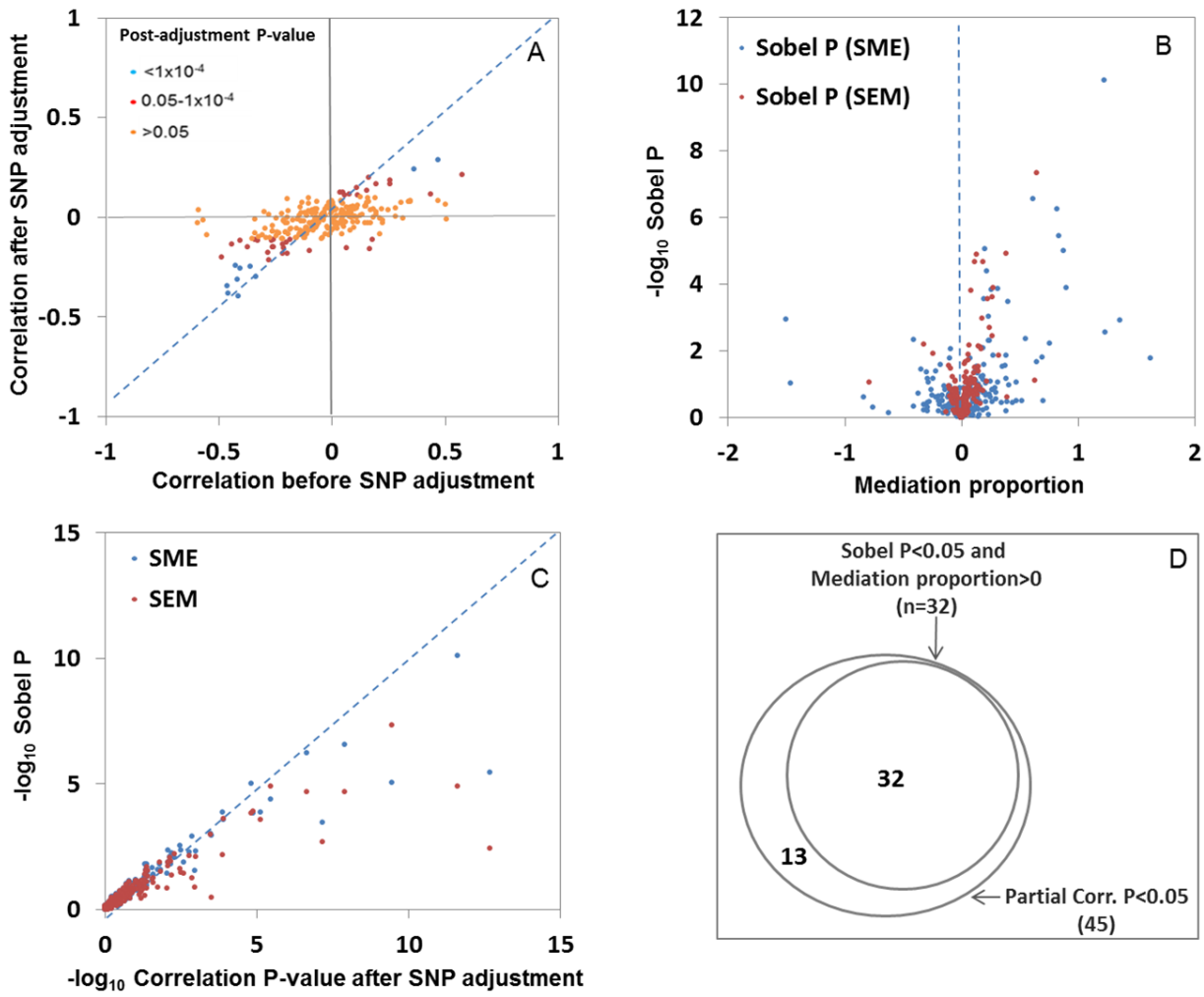
Supplementary Figure 6. Partial correlation and mediation analyses provide evidence for shared a regulatory mechanism (p_{12}=2.9x10^{-4}). Model for each of 2,098 potentially co-localized eQTL-mQTL pairs (using p_{12}=2.9x10^{-4}) includes adjustments for age, sex, and PCs from both the expression and methylation data (n=316). A: results from partial correlation analysis. B: Mediation analysis results for the SME and the SEM model. Mediation proportion outliers out of -3 to 3 ranges were removed from the figure and Sobel P outliers <10^{-15} were set to the 10^{-15}. C: Relationship between Sobel P from mediation analyses and the post-adjustment correlation P values from partial correlation analysis. Sobel P outliers <10^{-15} were set to the 10^{-15}. D: Venn diagram showing the concordance between mediation analysis and partial correlation analyses.



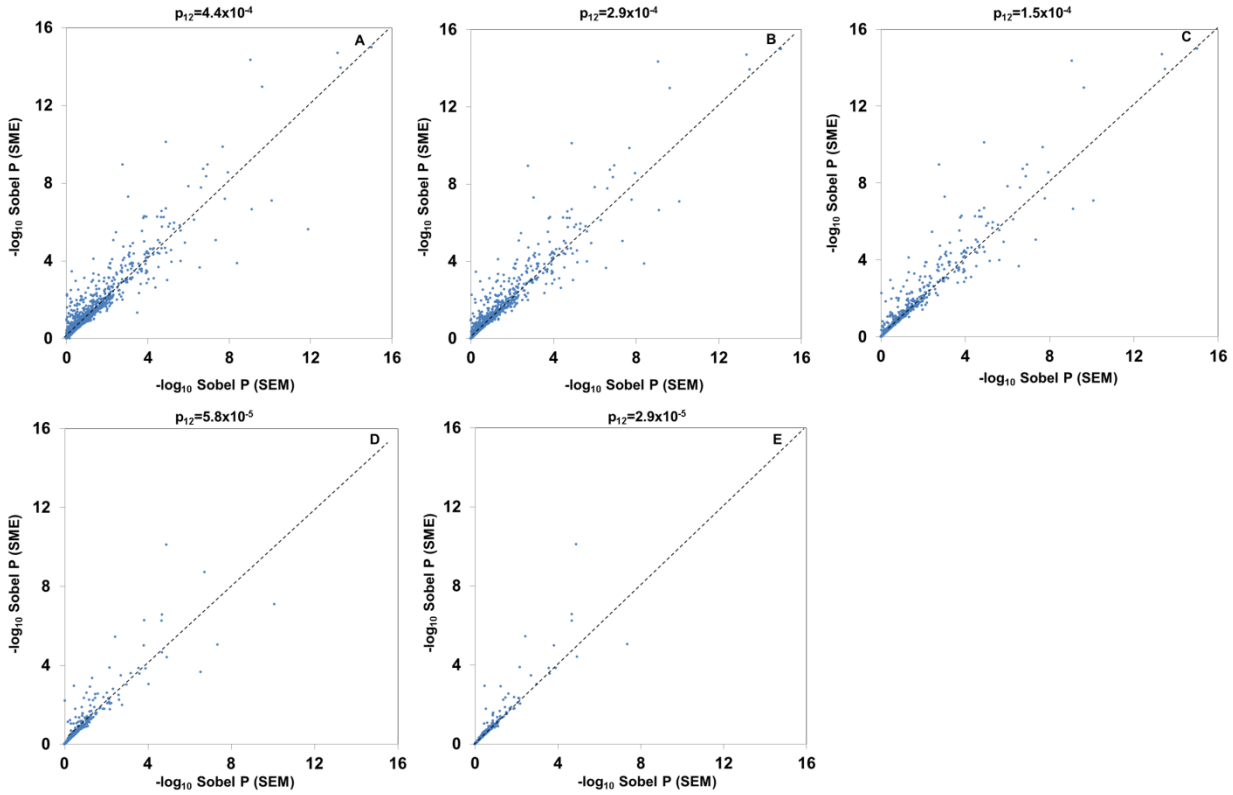
Supplementary Figure 7. Partial correlation and mediation analyses provide evidence for shared a regulatory mechanism (p_{12}=1.45x10^{-4}). Model for each of 1,047 potentially co-localized eQTL-mQTL pairs (using p_{12}=1.45x10^{-4}) includes adjustments for age, sex, and PCs from both the expression and methylation data (n=316). A: results from partial correlation analysis. B: Mediation analysis results for the SME and the SEM model. Mediation proportion outliers out of -3 to 3 ranges were removed from the figure and Sobel P outliers <10^{-15} were set to the 10^{-15}. C: Relationship between Sobel P from mediation analyses and the post-adjustment correlation P values from partial correlation analysis. Sobel P outliers <10^{-15} were set to the 10^{-15}. D: Venn diagram showing the concordance between mediation analysis and partial correlation analyses.



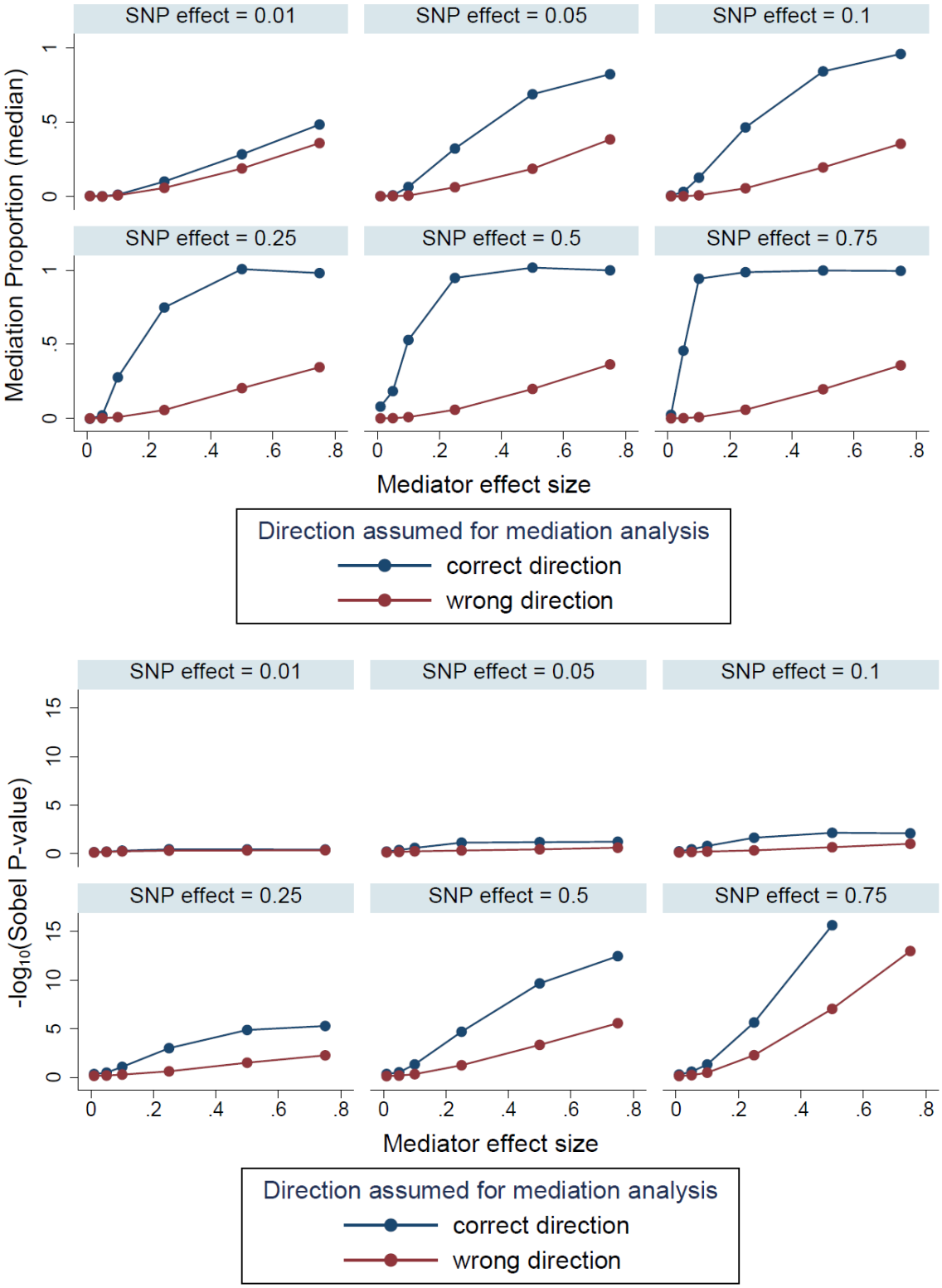
Supplementary Figure 8. Partial correlation and mediation analyses provide evidence for shared a regulatory mechanism (p_{12}=5.8x10^{-5}). Model for each of 473 potentially co-localized eQTL-mQTL pairs includes adjustments for age, sex, and PCs from both the expression and methylation data (n=316). A: results from partial correlation analysis. B: Mediation analysis results for the SME and the SEM model. C: Relationship between Sobel P from mediation analyses and the post-adjustment correlation P values from partial correlation analysis. D: Venn diagram showing the concordance between mediation analysis and partial correlation analyses.



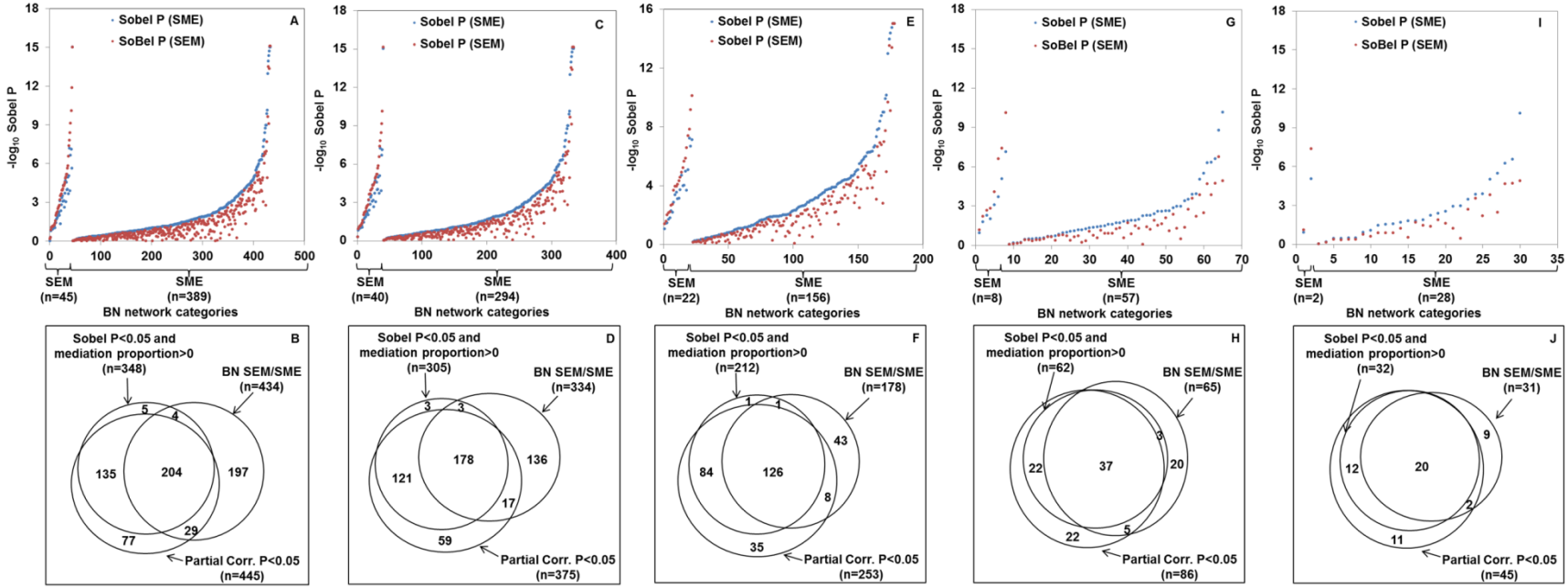
Supplementary Figure 9. Partial correlation and mediation analyses provide evidence for shared a regulatory mechanism (p_{12}=2.9x10^{-5}). Model for each of 266 potentially co-localized eQTL-mQTL pairs includes adjustments for age, sex, and PCs from both the expression and methylation data (n=316). A: results from partial correlation analysis. B: Mediation analysis results for the SME and the SEM model. C: Relationship between Sobel P from mediation analyses and the post-adjustment correlation P values from partial correlation analysis. D: Venn diagram showing the concordance between mediation analysis and partial correlation analyses.



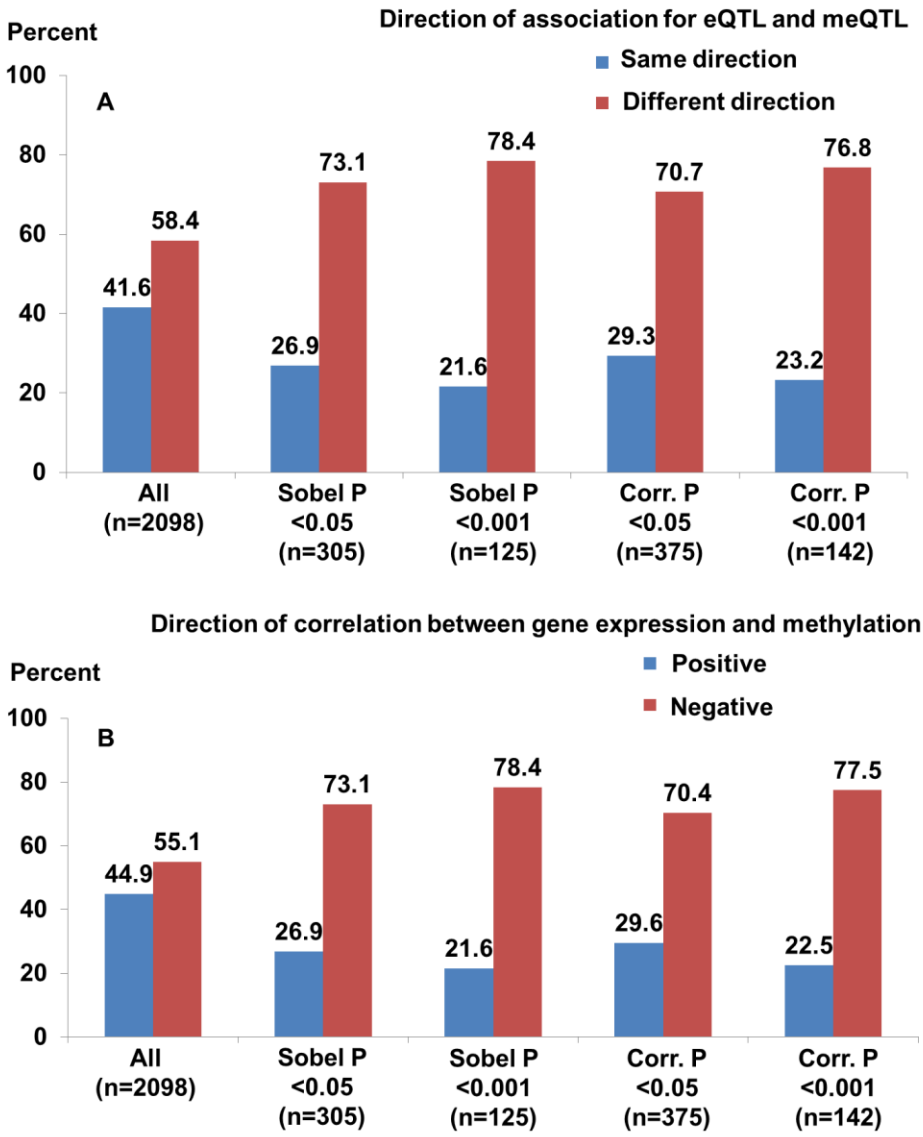
Supplementary Figure 10. Scatter plots of Sobel P values for SME and SEM models. A: p_{12}=4.4x10^{-4}; B: p_{12}=2.9x10^{-4}, C: p_{12}=1.45x10^{-4}, D: p_{12}=2.8x10^{-5}, E: p_{12}=2.9x10^{-5}



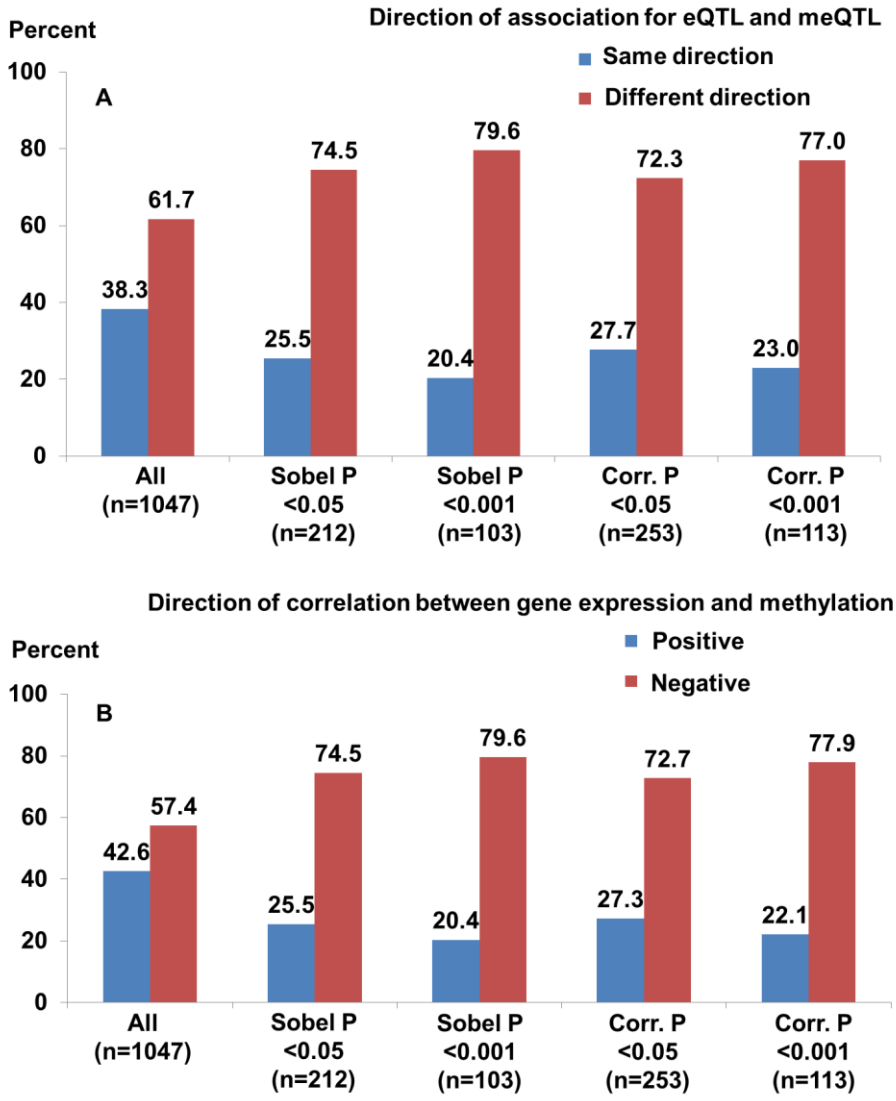
Supplementary Figure 11. Evidence for mediation will be stronger when the correct model is specified. Results are based on simulated data of sample size 316. The top panel reports the mediation proportion and the bottom panel reports the $-\log_{10}$(Sobel P), varying the effect sizes of the SNP and the mediator.



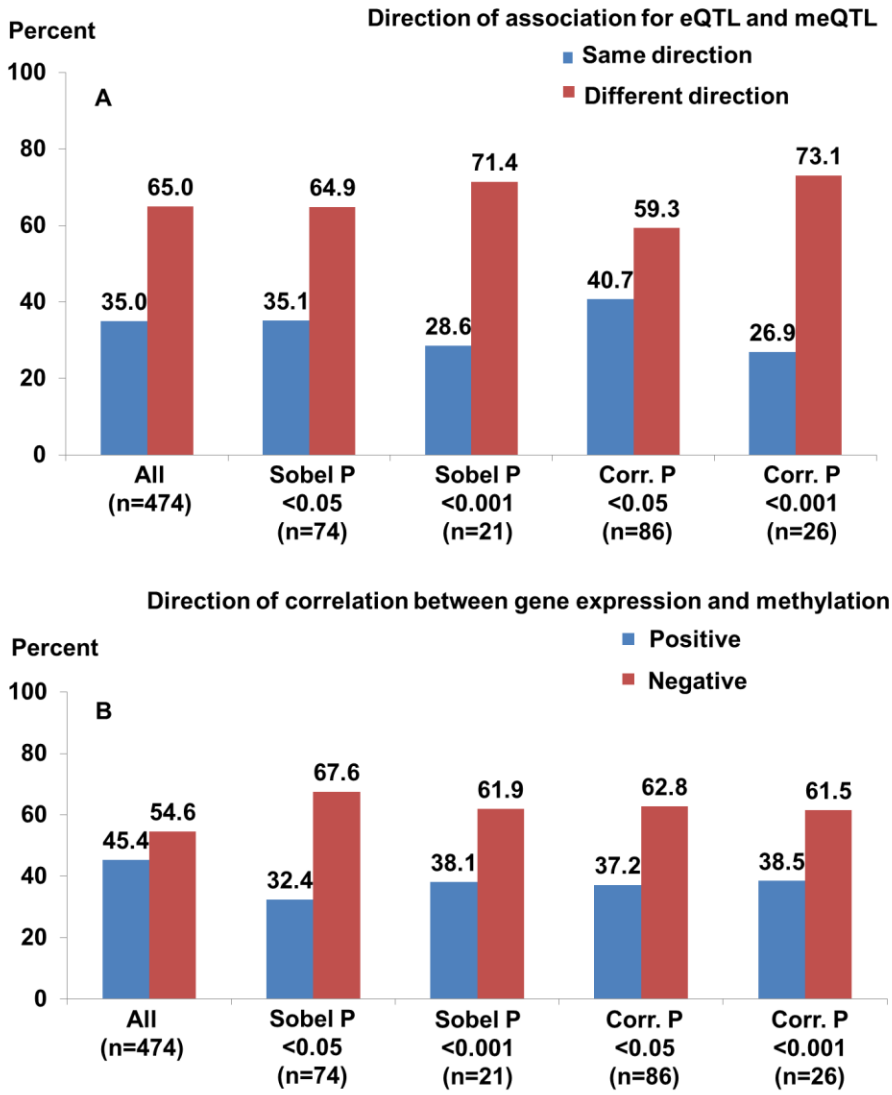
Supplementary Figure 12. Results from mediation analysis compared with Bayesian Network and partial correlation analyses. Upper panel: Sobel P values plotted according to the causal model selected by Bayesian network analyses. Lower panel: Venn Diagram demonstrating concordance among three methods for assessing evidence for a shared regulatory mechanism. Plot A and B: $p_{12}=4.4x10^{-4}$,Plot C and D: $p_{12}=2.9x10^{-4}$, Plot E and F: $p_{12}=1.5x10^{-4}$, Plot G and H: $p_{12}=5.8x10^{-5}$, Plot I and J: $p_{12}=2.9x10^{-5}$.



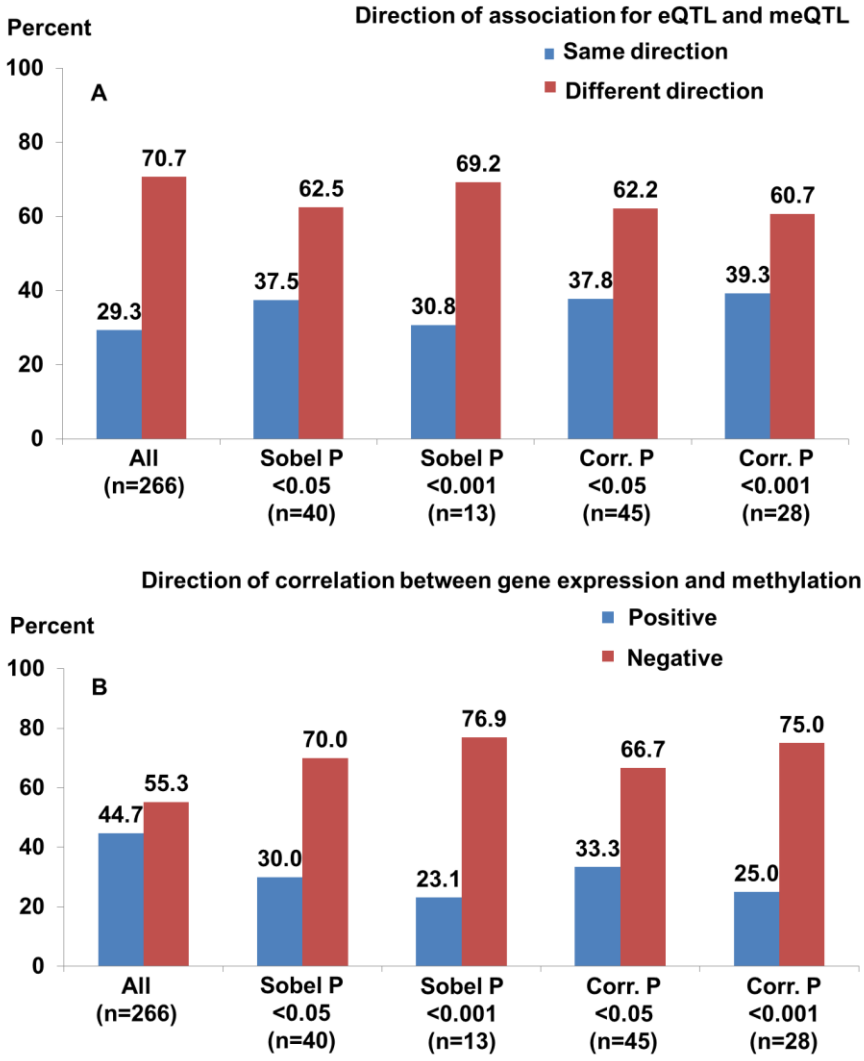
Supplementary Figure 13. Direction of QTL effects and associations between expression and methylation for co-localized eQTL-meQTL pairs. Co-localized pairs using a p_{12} value 2.9×10^{-4} are presented. Results are stratified according to P-values from mediation analysis (Sobel P) and partial correlation analysis (Corr. P). A: Histograms of the percentage of eQTL-meQTL pairs showing the same or different direction of association. B: Histograms of the percentage of eQTL-meQTL pairs for which the direction of association between gene expression and DNA methylation is positive or negative.



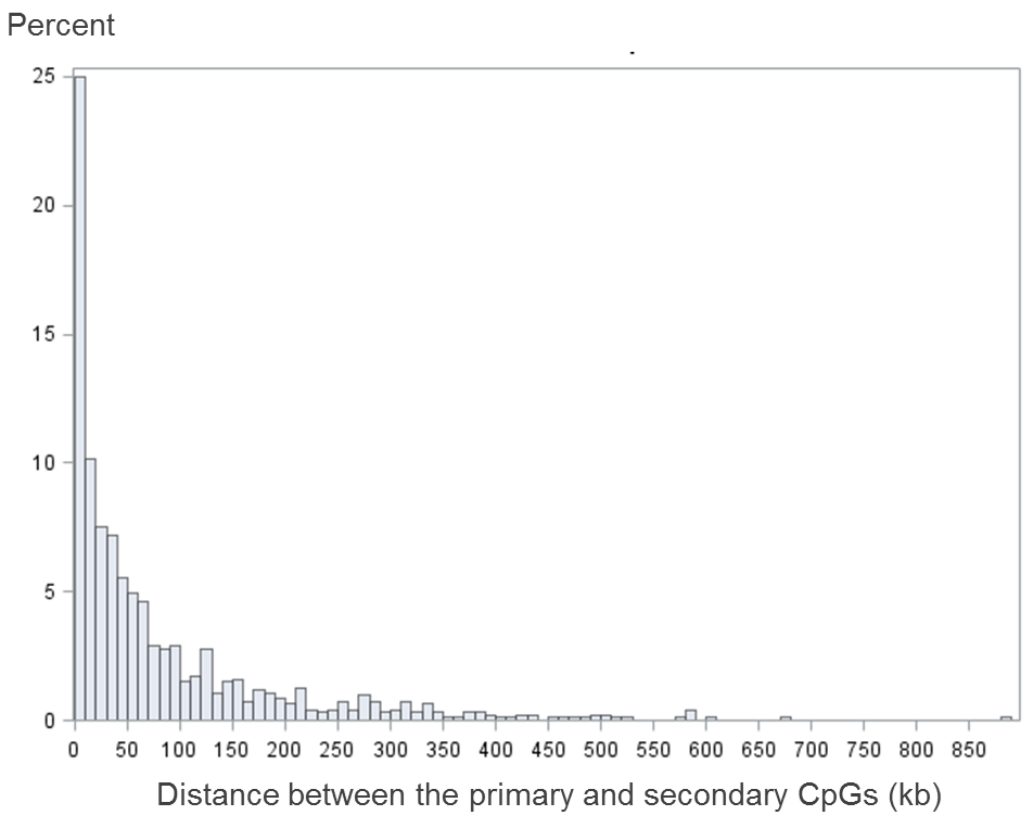
Supplementary Figure 14. Direction of QTL effects and associations between expression and methylation for co-localized eQTL-meQTL pairs. Co-localized pairs using a p_{12} value 1.45×10^{-4} are presented. Results are stratified according to P-values from mediation analysis (Sobel P) and partial correlation analysis (Corr. P). A: Histograms of the percentage of eQTL-meQTL pairs showing the same or different direction of association. B: Histograms of the percentage of eQTL-meQTL pairs for which the direction of association between gene expression and DNA methylation is positive or negative.



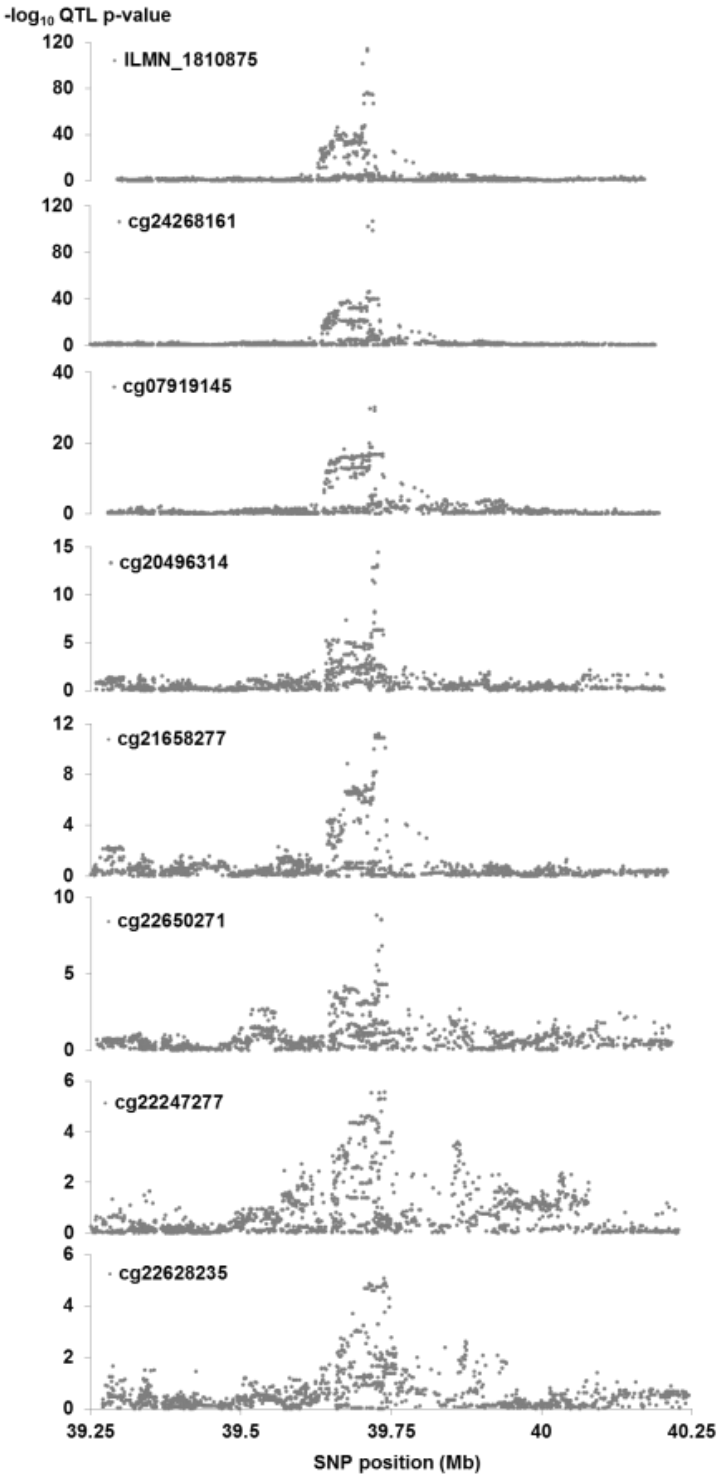
Supplementary Figure 15. Direction of QTL effects and associations between expression and methylation for co-localized eQTL-meQTL pairs. Co-localized pairs using a p_{12} value 5.8×10^{-5} are presented. Results are stratified according to P-values from mediation analysis (Sobel P) and partial correlation analysis (Corr. P). A: Histograms of the percentage of eQTL-meQTL pairs showing the same or different direction of association. B: Histograms of the percentage of eQTL-meQTL pairs for which the direction of association between gene expression and DNA methylation is positive or negative.



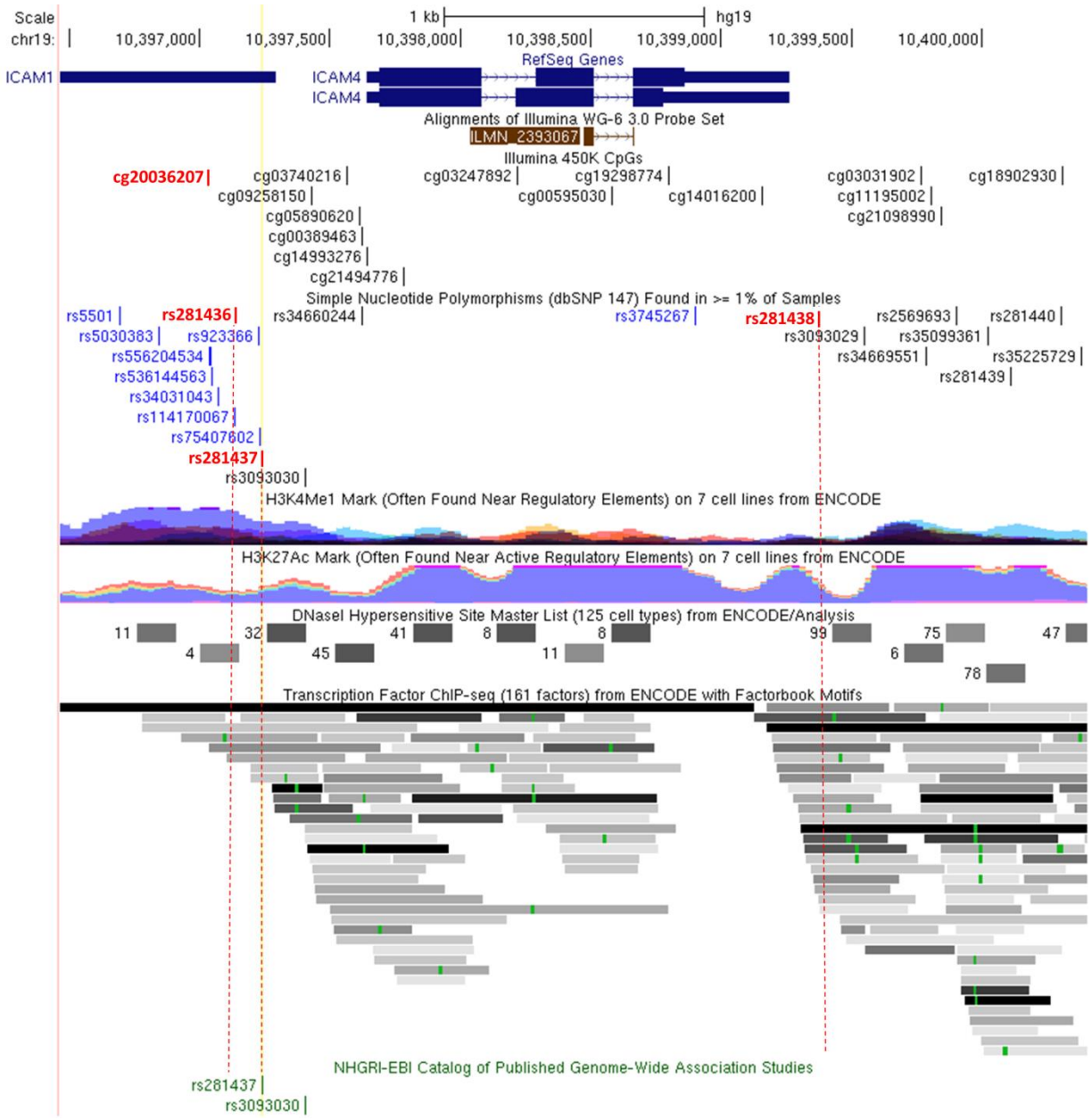
Supplementary Figure 16. Direction of QTL effects and associations between expression and methylation for co-localized eQTL-meQTL pairs. Co-localized pairs using a p_{12} value 2.9×10^{-5} are presented. Results are stratified according to P-values from mediation analysis (Sobel P) and partial correlation analysis (Corr. P). A: Histograms of the percentage of eQTL-meQTL pairs showing the same or different direction of association. B: Histograms of the percentage of eQTL-meQTL pairs for which the direction of association between gene expression and DNA methylation is positive or negative.



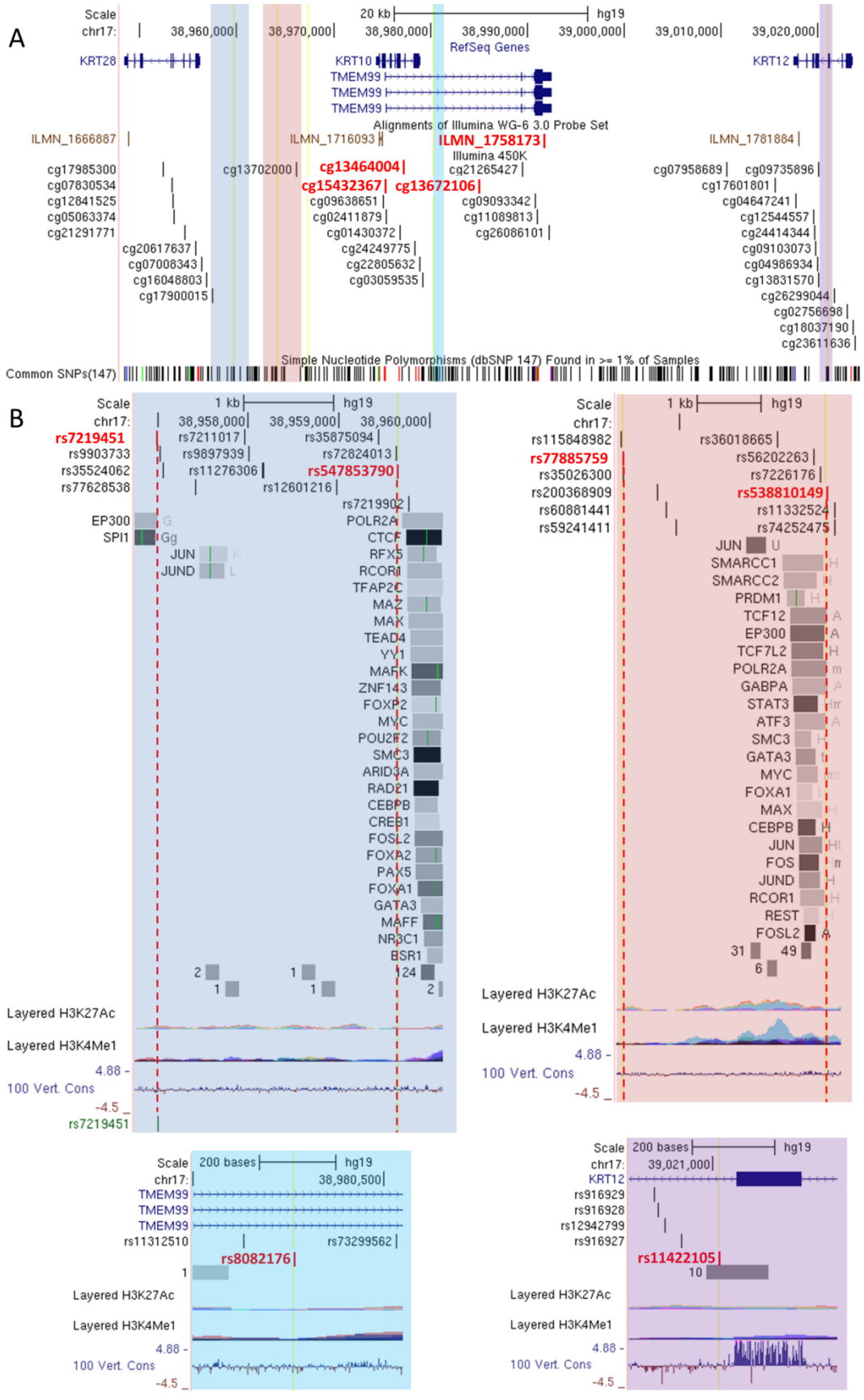
Supplementary Figure 17. Distribution of distance between the primary and secondary CpGs for n=955 cases with expression and primary methylation in the same direction but have at least one secondary CpG inversely associated with the CpG originally selected.



Supplementary Figure 18. Regional association plots for one eQTL affecting *SYNGR1* (ILMN_1810875) a co-localizing meQTL that affects seven nearby CpGs. The genomic region to which these association plots correspond is shown in Figure 8.



Supplementary Figure 19. Overlap with genomic annotations for three candidate causal SNPs for a co-localized eQTL-meQTL pair that shows strong evidence of mediation. Expression of the ICAM4 gene and methylation at nearby CpG cg20036207 (in red) are affected by a common causal variant. SNP rs281437 was the lead *cis*-eSNP for ILMN_2393067 ($P=10^{-23}$) which captures expression of all RefSeq isoforms of ICAM4. This eQTL co-localizes with a meQTL affecting methylation at cg20036207 (Probability of CCV>99%), with strong evidence of partial correlation (residual r= -0.30, $P=5x10^{-8}$) and mediation (SEM $P = 2x10^{-5}$; SME $P= 6x10^{-7}$). This SNP is in strong LD ($r^2>0.65$) with only two SNPs in the Bangladeshi population (1KG BEB), rs281436 ($r^2=0.97$) and rs281438 ($r^2=0.77$). The two SNPs showing the strongest association with methylation AND expression, rs281437 and rs281436, reside 107 bp apart, and rs281436 is ~ 100 bp from cg20036207.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Simple Nucleotide Polymorphisms (dbSNP 147) Found in >= 1% of Samples
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RAD21
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PAX5
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MAFF
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Supplementary Figure 20. Overlap with genomic annotations for six candidate causal SNPs for a co-localized eQTL-meQTL pair that shows strong evidence of mediation. Insertion rs538810149 was the lead *cis*-eSNP for expression probe ILMN_1758173 ($P=10^{-24}$) which captures expression of KMEM99 (Panel A). This eQTL co-localized with a meQTL associated with methylations at 3 CpG sites: cg13464004, cg15432367, and cg13672106 (Panel A). We observed strong evidence of partial correlation (residual r = -0.35; $P=3x10^{-10}$) and mediation (SEM $P=7x10^{-4}$; SME $P=5x10^{-8}$). This SNP is in strong LD with rs547853790 ($r^2=0.93$), rs7219451 ($r^2=0.93$), rs35026300 ($r^2=0.93$), rs8082176 ($r^2=0.92$), and rs11422105 ($r^2=0.86$). Panel B shows overlap of candidate causal variants with transcription factor binding sites, DNAse-I hypersensitivity sites, histone marks, and conversation among vertebrates, and GWAS SNPs (in that order). Panel B regions are color-coded to match the regions highlighted in Panel A. None of these SNPs show striking overlap with any of the regulatory features examined, other than rs11422105 which resides within a 10-tissue DNase-I hypersensitivity site.