

**Fig. S17. Opposite effect eQTLs.** Example of how multiple eQTLs may produce spurious signals of apparent “opposite effects” in SNP-by-SNP analyses. **(A)** Results from Bayesian multi-SNP analysis of gene ENSG00000167528 for two tissues (whole blood and skeletal muscle) indicate two different tissue-specific eQTLs in this region, one in each tissue. The x-axis labels the positions of interrogated SNPs relative to TSS; the y-axis shows the posterior probability assigned to each SNP being a casual eQTN, color-coded according to tissue specificity. (Due to LD, there is uncertainty about which SNP is the causal eQTN in each tissue — no posterior probability is close to 1, but the sums of the posterior probabilities from the blood-specific eQTLs and the skeletal muscle-specific eQTLs are both very close to 1.) **(B)** Plot of pairwise LD ( $r^2$ ) shows two blocks of SNPs: the SNPs showing strong signal in blood are in high LD, and the SNPs showing strong signal in skeletal muscle are in high LD. The two clusters are also moderately correlated ( $r^2 \sim 0.4$ ). **(C)** Estimated effect sizes in each tissue from a SNP-by-SNP analysis for the top SNP in each tissue in results from top panel. The SNPs show a significant effect in both tissues, but with effects in the opposite direction because the allele increasing expression in blood is positively correlated with the allele decreasing expression in skeletal muscle. **(D)** Effect size estimates from a standard linear regression of expression in each tissue on the two top SNPs. This joint analysis accounts for the modest LD between the two SNPs, and the apparent opposite effects from the SNP-by-SNP analysis disappear. Taken together, the results suggest that this region contains two eQTLs, one active in blood and the other active in skeletal muscle, and that LD between the two eQTLs produces a spurious pattern of opposite effects in the SNP-by-SNP analysis.

