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Supplemental Data

Are Interactions between *cis*-Regulatory Variants Evidence for Biological Epistasis or Statistical Artifacts?

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Supplemental Information

Supplemental Figures

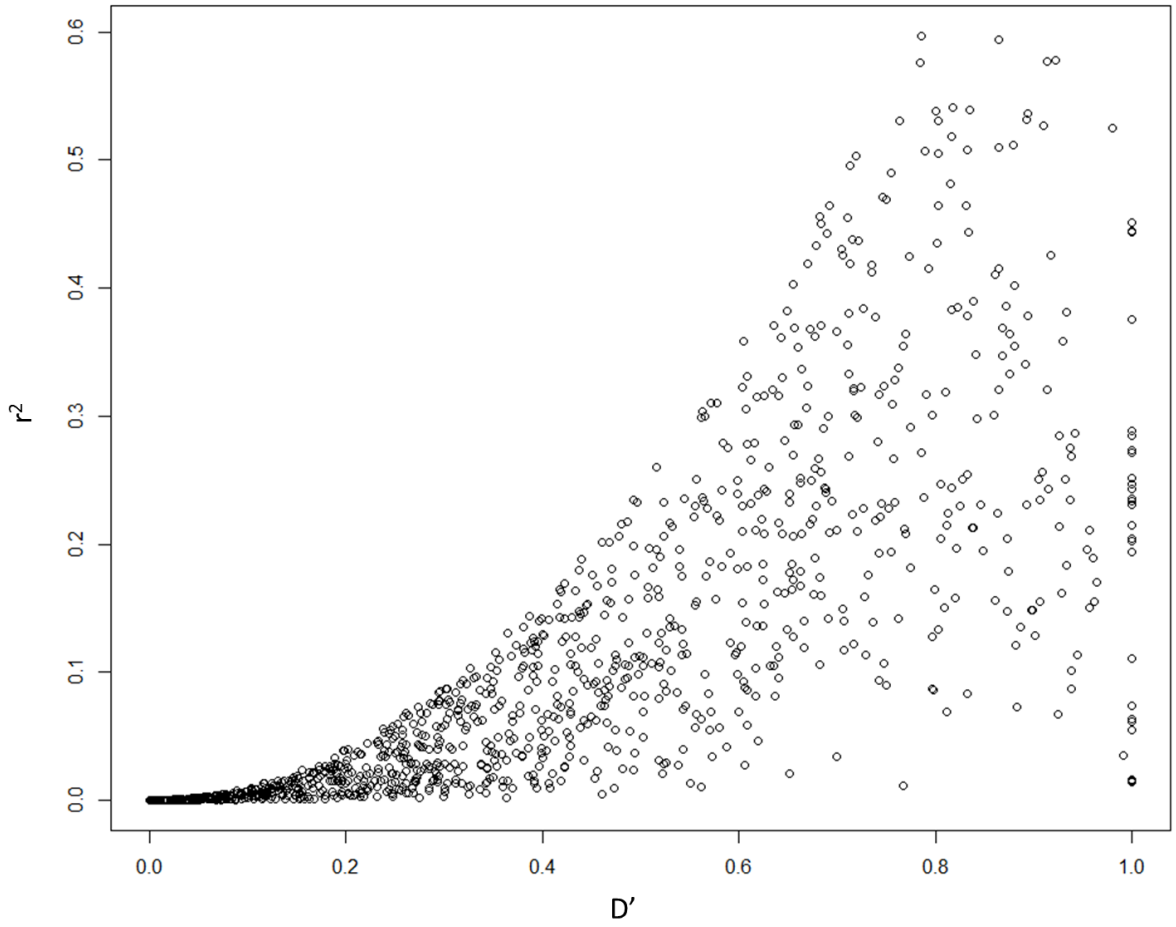


Figure S1. Linkage disequilibrium between interacting variants. We calculated LD between interacting variants using both r^2 and D' to determine if they were on the same haplotype. Interactions between variants in modest LD ($r^2 > 0.6$) had been removed from all stages of the analysis, and hence are not shown here.

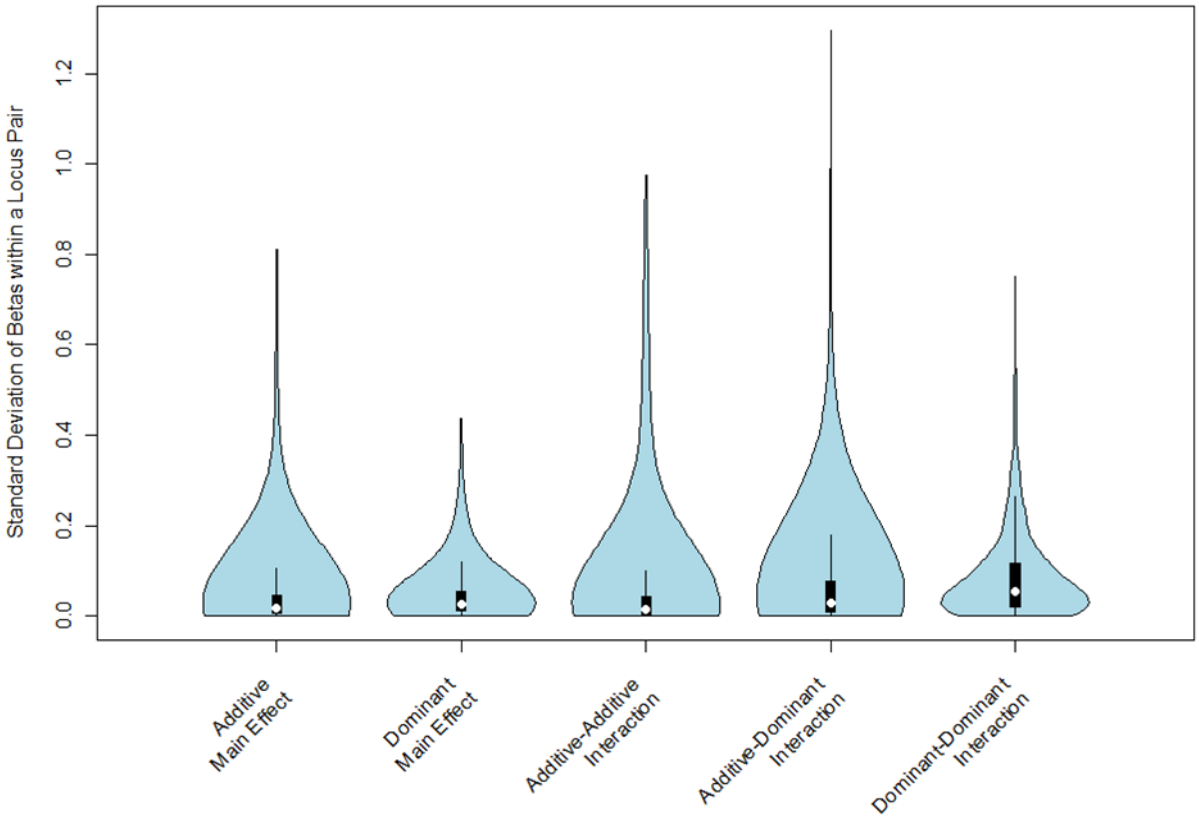


Figure S2. Redundant SNP-pairs have very similar parameter estimates. We grouped together all pairs of interacting SNPs (n=5,439) identified as being redundant through LD measures. For each group, we identified all terms that were significant in at least one of the associated interactions ($p < 0.05$). We extracted the βs for these significant terms from all interactions within the group. We then calculated the standard deviation of the βs for each significant term within each group to determine how similar the parameter estimates were across all interactions in the same group. The distribution of these standard deviations, categorized by type of variable, is shown above.

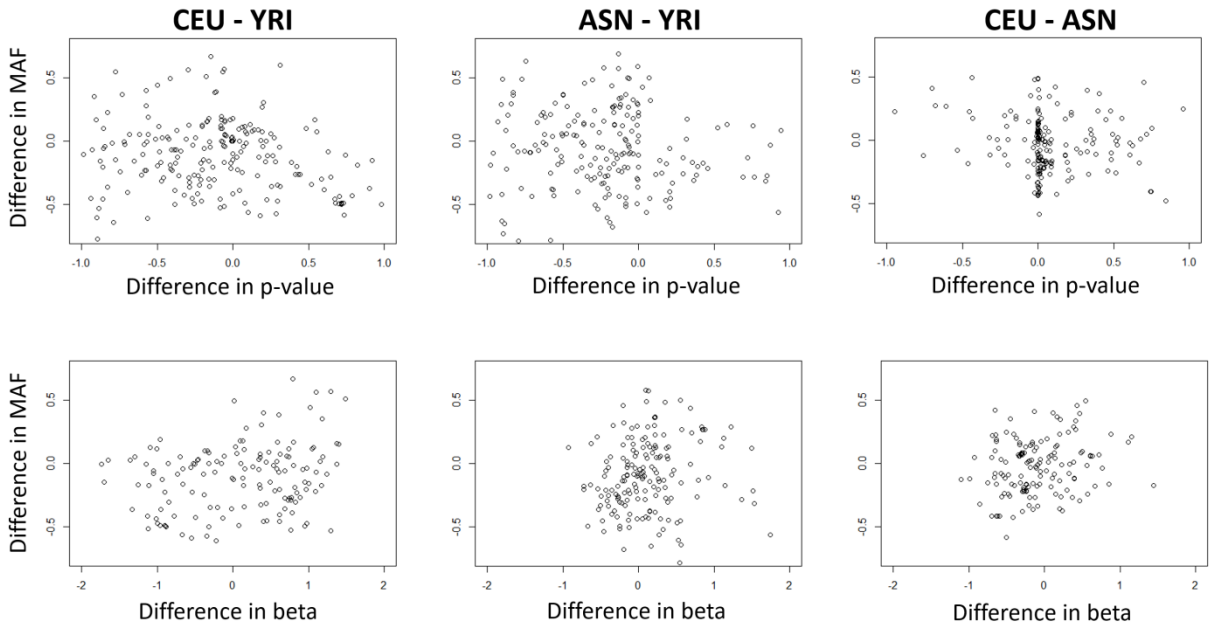
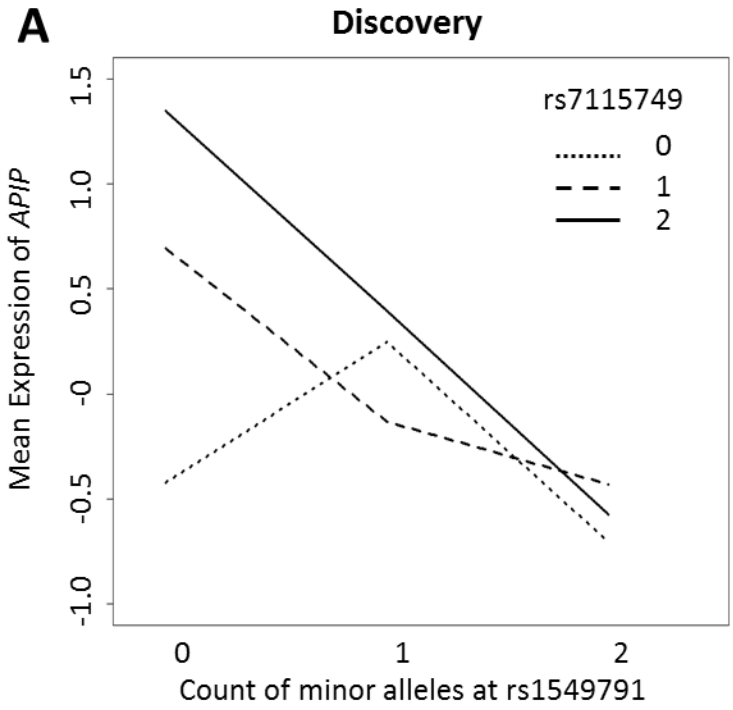


Figure S3. Investigation of population-specific *cis*-eQTL. To investigate whether or not population-specific *cis*-eQTL were caused by reduced power to detect significant marginal effects in the stratified analysis, or by different marginal effects for the same variant, we performed pairwise comparisons of MAF, additive β (marginal), and p-value (of the *cis*-eQTL) by ethnicity.



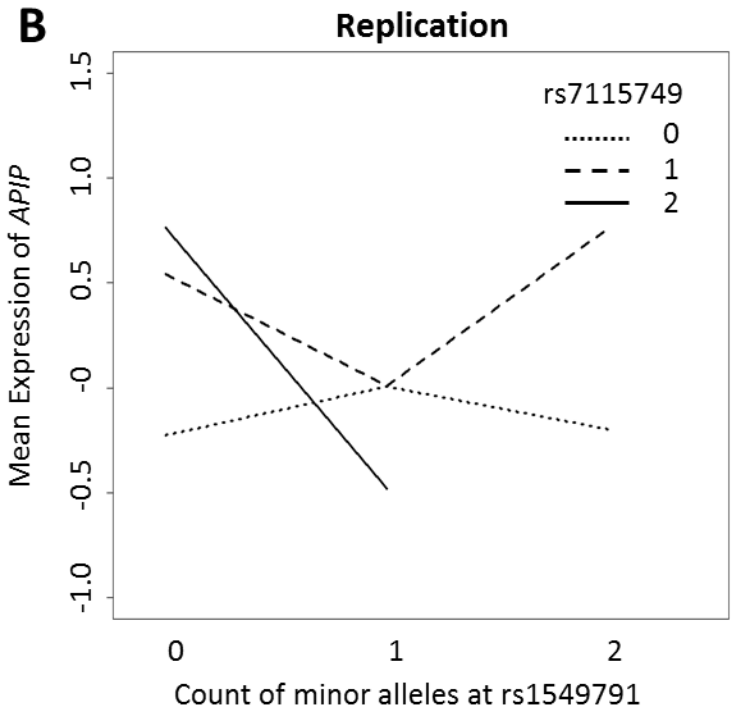


Figure S4. The interaction between rs1549791 and rs7115749 associated with the expression of *APIP* is not consistent between the discovery and replication datasets. In the

interaction plot, each individual is categorized according to their two-locus genotype at rs1549791 and rs7115749. This results in nine possible genotype combinations, and the mean expression of *APIP* for each combination is shown here for the (A) discovery and (B) replication datasets. There are markedly different patterns in gene expression by two-locus genotype between the two datasets, illustrating the putative interaction does not replicate with a consistent direction of effect.

Supplemental Tables

Low LD ($r^2 < 0.05$)				
MAF Range		Percentage	Effect Size	
Variant 1	Variant 2		Moderate	Large
0.05 <= MAF < 0.1	0.05 <= MAF < 0.1	0.02	0.0 ± 0.0	3.3 ± 10.5
	0.1 <= MAF < 0.2	0.22	2.0 ± 2.1	5.5 ± 1.9
	0.2 <= MAF < 0.3	0.55	3.5 ± 1.1	9.5 ± 2.4
	0.3 <= MAF < 0.4	0.87	5.5 ± 1.5	12.4 ± 3.0
	0.4 <= MAF <= 0.5	1.11	4.3 ± 1.1	11.9 ± 1.6
0.1 <= MAF < 0.2	0.1 <= MAF < 0.2	1.04	5.7 ± 1.4	16.7 ± 3.2
	0.2 <= MAF < 0.3	5.30	10.8 ± 1.1	25.8 ± 0.6
	0.3 <= MAF < 0.4	6.79	14.9 ± 1.2	33.3 ± 1.1
	0.4 <= MAF <= 0.5	8.16	16.2 ± 1.0	36.2 ± 1.1
0.2 <= MAF < 0.3	0.2 <= MAF < 0.3	4.47	21.6 ± 1.4	44.3 ± 1.2
	0.3 <= MAF < 0.4	10.59	30.9 ± 0.6	57.6 ± 1.3
	0.4 <= MAF <= 0.5	11.01	35.8 ± 0.7	62.7 ± 1.0
0.3 <= MAF < 0.4	0.3 <= MAF < 0.4	5.23	44.3 ± 1.0	71.1 ± 0.9
	0.4 <= MAF <= 0.5	10.58	50.3 ± 0.6	75.5 ± 0.8
0.4 <= MAF <= 0.5	0.4 <= MAF <= 0.5	4.75	55.3 ± 1.9	78.9 ± 0.6

Moderate LD ($0.05 <= r^2 < 0.3$)				
MAF Range		Percentage	Effect Size	
Variant 1	Variant 2		Moderate	Large
0.05 <= MAF < 0.1	0.05 <= MAF < 0.1	0.04	0.0 ± 0.0	1.4 ± 4.5
	0.1 <= MAF < 0.2	0.32	2.4 ± 1.8	4.9 ± 2.7
	0.2 <= MAF < 0.3	0.21	2.7 ± 2.5	6.6 ± 2.8
	0.3 <= MAF < 0.4	0.04	1.4 ± 4.3	4.3 ± 9.6
	0.4 <= MAF <= 0.5	0.02	3.3 ± 10.0	0.0 ± 0.0
0.1 <= MAF < 0.2	0.1 <= MAF < 0.2	0.86	4.2 ± 1.8	10.4 ± 1.9
	0.2 <= MAF < 0.3	1.88	7.6 ± 1.5	19.8 ± 1.7
	0.3 <= MAF < 0.4	1.43	10.2 ± 1.2	24.6 ± 2.9
	0.4 <= MAF <= 0.5	0.86	11.9 ± 1.8	31.2 ± 2.9
0.2 <= MAF < 0.3	0.2 <= MAF < 0.3	1.62	14.6 ± 0.7	32.1 ± 2.0
	0.3 <= MAF < 0.4	3.40	20.4 ± 1.7	42.5 ± 1.7
	0.4 <= MAF <= 0.5	3.34	22.5 ± 1.7	46.2 ± 1.5
0.3 <= MAF < 0.4	0.3 <= MAF < 0.4	2.18	25.9 ± 1.5	52.5 ± 2.4
	0.4 <= MAF <= 0.5	5.24	31.0 ± 0.8	56.0 ± 1.1
0.4 <= MAF <= 0.5	0.4 <= MAF <= 0.5	2.85	35.2 ± 1.7	61.6 ± 2.2

High LD ($0.3 <= r^2 < 0.6$)				
MAF Range		Percentage	Effect Size	
Variant 1	Variant 2		Moderate	Large
0.05 <= MAF < 0.1	0.05 <= MAF < 0.1	0.01	0.0 ± 0.0	0.0 ± 0.0
	0.1 <= MAF < 0.2	0.03	2.0 ± 6.0	2.0 ± 6.3
	0.2 <= MAF < 0.3	0.00	-	-
	0.3 <= MAF < 0.4	0.00	-	-
	0.4 <= MAF <= 0.5	0.00	-	-
0.1 <= MAF < 0.2	0.1 <= MAF < 0.2	0.20	1.0 ± 1.2	2.5 ± 2.4
	0.2 <= MAF < 0.3	0.29	2.1 ± 1.5	7.1 ± 3.6
	0.3 <= MAF < 0.4	0.02	0.0 ± 0.0	0.0 ± 0.0
	0.4 <= MAF <= 0.5	0.00	-	-
0.2 <= MAF < 0.3	0.2 <= MAF < 0.3	0.65	3.1 ± 0.9	12.2 ± 2.4
	0.3 <= MAF < 0.4	0.67	6.0 ± 2.1	17.1 ± 2.1
	0.4 <= MAF <= 0.5	0.11	7.3 ± 4.2	18.6 ± 10.2
0.3 <= MAF < 0.4	0.3 <= MAF < 0.4	0.82	7.8 ± 2.1	17.4 ± 3.9
	0.4 <= MAF <= 0.5	1.11	10.1 ± 2.1	22.9 ± 3.5
0.4 <= MAF <= 0.5	0.4 <= MAF <= 0.5	1.18	9.8 ± 1.7	24.9 ± 3.1

Table S1. Power to detect interactions by MAF and LD. Power to detect interactions is contingent upon both the MAF of the two variants and the LD between the variants. To calculate power, we randomly selected 20,000 pairs of variants tested in this analysis and simulated gene expression values with interaction effects at a moderate (median β of *cis*-eQTLs; β = 0.771) and a large (75^{th} percentile β of *cis*-eQTLs; β = 0.908) effect size (Methods). We then binned interactions according to their MAF and LD, and calculated power as the number of significant interactions divided by the total number of interactions within each bin. We repeated this process ten times, and computed the mean power and its standard deviation across all 10 runs for each bin, which is reported here. For each bin, we also report the percentage it accounted for of the 20,000 interactions.

Table S2. Significant interactions identified in the discovery analysis. This file provides all 5,439 interactions identified in the discovery analysis. When these interactions appeared to represent the same signal, due to LD, they were placed into groups (n = 1,119) and a representative interaction was chosen. We provide the group identifier for each of the interactions, and the group's representative interaction.

Table S3. Alternative explanations for significant interactions identified in the discovery analysis. We examined whether or not the 1,119 interactions could be explained by confounding factors. Here, we present which alternative explanations could account for each interaction.

Confounder	**Interactions inconsistent with confounding**
Missing Genotype Combination	662 of 1,119
High within-pair LD (r2 or D' > 0.6)	565 of 662
Population specific effects	409 of 565
Single Variants tagged through LD	100 of 409
Ceiling/Floor Effect	96 of 100
Variants in probe binding site	86 of 96

Table S4. Majority of ieQTL could have been filtered out due to confounding prior to the replication analysis. Of the 1,119 ieQTL identified as significant in the discovery analysis, we removed interactions consistent with confounding factors in the indicated order, which is in accordance with the trait-independent approach proposed in the discussion. In addition to these trait-independent filters, we additionally removed interactions influencing genes with variants in the probe's binding site. Ultimately, 86 of the 1,119 ieQTL identified in the discovery analysis were inconsistent with confounding factors.