

Supplementary Models

These models are fit to the same data sets, using the same conditional logistic regression, as is described in the methods section of the main text.

S0: eQTL $\sim$ MAF + Δ DAF + location

S1: eQTL $\sim$ H_IH + MAF + Δ DAF + location

S2: eQTL $\sim$ Δ iHH + MAF + Δ DAF + location

S3: eQTL $\sim$ iHS + MAF + Δ DAF + location

Marginal Probabilities provided to PantherDB

To generate a statistic to be used by PantherDB, the following sum was taken for each gene (as delineated by annovar, see main text) in each data set, from each of the supplementary models above (X = 1 through 3), except for S0:

$$\text{Eq. S1} \quad \text{Average all eQTLs (Marginal}_{SX} - \text{Marginal}_{S0}) + \text{Average all non-eQTLs (Marginal}_{S0} - \text{Marginal}_{SX})$$

These marginals are reported by the conditional logistic regression, described in the main body of the text, for each of the supplementary models fit to each of the 7 hypothesis-generation data sets (the model containing F_{st} did not converge in the Mangravite data set.) These averages are taken over each gene. This corresponds to the average likelihood gain for each prediction when the new variable is added to the logistic model.

These values are then used for a statistical enrichment test (non-parametric, as implemented in pantherDB) to test for an enrichment of extreme values, which reports p-values. These p-values are then combined across data sets (**NOT** across models) using Fisher's method (i.e., twice the opposite of the sum of the log p-values is tested against a distribution with 2N degrees of freedom, where N is the number of data sets for which a given GO category was present at all.)

Any GO category which in either tail at a one-tailed p-value of less than 0.01 (the same threshold as used in the main text of the paper, albeit for a permutation-based method) is then assigned to either Group 1 or Group 2.

Finally, these Group 1 and Group 2 assignments are tested for an interaction with the predictor as was done in the Hypothesis-Testing phase of the main manuscript (results given in Table S2, S3 and S4). None of the Group 1 vs. Group 2 distinctions are statistically significant; however, both Models S2 and S3 (utilizing Δ iHH and iHS respectively) recapitulate the expected direction of effect, with each unit of log p-value contributing more in Group 2 (GO categories with strong marginal differences in the Hypothesis-Generation data set) than in Group 1 (GO categories with weak marginal differences). On an individual group basis, iHS is a nominally significant predictor of eQTLs in Group 2, while Δ iHH is, paradoxically, a predictor of non-eQTL markers in Group 1.

Supplementary Results, GO Categories

Go enrichment tests implemented in PantherDB (see main text for references) were used to identify GO categories in which the addition of different positive-selection measures were strong predictors (Group 1), or extremely weak predictors. This resulted in the following GO categories from each of the supplementary models (see table below):

Group 1, H|H (Model S1)

<http://amigo.geneontology.org/amigo/term/GO:0034032>

purine nucleoside bisphosphate metabolic process

<http://amigo.geneontology.org/amigo/term/GO:0033875>

ribonucleoside bisphosphate metabolic process

<http://amigo.geneontology.org/amigo/term/GO:0033865>

nucleoside bisphosphate metabolic process

<http://amigo.geneontology.org/amigo/term/GO:0006921>

cellular component disassembly involved in execution phase of apoptosis

<http://amigo.geneontology.org/amigo/term/GO:0030262>

apoptotic nuclear changes

<http://amigo.geneontology.org/amigo/term/GO:0006817>

phosphate ion transport

<http://amigo.geneontology.org/amigo/term/GO:0050832>

defense response to fungus

<http://amigo.geneontology.org/amigo/term/GO:0044364>

disruption of cells of other organism

<http://amigo.geneontology.org/amigo/term/GO:0031640>

killing of cells of other organism

Group 2, H|H (Model S2)

<http://amigo.geneontology.org/amigo/term/GO:0009179>

purine ribonucleoside diphosphate metabolic process

<http://amigo.geneontology.org/amigo/term/GO:0009135>

purine nucleoside diphosphate metabolic process

<http://amigo.geneontology.org/amigo/term/GO:0009132>

nucleoside diphosphate metabolic process

<http://amigo.geneontology.org/amigo/term/GO:0071276>

cellular response to cadmium ion

<http://amigo.geneontology.org/amigo/term/GO:0046031>

ADP metabolic process

Group 1, ΔiHH (Model S1)

<http://amigo.geneontology.org/amigo/term/GO:0009451>

RNA modification

<http://amigo.geneontology.org/amigo/term/GO:0001510>

RNA methylation

<http://amigo.geneontology.org/amigo/term/GO:0045639>

positive regulation of myeloid cell differentiation

<http://amigo.geneontology.org/amigo/term/GO:0045637>

regulation of myeloid cell differentiation

<http://amigo.geneontology.org/amigo/term/GO:0000375>

RNA splicing, via transesterification reactions

<http://amigo.geneontology.org/amigo/term/GO:0008380>

RNA splicing

<http://amigo.geneontology.org/amigo/term/GO:0000398>

mRNA splicing, via spliceosome

<http://amigo.geneontology.org/amigo/term/GO:0000377>

RNA splicing, via transesterification reactions with bulged adenosine as nucleophile

<http://amigo.geneontology.org/amigo/term/GO:0006396>

RNA processing

<http://amigo.geneontology.org/amigo/term/GO:0032481>

positive regulation of type I interferon production

<http://amigo.geneontology.org/amigo/term/GO:0035455>

response to interferon-alpha

Group 2, ΔiHH (Model S2)

<http://amigo.geneontology.org/amigo/term/GO:0010818>

T cell chemotaxis

<http://amigo.geneontology.org/amigo/term/GO:0043950>

positive regulation of cAMP-mediated signaling

<http://amigo.geneontology.org/amigo/term/GO:0048247>

lymphocyte chemotaxis

<http://amigo.geneontology.org/amigo/term/GO:0007144>

female meiosis I

<http://amigo.geneontology.org/amigo/term/GO:0032722>

positive regulation of chemokine production

<http://amigo.geneontology.org/amigo/term/GO:0048513>

organ development

<http://amigo.geneontology.org/amigo/term/GO:0002483>

antigen processing and presentation of endogenous peptide antigen

<http://amigo.geneontology.org/amigo/term/GO:0019885>

antigen processing and presentation of endogenous peptide antigen via MHC class I

<http://amigo.geneontology.org/amigo/term/GO:0019883>

antigen processing and presentation of endogenous antigen

Group 1, iHS (Model S1)

<http://amigo.geneontology.org/amigo/term/GO:0045069>

regulation of viral genome replication

<http://amigo.geneontology.org/amigo/term/GO:0002244>

hematopoietic progenitor cell differentiation

<http://amigo.geneontology.org/amigo/term/GO:0006625>

protein targeting to peroxisome

<http://amigo.geneontology.org/amigo/term/GO:0072663>

establishment of protein localization to peroxisome

<http://amigo.geneontology.org/amigo/term/GO:0072662>

protein localization to peroxisome

<http://amigo.geneontology.org/amigo/term/GO:0043574>

peroxisomal transport

<http://amigo.geneontology.org/amigo/term/GO:0006182>

cGMP biosynthetic process

Group 2, iHS (Model S2)

<http://amigo.geneontology.org/amigo/term/GO:0071482>

cellular response to light stimulus

<http://amigo.geneontology.org/amigo/term/GO:1901072>

glucosamine-containing compound catabolic process

<http://amigo.geneontology.org/amigo/term/GO:0032735>

positive regulation of interleukin-12 production

<http://amigo.geneontology.org/amigo/term/GO:0006032>

chitin catabolic process

<http://amigo.geneontology.org/amigo/term/GO:0006030>

chitin metabolic process

<http://amigo.geneontology.org/amigo/term/GO:1901071>

glucosamine-containing compound metabolic process

<http://amigo.geneontology.org/amigo/term/GO:0046902>

regulation of mitochondrial membrane permeability

<http://amigo.geneontology.org/amigo/term/GO:0090559>

regulation of membrane permeability

<http://amigo.geneontology.org/amigo/term/GO:0032655>

regulation of interleukin-12 production

<http://amigo.geneontology.org/amigo/term/GO:0002687>

positive regulation of leukocyte migration

<http://amigo.geneontology.org/amigo/term/GO:0002685>

regulation of leukocyte migration

<http://amigo.geneontology.org/amigo/term/GO:0002690>

positive regulation of leukocyte chemotaxis

<http://amigo.geneontology.org/amigo/term/GO:0002688>

regulation of leukocyte chemotaxis

<http://amigo.geneontology.org/amigo/term/GO:0050819>

negative regulation of coagulation

<http://amigo.geneontology.org/amigo/term/GO:0050832>

defense response to fungus

Supplementary Hypothesis-Testing Phase (see Tables S2 through S4)

The above groupings are tested for an interaction in the same data set and the same manner as in the main text, except that an interaction with the “Group” designation is added to the predictor which is added to each supplementary model above.

Supplementary Tables

Table S1: Conditional logistic regression model fit parameters in the seven hypothesis-generation data sets.

Model	$\beta_{H H} \pm \sigma_{H }$ H	$\beta_{ \Delta DAF } \pm \sigma_{ \Delta DAF }$	$\beta_{\Delta DAF} \pm \sigma_{\Delta DAF}$	$\beta_{\Delta iHH} \pm \sigma_{\Delta iHH}$	$\beta_{Fst} \pm \sigma_{Fst}$	$\beta_{iHS} \pm \sigma_{iHS}$	$\beta_{MAF} \pm \sigma_{MAF}$	$\beta_{UTR} \pm \sigma_{UTR}$	$\beta_{intron} \pm \sigma_{intron}$	$\beta_{Flank} \pm \sigma_{Flank}$
Mangravite 2012										
Mod. 1	Model did not converge									
Mod. 2	0.03 ± 0.001	0.06 ± 0.011	-0.24 ± 0.016	0.002 ± 0.004	n/a	0.05 ± 0.006	1.07 ± 0.014	0.10 ± 0.040	-0.22 ± 0.032	-0.17 ± 0.041
Mod. 3	Model did not converge									
Mod. 4	Model did not converge									
Mod. 5	0.03 ± 0.001	0.08 ± 0.011	-0.23 ± 0.015	n/a	n/a	n/a	× GO	0.09 ± 0.040	-0.22 ± 0.032	-0.17 ± 0.041
Mod. 6	× GO	n/a	0.28 ± 0.014	n/a	n/a	n/a	× GO	0.10 ± 0.040	-0.21 ± 0.032	-0.17 ± 0.041
Montgomery 2010 - Exon										
Mod. 1	0.04 ± 0.003	0.16 ± 0.033	-0.25 ± 0.030	0.01 ± 0.007	-0.08 ± 0.019	-0.02 ± 0.010	0.97 ± 0.028	-0.25 ± 0.068	-0.83 ± 0.050	-0.58 ± 0.069
Mod. 2	0.04 ± 0.003	0.05 ± 0.020	-0.24 ± 0.030	0.005 ± 0.007	n/a	-0.03 ± 0.010	1.01 ± 0.026	-0.25 ± 0.068	-0.83 ± 0.050	-0.58 ± 0.069
Mod. 3	0.04 ± 0.003	0.17 ± 0.033	-0.25 ± 0.030	0.004 ± 0.007	-0.08 ± 0.019	-0.03 ± 0.010	× GO	-0.26 ± 0.068	-0.83 ± 0.050	-0.58 ± 0.069
Mod. 4	0.04 ± 0.003	0.17 ± 0.033	-0.26 ± 0.028	n/a	-0.08 ± 0.019	n/a	× GO	-0.26 ± 0.068	-0.83 ± 0.050	-0.58 ± 0.069
Mod. 5	0.04 ± 0.003	0.05 ± 0.020	-0.25 ± 0.028	n/a	n/a	n/a	× GO	-0.26 ± 0.068	-0.83 ± 0.050	-0.58 ± 0.069
Mod. 6	× GO	n/a	-0.29 ± 0.025	n/a	n/a	n/a	× GO	-0.25 ± 0.068	-0.83 ± 0.050	-0.58 ± 0.069
Montgomery 2010 - Transcript										
Mod. 1	0.04 ± 0.005	0.22 ± 0.061	-0.19 ± 0.052	0.04 ± 0.014	-0.10 ± 0.033	-0.04 ± 0.018	0.86 ± 0.050	-0.15 ± 0.120	-0.80 ± 0.088	-0.54 ± 0.122
Mod. 2	0.04 ± 0.005	0.09 ± 0.036	-0.18 ± 0.052	0.04 ± 0.014	n/a	-0.05 ± 0.018	0.92 ± 0.046	-0.14 ± 0.120	-0.80 ± 0.088	-0.54 ± 0.122
Mod. 3	0.04 ± 0.005	0.24 ± 0.062	-0.20 ± 0.052	0.04 ± 0.014	-0.11 ± 0.033	-0.04 ± 0.018	× GO	-0.18 ± 0.121	-0.80 ± 0.088	-0.55 ± 0.123
Mod. 4	0.04 ± 0.005	0.24 ± 0.062	-0.19 ± 0.052	n/a	-0.11 ± 0.034	n/a	× GO	-0.17 ± 0.121	-0.80 ± 0.088	-0.56 ± 0.123
Mod. 5	0.04 ± 0.005	0.09 ± 0.036	-0.18 ± 0.050	n/a	n/a	n/a	× GO	-0.17 ± 0.121	-0.80 ± 0.088	-0.56 ± 0.123
Mod. 6	× GO	n/a	-0.25 ±	n/a	n/a	n/a	× GO	-0.15 ±	-0.81 ±	-0.57 ±

			0.045					0.121	0.089	0.124
Schadt 2007										
Mod. 1	0.01 ± 0.006	0.10 ± 0.070	-0.32 ± 0.067	0.01 ± 0.016	-0.06 ± 0.042	0.004 ± 0.023	0.96 ± 0.061	0.03 ± 0.143	-0.80 ± 0.113	-0.73 ± 0.157
Mod. 2	0.01 ± 0.006	0.02 ± 0.043	-0.30 ± 0.066	0.01 ± 0.016	n/a	0.002 ± 0.023	0.99 ± 0.056	0.03 ± 0.143	-0.80 ± 0.113	-0.73 ± 0.157
Mod. 3	0.01 ± 0.006	0.11 ± 0.070	-0.32 ± 0.068	0.01 ± 0.016	-0.06 ± 0.042	0.005 ± 0.023	× GO	0.03 ± 0.144	-0.80 ± 0.113	-0.73 ± 0.157
Mod. 4	0.02 ± 0.006	0.12 ± 0.070	-0.31 ± 0.067	n/a	-0.06 ± 0.042	n/a	× GO	0.03 ± 0.144	-0.80 ± 0.113	-0.73 ± 0.157
Mod. 5	0.02 ± 0.006	0.03 ± 0.043	-0.29 ± 0.065	n/a	n/a	n/a	× GO	0.04 ± 0.144	-0.80 ± 0.113	-0.73 ± 0.157
Mod. 6	× GO	n/a	-0.33 ± 0.056	n/a	n/a	n/a	× GO	0.02 ± 0.144	-0.80 ± 0.113	-0.73 ± 0.158
Stranger 2007										
Mod. 1	0.02 ± 0.003	0.13 ± 0.031	-0.35 ± 0.032	-0.02 ± 0.008	-0.14 ± 0.018	-0.02 ± 0.011	1.1 ± 0.029	-0.14 ± 0.070	-0.55 ± 0.052	-0.43 ± 0.072
Mod. 2	0.02 ± 0.003	-0.04 ± 0.019	-0.31 ± 0.031	-0.02 ± 0.008	n/a	-0.03 ± 0.011	1.2 ± 0.027	-0.15 ± 0.070	-0.55 ± 0.052	-0.43 ± 0.072
Mod. 3	0.02 ± 0.003	0.16 ± 0.031	-0.36 ± 0.032	-0.02 ± 0.008	-0.16 ± 0.019	-0.02 ± 0.011	× GO	-0.16 ± 0.070	-0.56 ± 0.052	-0.44 ± 0.072
Mod. 4	0.02 ± 0.003	0.16 ± 0.031	-0.38 ± 0.032	n/a	-0.16 ± 0.019	n/a	× GO	-0.16 ± 0.070	-0.56 ± 0.052	-0.44 ± 0.072
Mod. 5	0.02 ± 0.003	-0.04 ± 0.019	-0.33 ± 0.030	n/a	n/a	n/a	× GO	-0.16 ± 0.070	-0.56 ± 0.052	-0.44 ± 0.072
Mod. 6	× GO	n/a	-0.30 ± 0.026	n/a	n/a	n/a	× GO	-0.16 ± 0.070	-0.56 ± 0.052	-0.45 ± 0.072
Veyrieras 2008										
Mod. 1	0.02 ± 0.003	0.22 ± 0.030	-0.04 ± 0.028	-0.02 ± 0.007	-0.22 ± 0.017	-0.01 ± 0.01	1.16 ± 0.028	-0.25 ± 0.064	-0.67 ± 0.048	-0.67 ± 0.069
Mod. 2	0.02 ± 0.003	-0.07 ± 0.017	0.006 ± 0.027	-0.02 ± 0.007	n/a	-0.02 ± 0.01	1.27 ± 0.026	-0.25 ± 0.064	-0.67 ± 0.048	-0.67 ± 0.069
Mod. 3	0.02 ± 0.003	0.22 ± 0.030	-0.04 ± 0.028	-0.02 ± 0.007	-0.22 ± 0.017	-0.007 ± 0.01	× GO	-0.25 ± 0.064	-0.67 ± 0.048	-0.66 ± 0.069
Mod. 4	0.02 ± 0.003	0.23 ± 0.030	-0.06 ± 0.027	n/a	-0.22 ± 0.016	n/a	× GO	-0.25 ± 0.064	-0.67 ± 0.048	-0.66 ± 0.068
Mod. 5	0.02 ± 0.003	-0.07 ± 0.017	-0.02 ± 0.026	n/a	n/a	n/a	× GO	-0.25 ± 0.064	-0.67 ± 0.048	-0.67 ± 0.068
Mod. 6	× GO	n/a	0.02 ± 0.023	n/a	n/a	n/a	× GO	-0.25 ± 0.064	-0.67 ± 0.048	-0.68 ± 0.069
Zeller 2010										
Mod. 1	0.03 ± 0.002	0.13 ± 0.019	-0.28 ± 0.018	0.01 ± 0.004	-0.08 ± 0.011	0.01 ± 0.006	0.88 ± 0.016	-0.08 ± 0.046	-0.43 ± 0.035	-0.47 ± 0.048
Mod. 2	0.03 ± 0.002	0.02 ± 0.012	-0.26 ± 0.017	0.01 ± 0.004	n/a	0.01 ± 0.006	0.92 ± 0.015	-0.08 ± 0.046	-0.43 ± 0.035	-0.47 ± 0.048
Mod. 3	0.03 ± 0.002	0.13 ± 0.019	-0.28 ± 0.018	0.01 ± 0.004	-0.08 ± 0.011	0.01 ± 0.006	× GO	-0.08 ± 0.046	-0.43 ± 0.035	-0.47 ± 0.048

	0.002	0.019	0.018	0.004	0.011	<i>0.006</i>		<i>0.046</i>	0.035	0.048
Mod. 4	0.03 ± 0.002	0.13 ± 0.019	-0.27 ± 0.017	n/a	-0.08 ± 0.011	n/a	× GO	-0.08 ± 0.046	-0.43 ± 0.035	-0.47 ± 0.048
Mod. 5	0.03 ± 0.002	0.03 ± 0.011	-0.25 ± 0.017	n/a	n/a	n/a	× GO	-0.08 ± 0.046	-0.43 ± 0.035	-0.47 ± 0.048
Mod. 6	× GO	n/a	-0.25 ± 0.015	n/a	n/a	n/a	× GO	-0.08 ± 0.046	-0.43 ± 0.035	-0.48 ± 0.048

Each column gives the effect size on a logistic scale (β) and, gives the standard error in that effect size (σ), for each variable (subscript) from the corresponding conditional logistic model fit (row; for both see text) for being an eQTL stratified by gene or intergenic region. Grey cells are fit on a per-GO term basis (choice results from Model 6 are given in Table 4); black cells are for variables not included in the corresponding model. SNPs in Exons are the default category, so all effect sizes for within-gene SNP location are given relative to the frequency of eQTLs within exons. Bold text indicates an absolute Z-score greater than 10; italicised text indicates an absolute Z-score less than 2 (this may differ from the apparent arithmetic due to rounding).

Table S2: Whole-blood *cis*-eQTL conditional logistic regression results, supplementary approach for H|H (model S1)

Dataset	Number of <i>cis</i> -eQTLs	Num. Genes and Regions	Total GTEx Markers	$\beta_{H H} \pm \sigma_{H H}$
Westra 2012 – Group 1 from S1	2,905	170	25,468	0.007 ± 0.005
Westra 2012 – Group 2 from S1	2,805	127	24,567	0.005 ± 0.005

Table S3: Whole-blood *cis*-eQTL conditional logistic regression results, supplementary approach for Δ iHH (model S2)

Dataset	Number of <i>cis</i> -eQTLs	Num. Genes and Regions	Total GTEx Markers	$\beta_{\Delta iHH} \pm \sigma_{\Delta iHH}$
Westra 2012 – Group 1 from S2	12,306	830	116,047	0.026 ± 0.008
Westra 2012 – Group 2 from S2	378	27	1,481	-0.041 ± 0.052

Table S4: Whole-blood *cis*-eQTL conditional logistic regression results, supplementary approach for iHS (model S3)

Dataset	Number of <i>cis</i> -eQTLs	Num. Genes and Regions	Total GTEx Markers	$\beta_{iHS} \pm \sigma_{iHS}$
Westra 2012 – Group 1 from S3	1,485	80	14,408	-0.001 ± 0.027
Westra 2012 – Group 2 from S3	4,294	199	41,941	-0.043 ± 0.016