Deciphering molecular circuits from genetic variation underlying transcriptional responsiveness to stimuli

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Supplementary Figures

Supplementary Note

Supplementary Tables

Supplementary Figure legends

Supplementary Figure 1. The variation signature genes. (**a**) Distribution of all and signature genes in InSignature classes. Shown is the fraction of classes (y axis) that include a certain number of genes (x axis) based on the number of all genes included in a class (blue) or the number of variation signature genes included in a class (red). (**b-d**) Dissection of results for the 424 signature genes based on the criterion by which they were selected (x axis, detailed in **Methods** and **Supplementary Note 2)**: I - heritability, by InSignature; II – biological relevance; III- positive responsiveness controls; IV- negative controls. Within the heritability (criterion I) group, genes are further partitioned by top InSignature score in class (I-a); biological relevance (I-b); responsiveness (I-c) and randomly selected from class (I-d). (**b**) Heritability in responsiveness to LPS (y axis). As expected, negative controls (group IV) have a significantly lower heritability compared to genes selected by InSignature (group I) (P-value < 10^{-9}), and top scoring genes (group I-a) outperform those randomly selected from the class (group I-d) (P<0.03). (**c**) *cis*-associations. For each group (x axis), the red-boundary bars show the fraction of *cis*-associated genes in the class (in at least one of stimulus) out of all associated genes (y axis). The black-boundary bars show the fraction of genes in this class among all 424 signature genes. *cis*-associated genes are enriched in the top-scoring group (I-a; P-value < 10^{-4}, hypergeometric test) and are depleted from negative control genes (group IV) ($P < 10^{-3}$). (**d**) LR scores. Shown are the median LR scores for all traits in each group, except those that attain their best LR score in *cis* (up to 10Mbp from the gene). Selection criteria that are based on InSignature are marked with a + sign at the bottom. Comparing matching 'pairs' of groups, the results highlight the utility of InSignature. For biologically relevant genes, selection based on InSignature (group I-b) outperforms selection based on biological relevance only (group II) (P-value < 0.02); for responding genes, selection based on InSignature (group I-c) is slightly better than based on responsiveness only (group III) (P-value <

0.09). (**e**) Sensitivity and specificity of InSignature in selecting *cis*-associated genes. Shown is the number of genes that are predicted as *cis*-associated (left column) and the remaining genes (non *cis*-associated, middle column) by InSignature (from array data), separated by whether they were subsequently found in the nCounter dataset as *cis*-associated (top row) or not (middle row) using a relatively permissive cutoff (LR score > 10). Thus, columns are based on analysis of the microarray dataset (6 BXD strains) whereas rows are based on the nCounter dataset (44 BXD strains). Hence, there is a high specificity (91%), moderate sensitivity (45%) and a moderate false negative rate (54%).

Supplementary Figure 2. **Consistency and reproducibility of nCounter assay.** (**a**) Shown are the expression levels for a pilot set of 16 genes with significant scores for inter-individual variation (>5.5, **Methods**, rows) measured in the same samples with both technologies across individual mice (columns; two individuals per strain consecutively). Intensity corresponds to inter-strain fold changes relative to the average level in B6 (Red (blue) - higher (lower) than B6). The bar chart (left) shows the correlation between the microarray and nCounter profiles for each gene. The four genes with lower correlations (1190002H23Rik, Il1a, Tnf and Ccl4) show higher heritability based on the nCounter measurements than with microarrays (data not shown), suggesting that the nCounter assay is more sensitive, consistent with previous studies (Amit et al, 2009). (**b**) Shown is the distribution of nCounter-microarray correlation of gene profiles from (a) (red) compared to the distribution of correlations when reshuffling the measurements of each gene separately (black). (**c**) Comparison of inter-strain fold changes (y-axis) across the mice individuals (x-axis) between microarray (red) and nanostring nCounter (blue) measurements. Top: Cxcl11, bottom: Lta. Between-strain variability is significantly higher than within-strain variability (**d**) A scatter plot of Nanostring nCounter measured responsiveness levels in two

independently repeated experiments with DCs from a single mouse individual from strain BXD89 following LPS stimulation (6 hours).

Supplementary Figure 3. Association of responsiveness traits in *cis*. (**a**) Significant interactions effect between *cis*-acting reQTLs and stimuli. Shown is the distribution of reQTL-stimuli interactions (-log p-value, X axis, **Methods**) in the dataset (black) and in reshuffled data (gray). (**b)** High responsiveness is required but not sufficient for high LR scores. Shown is a scatter plot of LR scores (x axis) and absolute responsiveness (y axis) across all traits presented in **Fig. 3a**. Absolute responsiveness values are normalized by the maximum absolute log ratio attained for that gene under any of the stimulations and strains. (**c-e**) The relation of LR score and responsiveness in the Mina (**c**), Ube2m (**d**) and St3Gal5 (**e**) genes. Left: Shown are the time courses of gene expression levels (X axis) in three stimuli (PAM (left), poly IC (middle), LPS (right)) in strains with a B6 (black) or D2 (grey) genotype in *cis*. Right: Shown are the responsiveness levels for BXD strains that inherited the genotype in *cis* from B6 (columns 1,3,5) and D2 (columns 2,4,6) following stimulation of PAM (columns 1,2), Poly IC (columns 3,4) and LPS (columns 5,6). For example, the gene Ube2m (**d**) is highly responsive in LPS and PAM but *cis*-associated only in LPS. (**f**) Stimulus-specific *cis*-reQTLs have smaller effects. Shown are the LR scores for stimulus-specific *cis*-reQTLs (left) and stimulus non-specific *cis*-reQTLs (right). In each box, the central mark is the median; edges are the 25th and 75th percentiles; whiskers extend to the most extreme data points not considered outliers; and outliers are plotted individually. (**g**) Higher LR scores for *cis*-associations than for *trans*. Shown is the distribution of LR scores in *cis* (black) and *trans* (red).

Supplementary Fig. 4. Examples of merge steps in InVamod. Detailing the steps shown in Fig. 4a. In **(a)** trait t1 forms a single-trait seed module (exceeds c1 in position A), but trait t2 does not. The traits are merged to a legal module of size 2 that remains associated at A, the best association for both traits. The new association score of the module equals its optimum (2+5=7, loss fraction $\varepsilon = 0 \leq$ maximum permitted loss of 0.1), and both traits exceed the double-trait cutoff c2 in position A, thus forming a legal module. **(b)** Traits t3 and t4 each form a single-trait seed modules (each exceed c1) at positions C and D, respectively. They are merged into a new legal module, associated at position F, which maximizes the association score when considering both traits. Both traits exceed c2 at position F, and the module's association score is 11 (5.5+5.5), the optimal score is 12 (6+6) and the loss fraction is $\varepsilon = (12-11)/12 <= 0.1$. **(c)** Each of traits t1 and t6 form single-trait seed modules (exceed c1 in positions A, E, respectively). They cannot form a legal module since when merged their loss fraction ε is higher than 0.1. In particular, the maximal joint association score (in B) is 10 (5+5) resulting in a loss fraction $\varepsilon = (13-10)/13 > 0.1$.

Supplementary Figure 5. **Association of responsiveness traits in *trans*.** (**a**) Module sizes. Shown is a scatter-plot of module sizes (x-axis) and the degree of stimulus specificity of the traits in the module (y-axis), defined as minus Shannon entropy measure applied on the distribution of module traits in each of the stimuli. The score is low for a non-specific module, (consisting of the same number of traits in each stimulus) and higher when the traits are unevenly distributed across stimuli. Shown are all InVamod modules generated from our dataset (orange) and on permuted data (black), generated only by independently reshuffling each gene's measurements. Module with at least 14 traits are highly unlikely to be generated at random ($P<0.001$; vertical grey line). The six modules that cross this threshold (modules #1-#6) are

stimulus-dependent. (**b**,**c**) High heritability and high % explained heritability in Modules #1-#6. Shown are the average heritability (H^2, **b**) and average percentage of heritability explained by the module's reQTL (**c**) for each module. In each box, the central mark is the median; edges are the 25th and 75th percentiles; whiskers extend to the most extreme data points not considered outliers; and outliers are plotted individually. (**d**) Gene members of each module. Shown are the association profiles (left, orange: associated) of the member genes (rows) and their responsiveness profiles (right, grey: responsive, as in **Fig. 3a**). Distinct RPs are marked (right). Genes related to more than one module (in different conditions), or associated only under a stimulus in which the reQTL is predicted to be inactive, are excluded for simplicity. The full module membership is reported in **Supplementary Table 5**.

Supplementary Figure 6. The InCircuit procedure for positioning reQTLs in a wiring diagram. (a) InCircuit takes as input the responsiveness profiles of module genes (RPs, top left), the linked traits of the module (top right) (depicted as in **Fig. 4c**, **Supplementary Fig. 5d**), and a regulatory wiring diagram (bottom left), consisting of three stimuli (S1, S2, S3) and 3 RPs (RP1, RP2, RP3). In step 1, leading responsiveness profiles (RPs) are marked on the diagram (RP1 and RP2, orange). In step 2, the stimuli under which the reQTL is active are marked (S1, orange). In step 3, InCircuit searches a branch coupling the upstream active stimulations and the downstream leading RPs. If such a branch is found, an reQTL is positioned on it (colored orange circle). **(b)** Examples of reQTL positioning by InCircuit. Shown are combinations of leading responsiveness profiles (column 1), reQTL activity profiles (column 2), and the reQTL predicted position (orange circle) on the wiring diagram (column 3). (**1**): reQTL positioned on branch 3, the only branch downstream of S1, which is upstream to both RP1 and RP2. (**2**) reQTL positioned on branch 2, the only branch downstream of both S1 and S2 and upstream of only RP1. (**3**) No

known branch exists downstream of S3 and upstream to RP1; InCircuit refines the model by adding this branch (dashed line). (**4**) Both branch 1 and 3 (orange) are downstream of S1 and upstream of RP1, as required. InCircuit positions the reQTL on the branch (Branch 1) consisting of a smaller number of downstream RPs, and hence higher specificity.

Supplementary Figure 7. Positioning *cis*-reQTLs in a wiring diagram. (**a**) Responsiveness and association profiles for genes in each of groups I-IV (as in **Fig. 3a**). (**b**) Shown are *cis*-reQTLs (black circles) associated with genes in each of these groups (I-IV) and their predicted positioning in relevant wiring diagram (LPS, poly IC, PAM: stimuli; Horizonal grey ovals: inflammatory response; vertical grey ovals: antiviral response). In each case, the *cis*-reQTL is positioned proximally to its *cis*-linked gene, and is downstream of the stimuli in which the association is observed (e.g. LPS and PAM in Group II). The linked target gene may be connected to additional signal based on its responsiveness profile (e.g. poly IC in Group II).

Supplementary Figure 8. The positioning of responsiveness profiles in the wiring diagram is supported by TF binding. Genes in modules #1-#6 were grouped into responsiveness profiles based on their responsiveness to LPS-PAM, LPS-Poly IC and PAM-LPS-Poly IC (**Supplementary Fig. 5d**). For each group of genes that have the same responsiveness profiles (x axis), shown is their hyper-geometric enrichment score (–log P-value) with NFkB targets (white), and Stat1 or Irf3 targets (black) (y-axis), as determined by ChIP-Seq or genetic perturbation in DCs (Amit et al, 2009; Garber et al, 2012). As expected, LPS-PAM and PAM-LPS-Poly IC RPs are enriched with NFκB targets, whereas LPS-Poly IC and PAM-LPS-Poly IC are enriched with Irf3/Stat1 targets. These strongly support their differential positioning in our circuit.

Supplementary Figure 9. **Module #2.** (**a**) **LR scores for expression traits of eight target genes of module #2.** Shown are the LR scores (Y axis) at each genomic position (X axis) for the expression traits of eight target genes (color code, side legend) measured at 6 hours following poly IC stimulation. (**b**) **Rgs16 effect on gene transcript levels in module #2.** Shown is a distribution of the effect of knockdown of Rgs16 on transcripts levels. Shown as in **Fig. 6c**, except that the results are presented for another shRGS16 (here, shRGS16(2)) whose knockdown efficiency is lower (**Fig. 6b**). *P<0.1 ; **P<0.001.

Supplementary Figure 10. Responsiveness versus transcript abundance: comparison of genetic associations and gene-environment interaction. Shown is a distribution of the association scores (-log p-value; **a**) and QTL-stimulus interactions (-log p-value; **b)**, calculated based on a full ANOVA model (**Methods**), based on either expression traits (eQTLs, abundance, red) or responsiveness traits (reQTLs, black). Each plot presents data for all variation signature genes that were measured on the Nanostring nCounter. Compared to abundance traits, association of responsiveness tends to be lower (a, KS test $P<10^{-5}$), but QTL-stimuli interactions tend to be higher (b, KS test $P<10^{-4}$), suggesting the importance of gene-environment interactions in the context of responsiveness traits.

Supplementary Figure 11. The InSignature method. InSignature takes as input genome-wide profiles from different strains and conditions. In step 1 (top) it predicts, for each gene, an underlying 'InSignature pattern' based on a maximum likelihood ratio fitting of two (or three) Gaussians. The maximum likelihood ratio is referred to as 'InSignature score'. In step 2 (middle), genes are grouped based on their InSignature patterns. Each such group is referred to

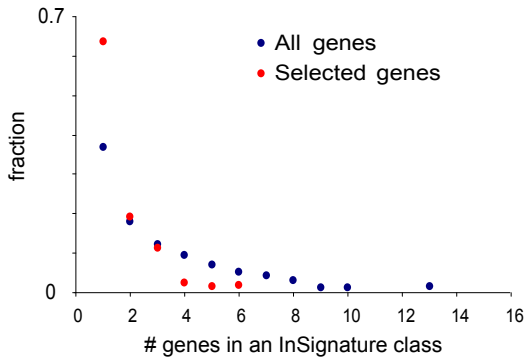
as ‘InSignature class’ or, in short, ‘class’. In step 3 (bottom), InSignature selects the best-scoring genes within each class; these form the ‘variation signature’ genes.

Supplementary Figure 12. InSignature scores in microarray data. Shown is a distribution of the InSignature scores (X axis, **Methods**) calculated from the microarray data (**Supplementary Table 1**; red) and in a randomized dataset (black) generated only by reshuffling the measurements of each gene independently, thus disrupting only the matching between pairs of individuals of the same genetic background. The InSignature score threshold corresponding to an FDR of 0.05 is 5.5, indicated in gray vertical line.

Supplementary Figure 13. A visualization of confounders such as population stratification. Shown are P-P plots for the association of Nfκb (left) and Tnf (right) responsiveness following poly IC stimulation (6 hours). Observed -log10 P values (y axis) for all SNPs are plotted against the expected null distribution (x axis). To calculate P-values, LR scores were transformed to fit an F distribution (scheffe, 1959). The observed distribution matches the expected distribution closely, with a modest genome-wide inflation (genomic control $\lambda = 1.0005$ and 0.9995) and an excess only at the tail.

Supp. Figure 1

a



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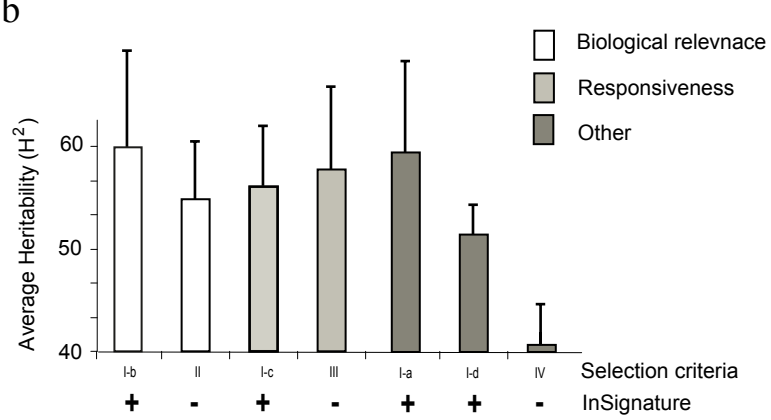
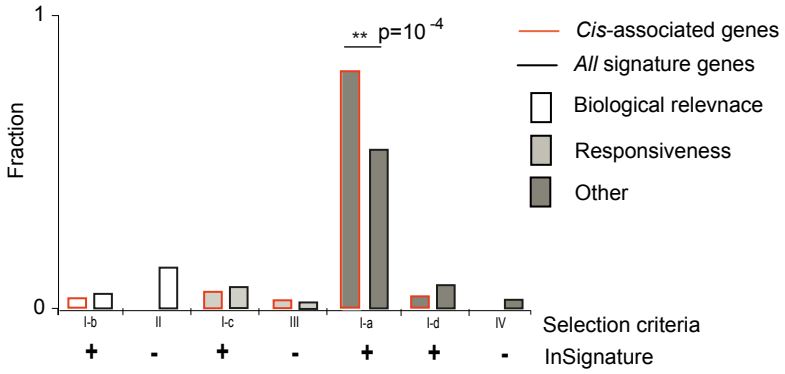
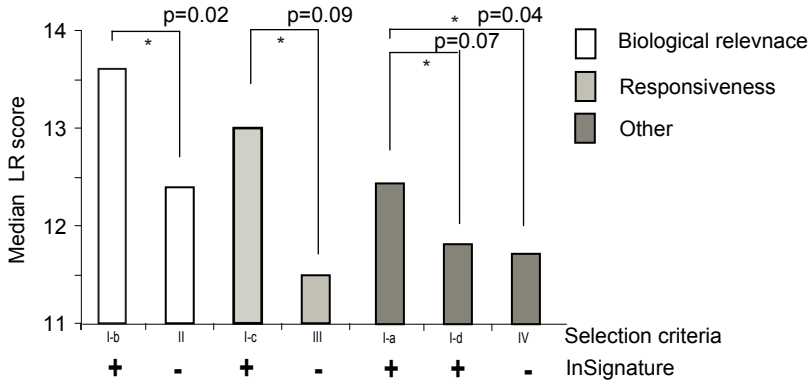


c

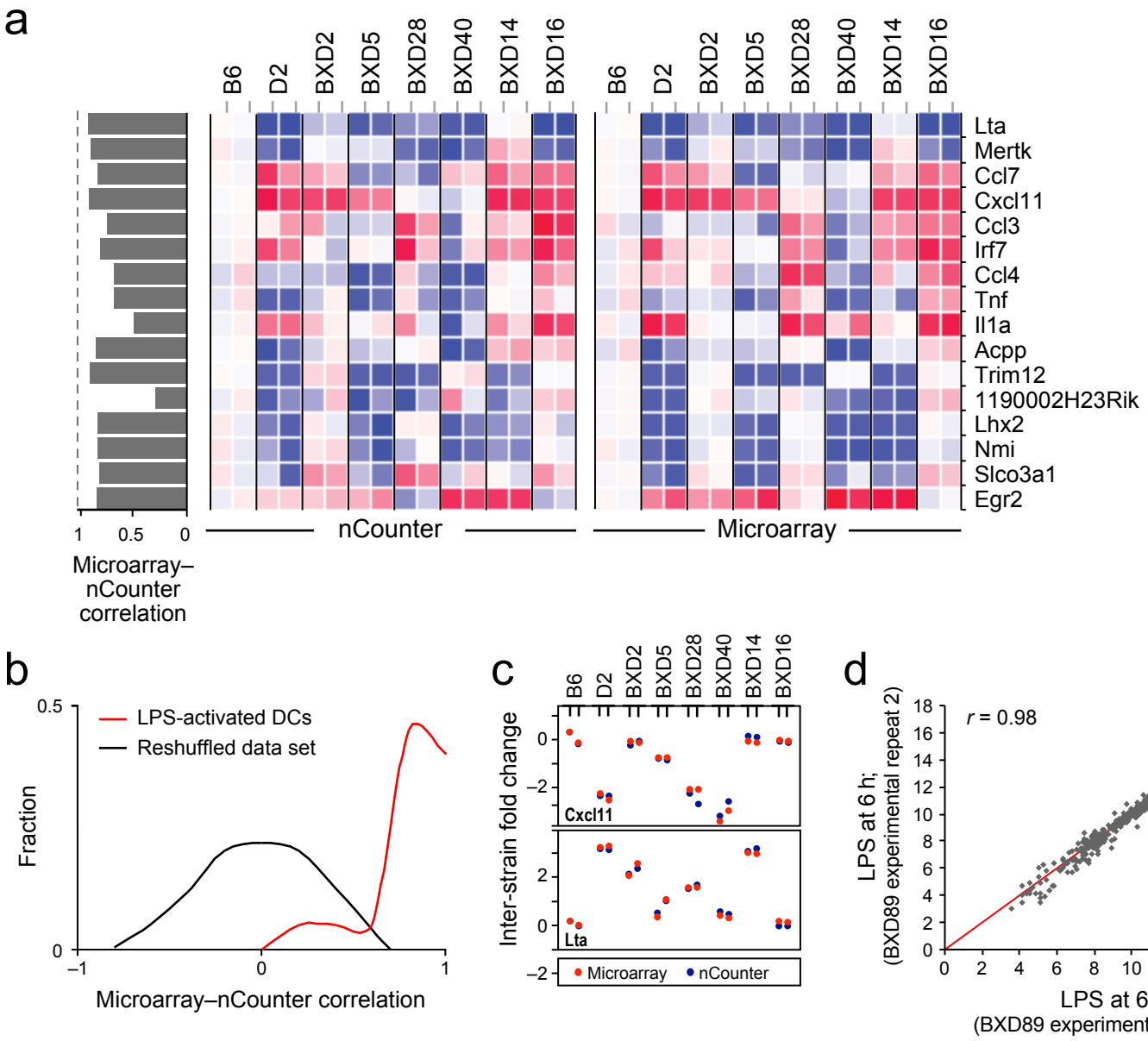


d



e

	InSignature *cis*	InSignature non-*cis*	Sum
nCounter, *cis*	25	30	55
nCounter, non-*cis*	33	336	369
Sum	58	366	= 424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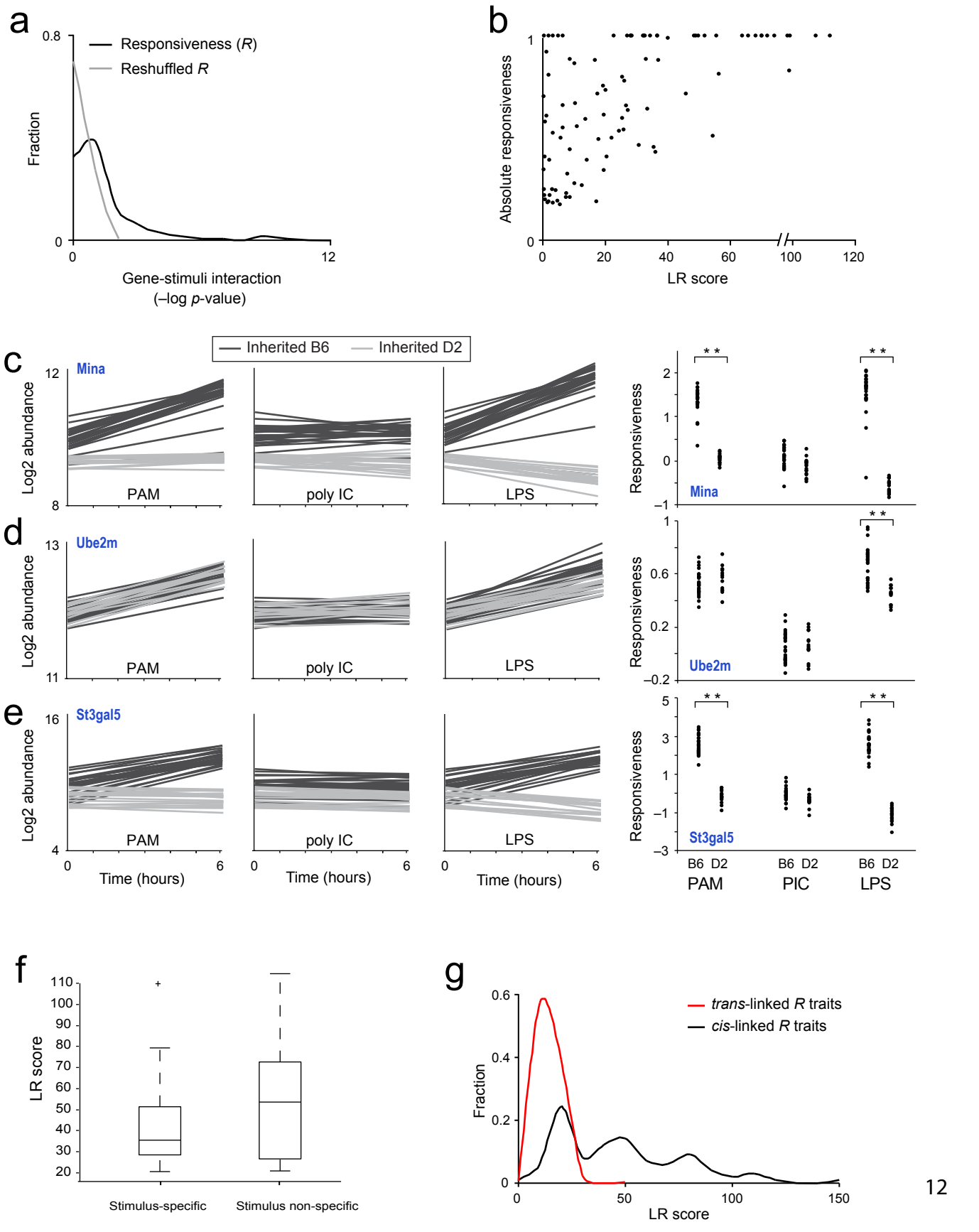
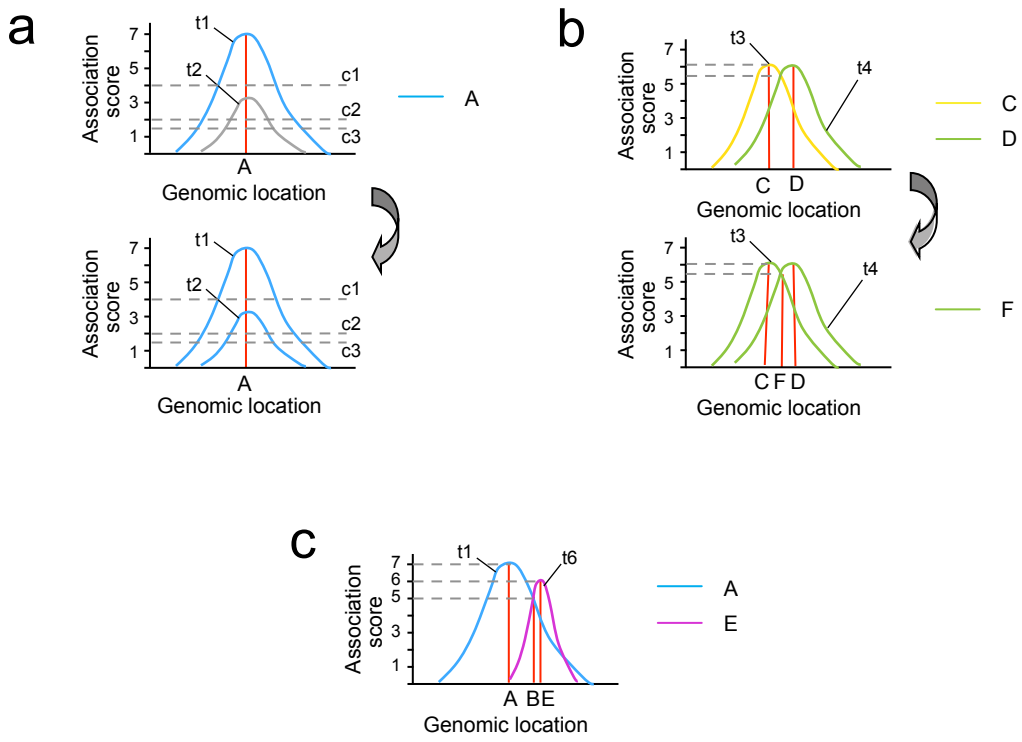
B6
D2
BXD2
BXD5
BXD28
BXD40
BXD14
BXD16
Lta
Mertk
Ccl7
Cxcl11
Ccl3
Irf7
Ccl4
Tnf
Il1a
Acpp
Trim12
1190002H23Rik
Lhx2
Nmi
Slco3a1
Egr2
nCounter
Microarray
1
0.5
0
Microarray–
nCounter
correlation
b
LPS-activated DCs
Reshuffled data set
Fraction
0.5
0
–1
0
1
Microarray–nCounter correlation
c
Inter-strain fold change
Cxcl11
Lta
Microarray
nCounter
d
r = 0.98
LPS at 6 h;
(BXD89 experimental repeat 2)
LPS at 6 h
(BXD89 experimental repeat 1)


a
Responsiveness (R)
Reshuffled R
Fraction
Gene-stimuli interaction
(–log p-value)
b
Absolute responsiveness
LR score
c
Inherited B6
Inherited D2
Mina
Log2 abundance
PAM
poly IC
LPS
Responsiveness
d
Ube2m
e
St3gal5
Time (hours)
B6 D2
PAM
PIC
LPS
f
LR score
Stimulus-specific
Stimulus non-specific
g
trans-linked R traits
cis-linked R traits
Fraction
LR score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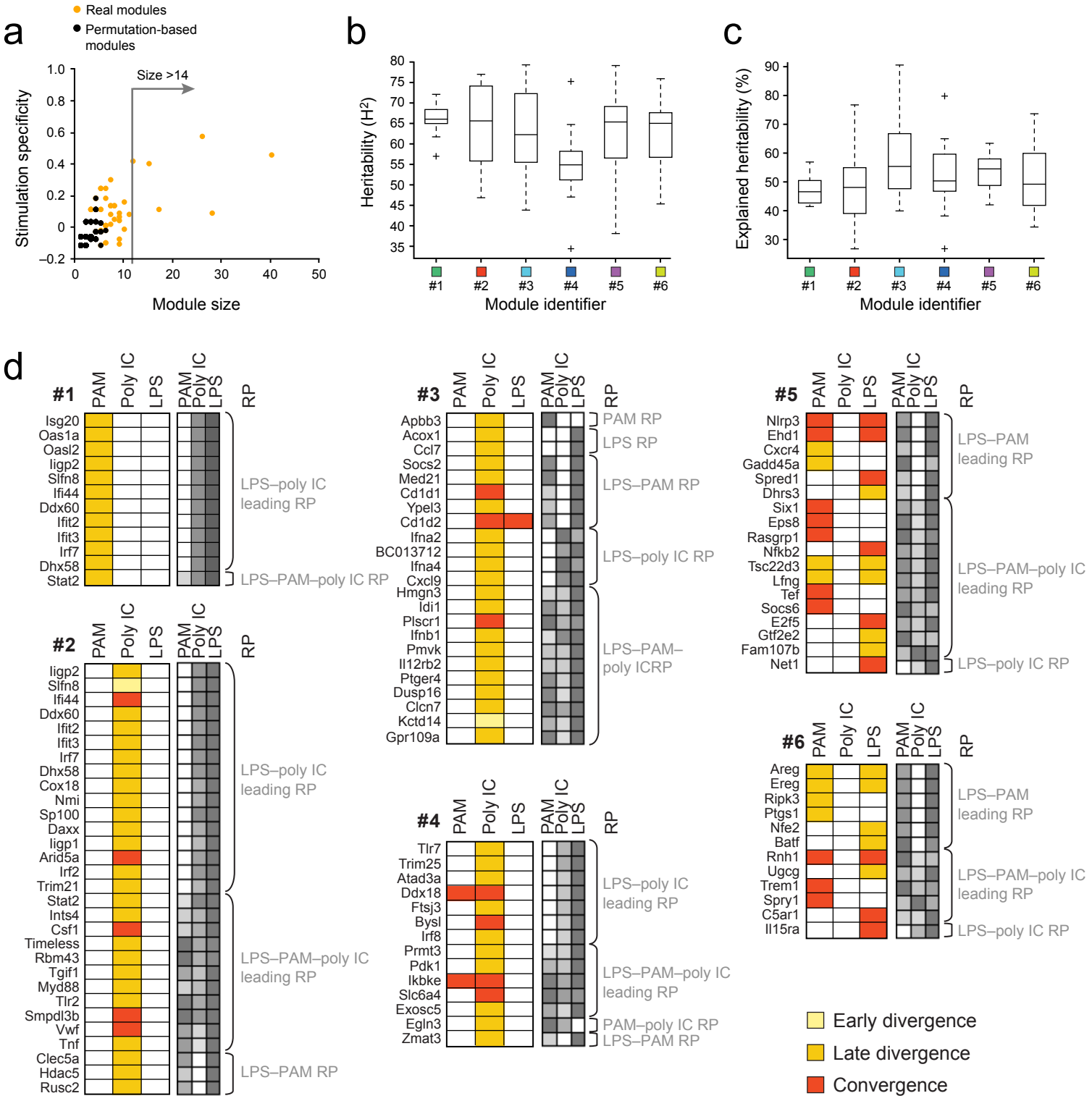
Association score
7
5
3
1
t1
t2
c1
c2
c3
A
Genomic location
A
b
t3
t4
C
D
C D
Genomic location
F
C F D
c
t6
A
E
A BE


a
Real modules
Permutation-based modules
Size >14
Stimulation specificity
Module size
b
Heritability (H2)
Module identifier
c
Explained heritability (%)
Module identifier
d
#1
#2
#3
#4
#5
#6
PAM
Poly IC
LPS
PAM Poly IC LPS
RP
LPS–poly IC leading RP
LPS–PAM–poly IC RP
LPS–PAM–poly IC leading RP
LPS–PAM RP
PAM RP
LPS RP
LPS–PAM RP
LPS–poly IC RP
LPS–PAM–poly ICRP
LPS–poly IC leading RP
LPS–PAM–poly IC leading RP
PAM–poly IC RP
LPS–PAM RP
LPS–PAM leading RP
LPS–PAM–poly IC leading RP
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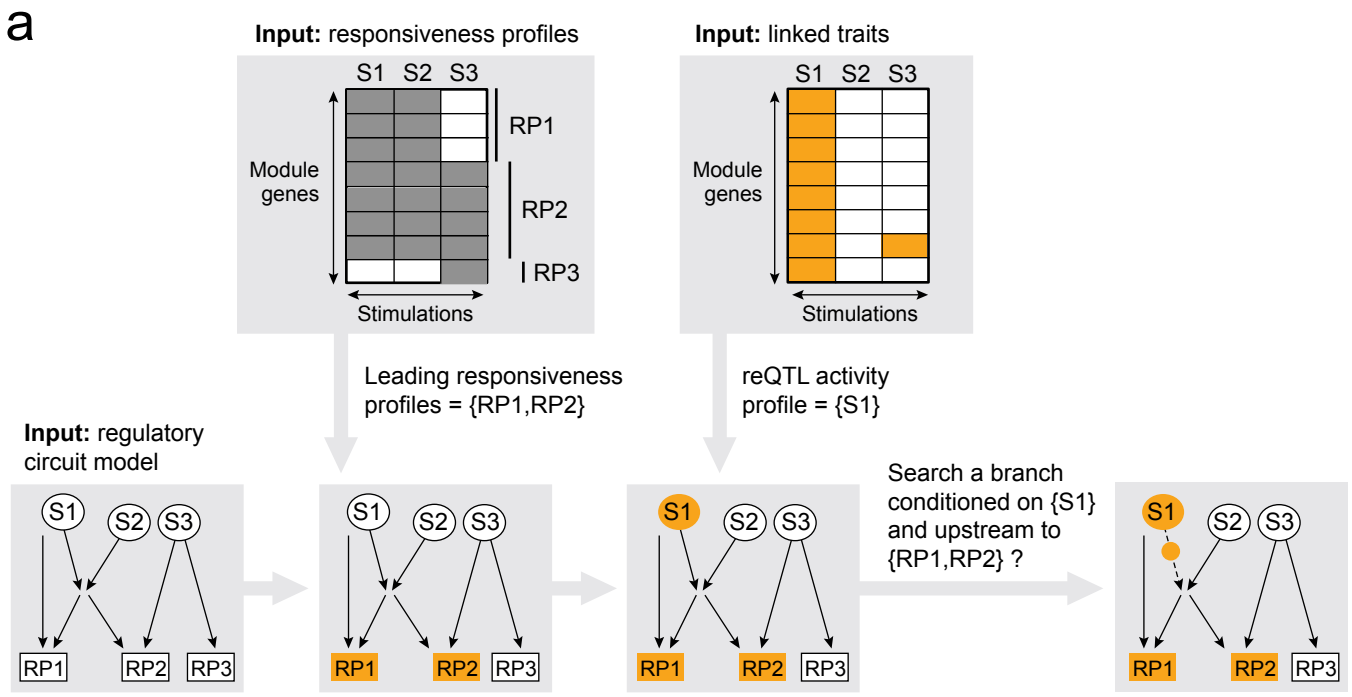
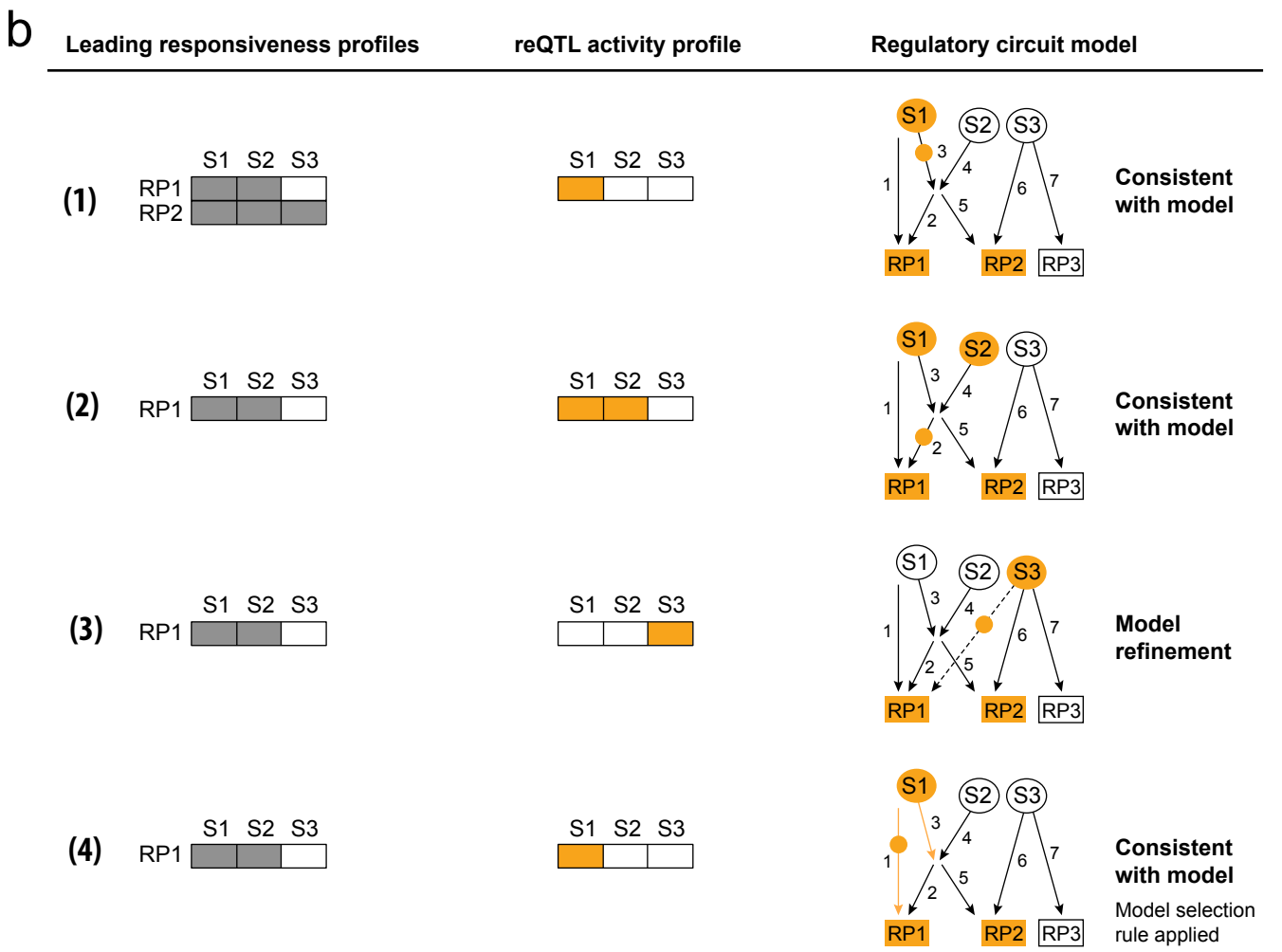
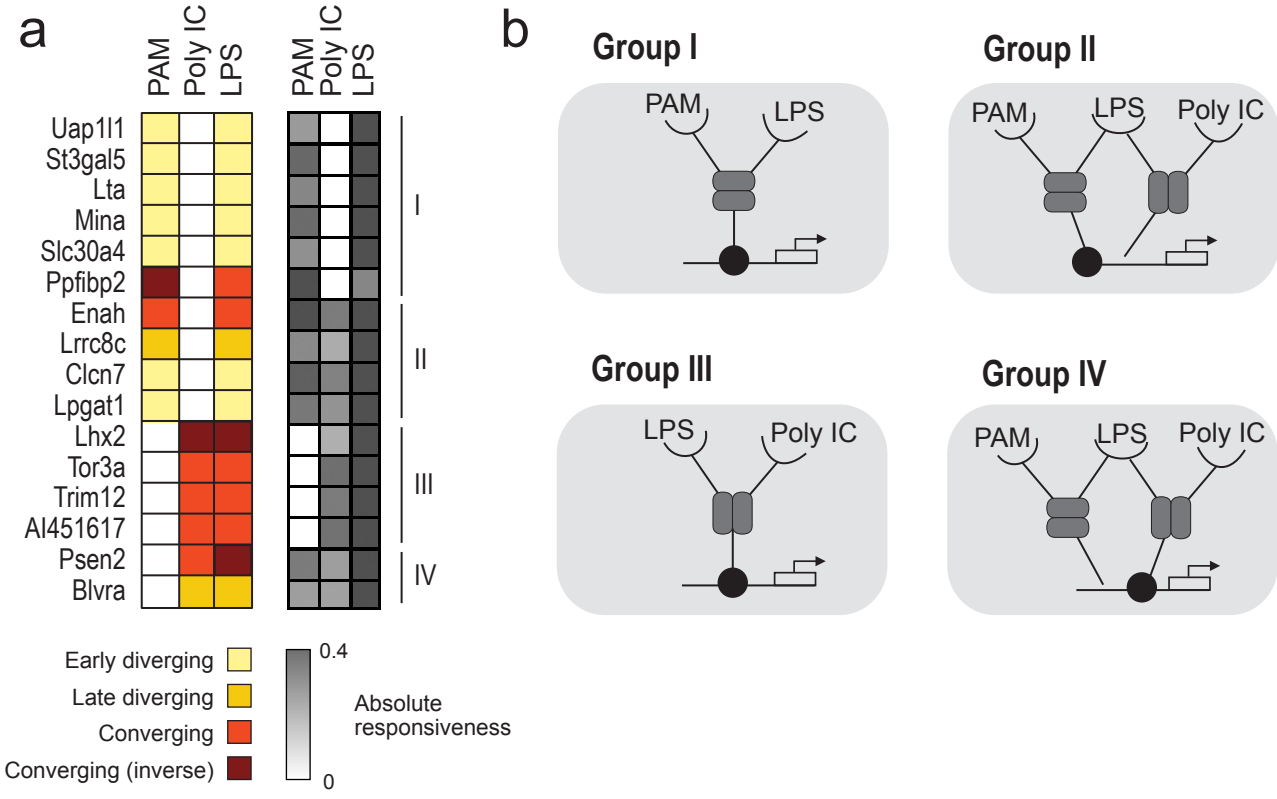
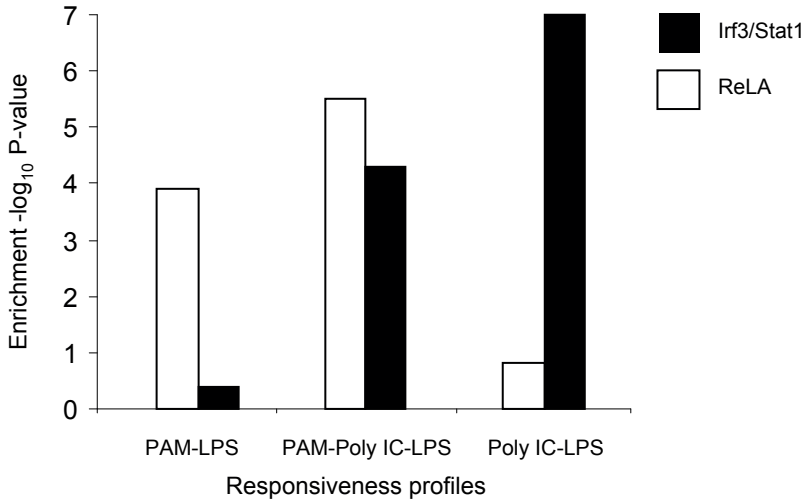
LPS–PAM leading RP
LPS–PAM–poly IC leading RP
LPS–poly IC RP
Early divergence
Late divergence
Convergence


a
Input: responsiveness profiles
S1 S2 S3
Module genes
RP1
RP2
RP3
Stimulations
Input: linked traits
S1 S2 S3
Module genes
Stimulations
Leading responsiveness profiles = {RP1,RP2}
reQTL activity profile = {S1}
Input: regulatory circuit model
Search a branch conditioned on {S1} and upstream to {RP1,RP2} ?
S1 S2 S3
RP1 RP2 RP3

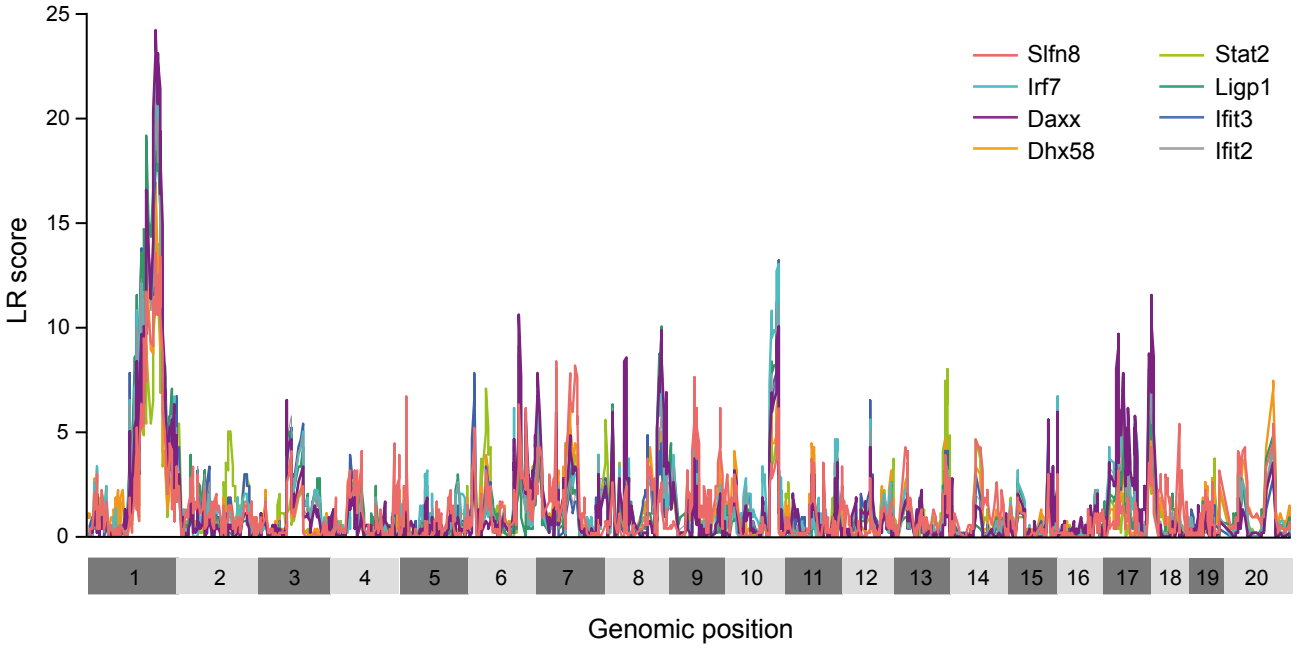

b
Leading responsiveness profiles
reQTL activity profile
Regulatory circuit model
(1)
RP1
RP2
S1 S2 S3
Consistent with model
(2)
RP1
Consistent with model
(3)
RP1
Model refinement
(4)
RP1
Consistent with model
Model selection rule applied


a
PAM
Poly IC
LPS
PAM
Poly IC
LPS
Uap1l1
St3gal5
Lta
Mina
Slc30a4
Ppfibp2
Enah
Lrrc8c
Clcn7
Lpgat1
Lhx2
Tor3a
Trim12
AI451617
Psen2
Blvra
I
II
III
IV
Early diverging
Late diverging
Converging
Converging (inverse)
0.4
0
Absolute responsiveness
b
Group I
PAM
LPS
Group II
PAM
LPS
Poly IC
Group III
LPS
Poly IC
Group IV
PAM
LPS
Poly IC

Supp. Figure 8



a


LR score
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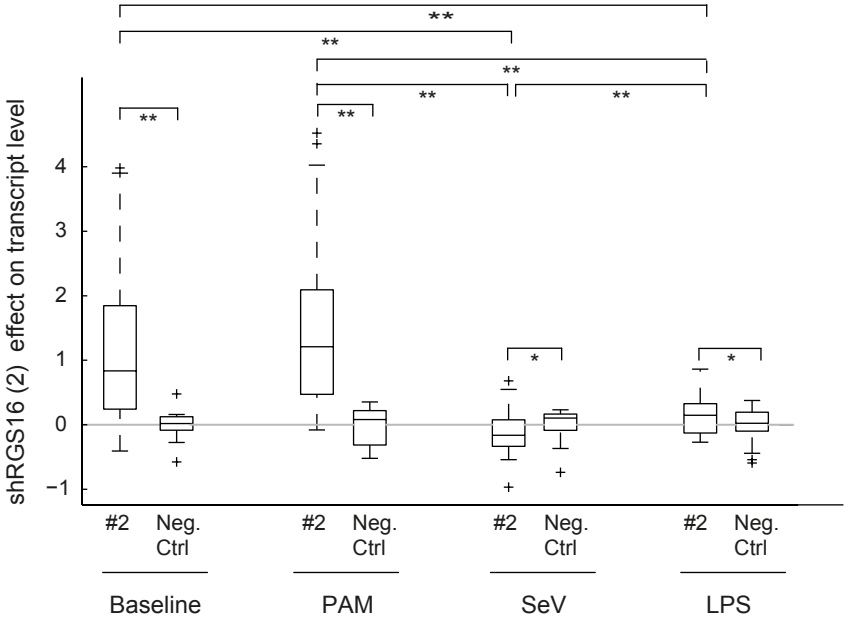
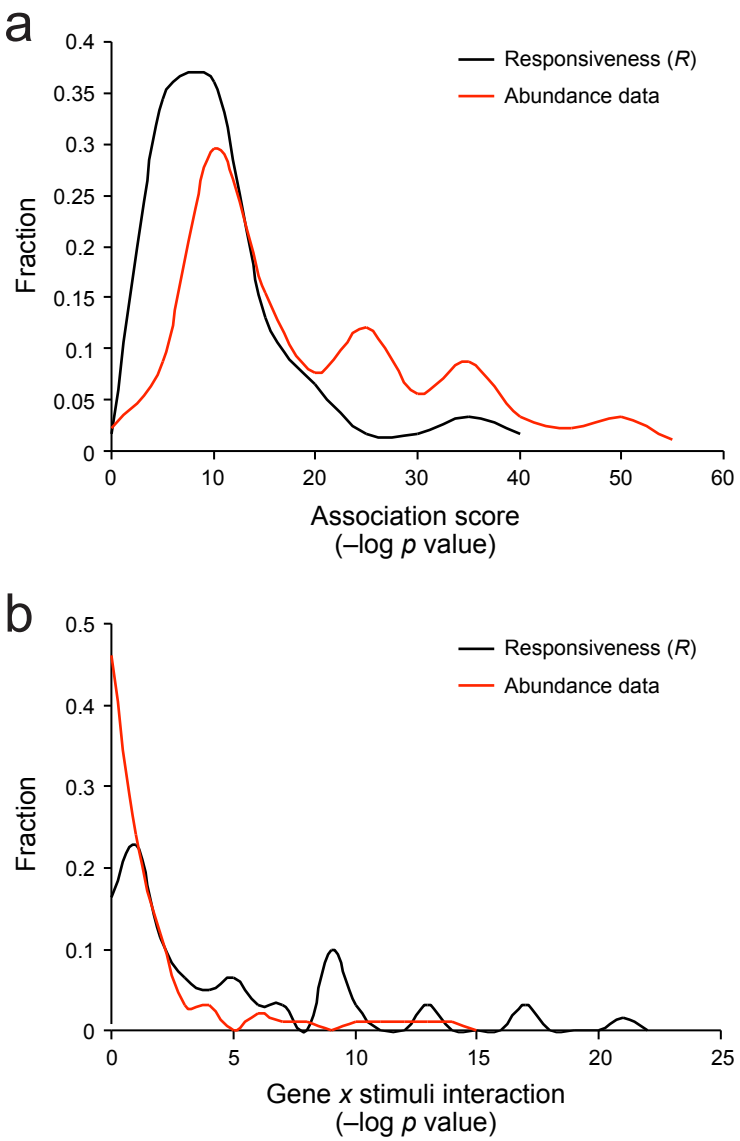
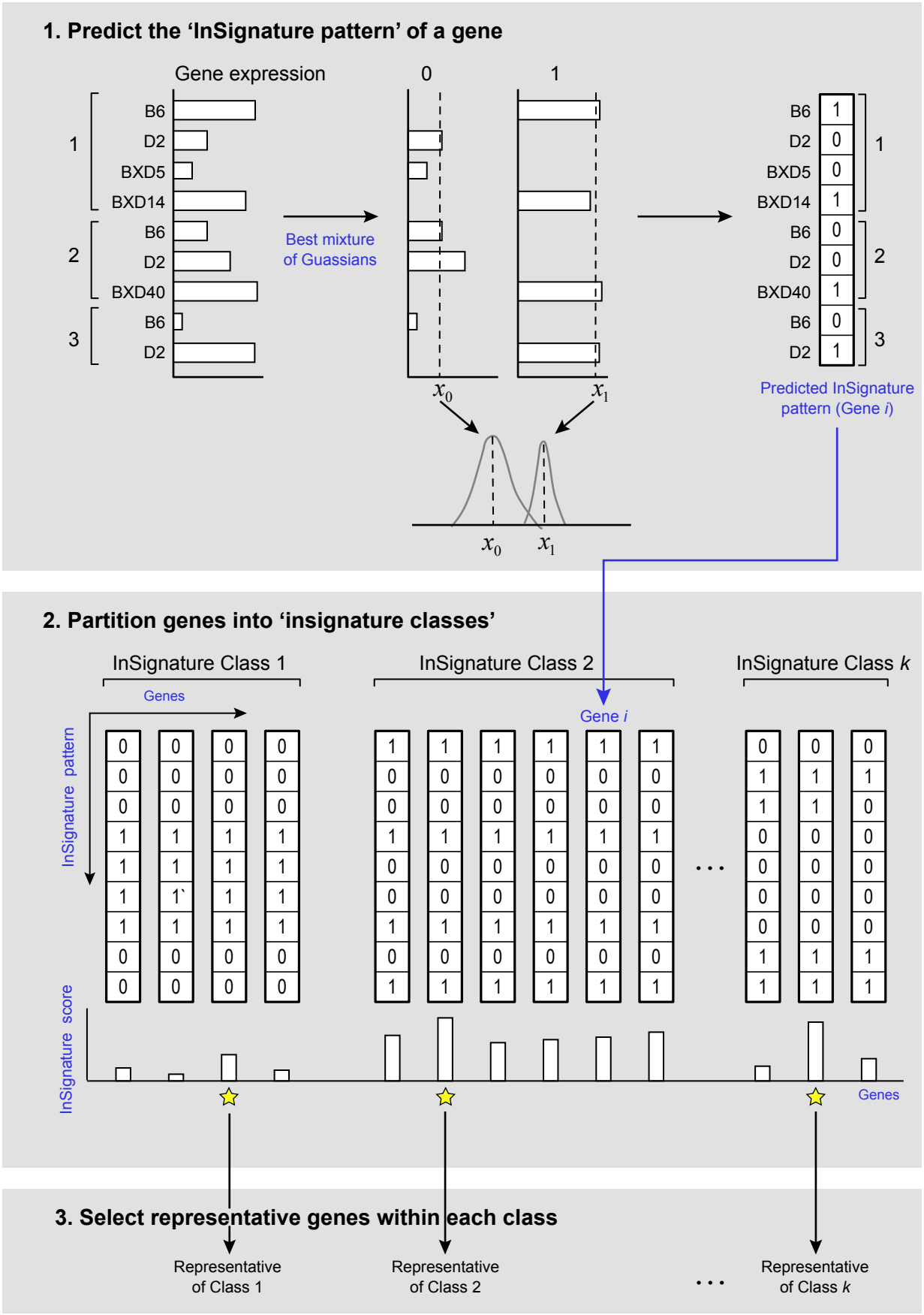
20
15
10
5
0
Slfn8
Irf7
Daxx
Dhx58
Stat2
Ligp1
Ifit3
Ifit2
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
Genomic position

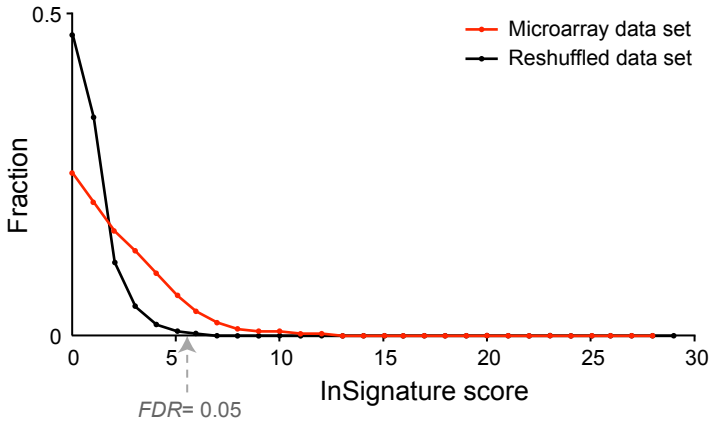
b


shRGS16 (2) effect on transcript level
4
3
2
1
0
−1
**
**
**
**
**
**
*
*
#2
Neg. Ctrl
#2
Neg. Ctrl
#2
Neg. Ctrl
#2
Neg. Ctrl
Baseline
PAM
SeV
LPS

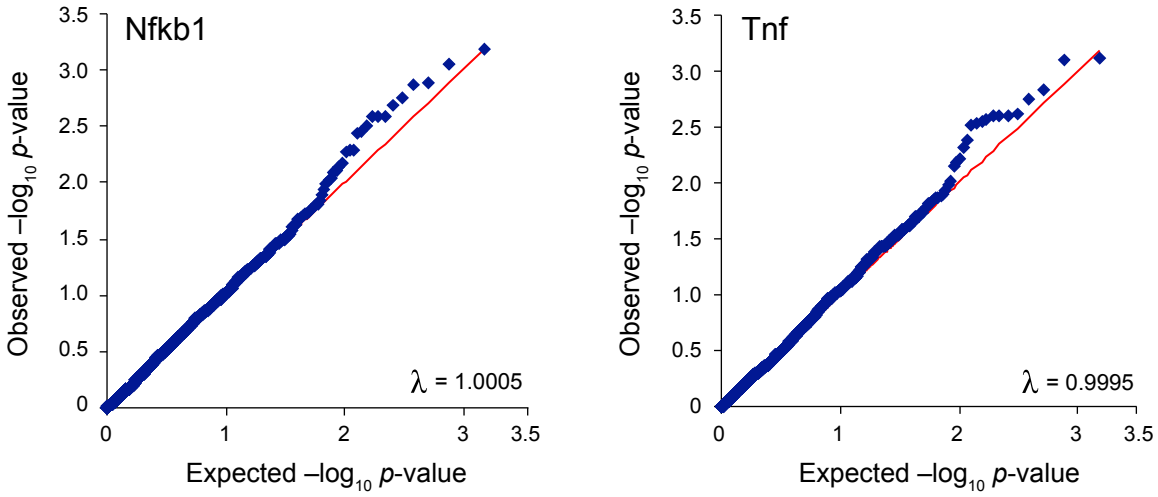

a
Responsiveness (R)
Abundance data
Fraction
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
10
20
30
40
50
60
Association score
(–log p value)
b
Responsiveness (R)
Abundance data
Fraction
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
Gene x stimuli interaction
(–log p value)


1. Predict the 'InSignature pattern' of a gene
Gene expression
0
1
B6
D2
BXD5
BXD14
B6
D2
BXD40
B6
D2
1
2
3
Best mixture of Guassians
x_0
x_1
x_0
x_1
B6 1
D2 0
BXD5 0
BXD14 1
B6 0
D2 0
BXD40 1
B6 0
D2 1
1
2
3
Predicted InSignature pattern (Gene i)
2. Partition genes into 'insignature classes'
InSignature Class 1
InSignature Class 2
InSignature Class k
Genes
Gene i
InSignature pattern
InSignature score
Genes
3. Select representative genes within each class
Representative of Class 1
Representative of Class 2
Representative of Class k

Supp. Figure 12



Supp. Figure 13

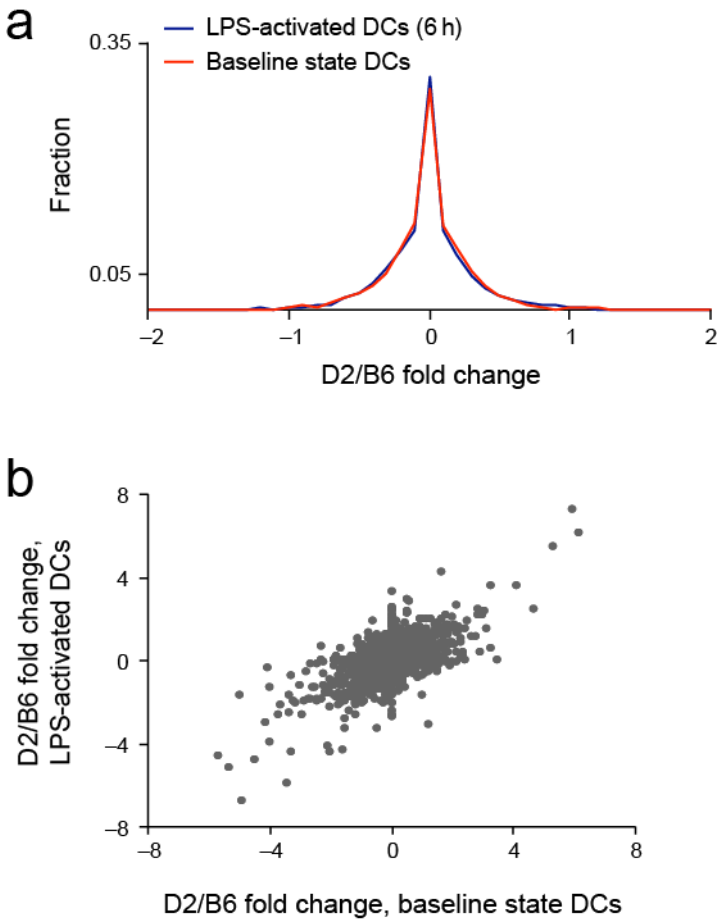


Supplementary Note

Supplementary Note 1. Genome-wide heritable variation in the transcriptional response to pathogenic components

We measured 30 genome-wide transcription profiles in resting and stimulated DCs from two parental strains (B6 and D2) and six BXD strains (**Supplementary Table 1**). For the parental strains, we profiled a pool of two individuals from each strain pre-stimulation and at 2 and 6 hours after treatment with LPS, poly IC, or PAM3CSK ('PAM') (TLR4, 3, and 2 agonists, respectively). For the six BXD strains, we measured expression profiles in two individuals from each strain stimulated with LPS, the stimulus with the broadest effect on gene expression.

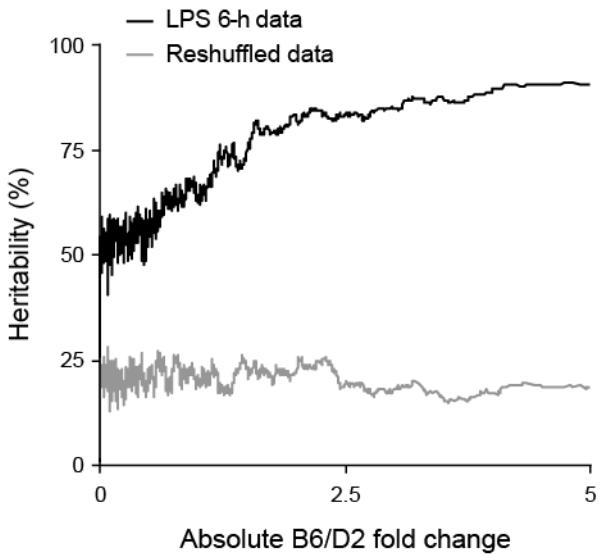
We used the 30 genome-wide profiles to identify loci with inherited expression variation, by testing whether the parental strains have major gene expression differences following stimulation, and whether these parental differences are inherited. First, we calculated the fold change difference among B6 and D2 *(B6/D2 fold change)* to evaluate for each gene the extent to which its expression in the parental strains differs under the same stimulation and time point (**Methods**). There are substantial D2/B6 fold changes, with 11% of the genes exceeding a 2-fold change in at least one stimulus. In particular, 162, 132, and 97 genes have an absolute log B6/D2 fold change that is higher than 2 at 6 hours after exposure to LPS, poly IC and PAM, respectively. The overall distribution of D2/B6 fold-changes is similar in baseline profiles and under stimulations (**SN Fig. 1a**), although the fold changes of individual genes may substantially differ in the baseline versus stimulated state (**SN Fig. 1b**).



SN Figure 1. **D2/B6 fold changes.** (**a**) Shown is the distribution of D2/B6 fold changes (X axis) before activation (red) and at 6 hours following LPS stimulation (black). (**b**) Shown are the D2/B6 fold changes before activation (X axis) and at 6 hours following LPS stimulation (Y axis).

Next, we tested which of the D2/B6 fold changes under stimulation are inherited, by calculating for each gene its broad-sense heritability (H^2), as the percentage of between-strain variation out of the total amount of expression variation. Higher heritability indicates a more significant difference between the mean gene expression values of the BXD strains, compared to the within-strain variation (**Methods**). The observed heritability values are significantly higher than expected by chance (t-test $P<10^{-200}$, **SN Fig. 2**). Although no information from the parental strains was used to infer heritability, the D2/B6 fold changes are significantly correlated to H^2 at

the same condition (LPS at 6 hours, Pearsons's $r = 0.43$, $P << 10^{-200}$, **SN Fig. 2**), suggesting that the differences among parental strains are inherited.



SN Figure 2. **Heritability of variation in gene expression.** Shown is the heritability of gene expression in BXD RI strains (Y axis) vs. the fold change in expression between the parental inbred strains (X axis) for data collected at 6h post LPS stimulation (black) and for reshuffling measurements of each gene (gray). The plots were generated by using a moving average of a window of 100 genes.

Supplementary Note 2. The variation signature selection pipeline.

In this study, we used a signature of 424 genes – the maximal number of genes that could be reliably assayed using the meso-scale nCounter technology at the time, given the expression levels and cell numbers used in our system.

We used the following selection pipeline. First, we selected genes based on heritable variation in responsiveness, as determined by InSignature analysis of the global profiles across a small

number of strains (criterion I). This analysis is designed to represent the different underlying genetic factors and their associated genes in an unbiased manner (**Methods**). To these, we added, in order, genes based on prior knowledge on their biological relevance in this sytem (criterion II), positive control genes based on responsiveness to the relevant stimuli (criterion III), and negative control genes (criterion IV). **Supplementary Table 3** summarizes the number of genes that were added in each step of this pipeline. **Supplementary Table 2** provides a full list of all signature genes, organized by the particular pipeline criteria. Below we describe each step.

Criterion I: An heritability-based (genetic-based) selection: selecting genes that represent different underlying genetic factors in an unbiased manner. A naïve 'systems genetic' approach can select the genes with the highest heritability or highest association to any of the genome-wide genetic variants under one or a few of the stimuli. However, there are two drawbacks to this approach. First, due to the complexity of the genetic landscape, it is impossible to assume that the same genetic variant is functional under all stimuli. As the selection of signature genes is based on only a few genetic backgrounds, it is impossible to apply a standard association test on each of the stimuli. Second, choosing signature genes based on the association or heritability score alone might lead to an imbalanced selection of many genes that are significantly associated with only a few (pleiotropic) genetic variants.

InSignature addresses these challenges as follows. First, InSignature associates each expression trait with the most likely genotype in each of the strains and stimulations. The most likely genotype is called a 'InSignature pattern' and its score is called an 'InSignature score'. The prediction and scoring scheme is designed to fit the special case of a different (or no) genetic variant under each stimulus, and as few as one or two profiled strains in some of the stimuli.

Genes whose InSignature pattern exactly matches the genotype in their proximity are termed *cis* predictions, and the rest are termed *trans* predictions. Note that the *cis* predictions at this stage are not necessarily controlled in *cis*, since using only a few genetic backgrounds, a large fraction of the genome share the same genotype (*e.g.*, for 6 BXD strains, a fraction of 1:32 of the genome have exactly the same genetic information). Second, InSignature groups responsiveness traits based on their InSignature pattern. Such a group, referred to as an 'InSignature class' (**Methods**), consists of all genes that have a certain InSignature pattern: Two genes within the same class have an identical InSignature pattern, whereas two genes at different classes have a distinct InSignature pattern.

The partition into classes allows selection of genes that are associated with a variety of genetic factors in an unbiased manner. To this end, InSignature first randomly selects a class and then selecting a gene (if available) within that class. Four alternative criteria have been used to select a gene within a sampled class:

I-a: 'Top in class' (232 genes). Selecting the gene with the highest InSignature score within a class.

I-b. Biological relevance (20 genes). Selecting a gene in the class that is a key immune-related or disease-related gene based on prior knowledge. In this study, we used the annotation in the Ingenuity knowledge base (Ingenuity Systems, Mountain View, CA, USA).

I-c. Responsiveness (35 genes). Selecting genes in the class with high responsiveness levels under (one or a few) of the stimuli in an unbiased manner. In this study, we used a dataset of

DCs responsiveness under LPS, PAM or polyIC measured at nine time points (Amit et al. 2009).

I-d. **Random (35 genes)**. Randomly selecting one of the class genes.

The researcher needs to decide in advance how many genes are selected based on each of the criteria. Here, the distribution of number of genes that were selected using each of these categories is detailed in **Supplementary Table 3**, and noted next to each criterion above. The analysis in **Supplementary Fig. 1** highlight the eventual relative utility of these different options, and can guide future users to prefer for example high scoring genes over random ones in the class.

Supplementary Fig. 1a summarizes the distribution of number of genes that were from each InSignature class. Each of the 20 genes selected based on biological relevance resides in a different class. In the case of responsiveness-based and random-based selection, two and three classes (respectively) include two selected genes whereas the remaining includes exactly one selected gene.

Criterion II: Selection based on biological relevance (knowledge-based selection). In this step, we added genes that have a known key role in immune response or relevant diseases, although they have no significant InSignature score. This serves two purposes. First, previous studies reported an enrichment of genetically-linked genes among such genes (Barreiro et al, 2012). Second, such genes are of broad interest to biologists studying the system. In our experience in this and other studies, a biologist researcher knowledgeable in a system would opt

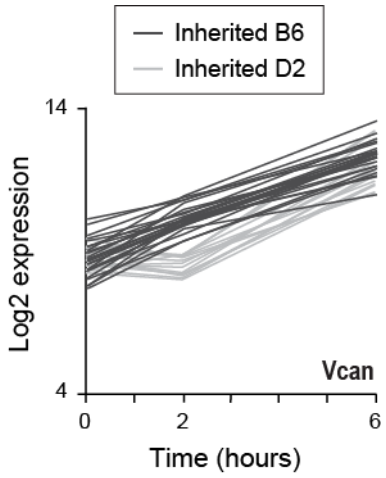
to include such "biological relevance" genes in a signature. In this study, we selected 61 genes manually based on their annotation in the Ingenuity Knowledge based (Ingenuity Systems, Mountain View, CA, USA). Analysis of our eventual signature data (**Supplementary Fig. 1**) indicate that such a knowledge-based selection was indeed valuable for identifying additional associations.

Criterion III: Selection of positive responsiveness controls. In this step, we added 20 genes based on their high responsiveness levels to the relevant stimuli, despite having no significant InSignature score. Such genes serve two purposes. First, previous studies have reported the enrichment of reQTLs underlying highly responding genes (Barreiro et al, 2012). Second, they are positive controls for the overall success of the stimulation experiment. In this study, we used a dataset of DCs responsiveness under LPS, PAM or poly IC across nine different time points (Amit et al, 2009). Analysis of our eventual signature data (**Supplementary Fig. 1**) indicate that a selection based on responsiveness criteria was indeed valuable for identifying *cis*- and *trans*-associations.

Criterion IV: Selection of negative control genes. The negative controls are genes with low observed variation among time points, strains and individuals. These are used to evaluate false positive and true negative genes in our association study. Since variation depends on the intensity of gene expression, we chose those genes with lowest variance-to-average ratio. To cover various different levels of intensity, genes were grouped into four bins based on their level of gene expression, and five (or six) genes with lowest variance-to-average ratio were selected from each such bin.

Supplementary Note 3. The vast majority of *cis*-linked genes are detected at both 2 and 6 hours.

To test whether 6-hour data recapitulates *cis* signals acting during the early response, we measured the expression of the signature genes in DCs from the same 96 mice at 2 hours following stimulation with LPS, and defined their 2-hours responsiveness traits. We find a high agreement between *cis*-linked responsiveness traits at 2- and 6-hours: each of the 31 *cis*-linked genes at 6 hours (**Fig. 3a**) is also *cis*-linked at 2-hours. 31 of 32 (96%) of the cis-linked genes at 2-hours are also *cis*-linked at 6 hours. The only exception is *Vcan*, which is *cis*-linked only at 2h, consistent with its early response in B6 but not in D2 genetic background (**SN Figure 3**).



SN Figure 3. **Expression of the Vcan gene**. Shown are the log2 expression levels (Y axis) of Vcan gene at 0, 2 and 6 hours following LPS (X axis) for parental and BXD strains carrying the B6 (black) and D2 (grey) allele at the proximity of the gene.

References:

- Amit I, Garber M, Chevrier N, Leite AP, Donner Y, Eisenhaure T et al. (2009) Unbiased reconstruction of a mammalian transcriptional network mediating pathogen responses. *Science* **326:** 257-263
- Barreiro LB, Tailleux L, Pai AA, Gicquel B, Marioni JC, Gilad Y (2012) Deciphering the genetic architecture of variation in the immune response to Mycobacterium tuberculosis infection. *Proc Natl Acad Sci U S A* **109:** 1204-1209

Supplementary Tables

strain	stimulation	time	#individuals	# biological repeats
B6	no stimulation	Baseline	1	2
D2	no stimulation	Baseline	1	2
BXD2	LPS	6 hours	1	2
BXD5	LPS	6 hours	1	2
BXD14	LPS	6 hours	1	2
BXD16	LPS	6 hours	1	2
BXD28	LPS	6 hours	1	2
BXD40	LPS	6 hours	1	2
B6	LPS	6 hours	1	2
D2	LPS	6 hours	1	2
B6	PAM	6 hours	1	1
D2	PAM	6 hours	1	1
B6	Poly IC	6 hours	1	1
D2	Poly IC	6 hours	1	1
B6	LPS	2 hours	1	1
D2	LPS	2 hours	1	1
B6	PAM	2 hours	1	1
D2	PAM	2 hours	1	1
B6	Poly IC	2 hours	1	1
D2	Poly IC	2 hours	1	1
Total number of arrays:				**30**

Supplementary Table 1. Experimental design of microarray study. Shown are mice strains (column 1) and the experiment for each strain (stimulation and time point in columns 2 and 3, respectively). Column 4 provides the number of individuals in each array. Column 5 provides the number of biological replicates. For each strain, we have measured one or two individuals; each is a biological replicate and has been monitored in a *separate* array.

Supplementary Table 2. Nanostring nCounter design

Symbol	Entrez ID	Chr	Strand	Start	End	Selection criterion name	Selection criterion
Bcl2l11	12125	2	+	127951773	127988283	heritability (Biological relevance)	criterion I-b
Ctnnb1	12387	9	+	120842517	120869624	heritability (Biological relevance)	criterion I-b
Ctse	13034	1	+	133534890	133572084	heritability (Biological relevance)	criterion I-b
Cxcr4	12767	1	-	130484776	130488870	heritability (Biological relevance)	criterion I-b
Ddx60	234311	8	+	64406885	64516492	heritability (Biological relevance)	criterion I-b
Fcgr4	246256	1	+	172949056	172959892	heritability (Biological relevance)	criterion I-b
Hdac5	15184	11	-	102057060	102091486	heritability (Biological relevance)	criterion I-b
Ltb	16994	17	+	35331451	35333250	heritability (Biological relevance)	criterion I-b
Myc	17869	15	+	61816895	61821916	heritability (Biological relevance)	criterion I-b
Nlrp3	216799	11	+	59356187	59380458	heritability (Biological relevance)	criterion I-b
Notch2	18129	3	+	97817460	97954290	heritability (Biological relevance)	criterion I-b
Pltp	18830	2	-	164665017	164683208	heritability (Biological relevance)	criterion I-b
Ptger4	19219	15	-	5183405	5193682	heritability (Biological relevance)	criterion I-b
Ptgs1	19224	2	+	36085945	36107789	heritability (Biological relevance)	criterion I-b
Rasgrp1	19419	2	-	117105728	117168613	heritability (Biological relevance)	criterion I-b
Sqle	20775	15	+	59146646	59162748	heritability (Biological relevance)	criterion I-b
Tgfbr1	21812	4	+	47366176	47427796	heritability (Biological relevance)	criterion I-b
Tk1	21877	11	-	117676832	117687328	heritability (Biological relevance)	criterion I-b
Tnf	21926	17	-	35336335	35338941	heritability (Biological relevance)	criterion I-b
cxcl11	56066	5	-	92788570	92792303	heritability (Biological relevance)	criterion I-b
Emr4	52614	17	+	55889248	55992927	heritability (random selection)	criterion I-d
2410002F23	66976	7	+	51502091	51507688	heritability (random selection)	criterion I-d
Adi1	104923	12	+	29360096	29367040	heritability (random selection)	criterion I-d
Ap1m1	11767	8	+	74764030	74781278	heritability (random selection)	criterion I-d
Cct8	12469	16	-	87484121	87496085	heritability (random selection)	criterion I-d
Cdc20	107995	4	-	118105505	118109948	heritability (random selection)	criterion I-d
Cep55	74107	19	+	38129531	38148915	heritability (random selection)	criterion I-d
Dnajc2	22791	5	-	21263094	21290983	heritability (random selection)	criterion I-d
Egln3	112407	12	-	55279968	55304861	heritability (random selection)	criterion I-d
Elavl4	15572	4	-	109876341	109960116	heritability (random selection)	criterion I-d
Esf1	66580	2	-	139945619	139996300	heritability (random selection)	criterion I-d
Exosc5	27998	7	+	26444171	26453050	heritability (random selection)	criterion I-d
Fam107b	66540	2	+	3630729	3699406	heritability (random selection)	criterion I-d
Fdft1	14137	14	-	63763987	63796630	heritability (random selection)	criterion I-d
Idi1	319554	13	+	8884851	8891641	heritability (random selection)	criterion I-d
Il17ra	16172	6	+	120413214	120433744	heritability (random selection)	criterion I-d
Itga6	16403	2	+	71625139	71694815	heritability (random selection)	criterion I-d
Kif3b	16569	2	+	153117151	153159123	heritability (random selection)	criterion I-d
Kitl	17311	10	+	99478457	99563045	heritability (random selection)	criterion I-d
Klf4	16600	4	-	55540008	55545347	heritability (random selection)	criterion I-d
Lair1	52855	7	-	3958674	4014806	heritability (random selection)	criterion I-d
Lss	16987	10	+	75994371	76016679	heritability (random selection)	criterion I-d
Mcm2	17216	6	-	88833467	88848774	heritability (random selection)	criterion I-d
Pmvk	68603	3	+	89263039	89272930	heritability (random selection)	criterion I-d
Pqlc2	212555	4	-	138853919	138866615	heritability (random selection)	criterion I-d
Rgs10	67865	7	-	135517138	135561686	heritability (random selection)	criterion I-d
Setd4	224440	16	-	93583705	93604060	heritability (random selection)	criterion I-d

Supplementary Table 2. Nanostring nCounter design (cont)

Symbol	Entrez ID	Chr	Strand	Start	End	Selection criteria	Selection criterion
Sgk1	20393	10	+	21714471	21719706	heritability (random selection)	criterion I-d
Slc6a8	102857	20	+	70918471	70927837	heritability (random selection)	criterion I-d
Socs2	216233	10	-	94874123	94879491	heritability (random selection)	criterion I-d
Socs6	54607	18	-	89037271	89063599	heritability (random selection)	criterion I-d
Timp2	21858	11	-	118162374	118216725	heritability (random selection)	criterion I-d
Tjp2	21873	19	-	24168991	24299444	heritability (random selection)	criterion I-d
Tmem37	170706	1	-	121963953	121970357	heritability (random selection)	criterion I-d
Zmat3	22401	3	-	32233715	32264587	heritability (random selection)	criterion I-d
Adhfe1	76187	1	+	9538126	9568049	heritability (responsiveness)	criterion I-c
Bysl	53414	17	-	47736279	47748441	heritability (responsiveness)	criterion I-c
Ccdc86	108673	19	-	11015970	11023756	heritability (responsiveness)	criterion I-c
Cd1d2	12480	3	+	86790507	86793454	heritability (responsiveness)	criterion I-c
Cd38	12494	5	+	44260065	44303613	heritability (responsiveness)	criterion I-c
Cox18	231430	5	-	90643751	90653021	heritability (responsiveness)	criterion I-c
Dusp6	67603	10	+	98725864	98730122	heritability (responsiveness)	criterion I-c
E2f5	13559	3	+	14578670	14606309	heritability (responsiveness)	criterion I-c
H2-Oa	15001	17	+	34229323	34232179	heritability (responsiveness)	criterion I-c
Ikbke	56489	1	-	133151178	133176140	heritability (responsiveness)	criterion I-c
Il12rb2	16162	6	-	67242011	67326131	heritability (responsiveness)	criterion I-c
Itgav	16410	2	+	83564553	83647073	heritability (responsiveness)	criterion I-c
Lamc1	226519	1	-	155066051	155179916	heritability (responsiveness)	criterion I-c
Lgals9	16859	11	-	78776480	78798426	heritability (responsiveness)	criterion I-c
Nr4a1	15370	15	+	101097276	101105223	heritability (responsiveness)	criterion I-c
Oasl2	23962	5	+	115346942	115362254	heritability (responsiveness)	criterion I-c
Palld	72333	8	-	63993819	64381487	heritability (responsiveness)	criterion I-c
Ppa1	67895	10	+	61111368	61136913	heritability (responsiveness)	criterion I-c
Pwp1	103136	10	+	85334575	85351847	heritability (responsiveness)	criterion I-c
Ripk2	192656	4	-	16050521	16090645	heritability (responsiveness)	criterion I-c
Rrs1	59014	1	+	9535488	9537535	heritability (responsiveness)	criterion I-c
Slc30a4	22785	2	-	122506974	122528399	heritability (responsiveness)	criterion I-c
Slc7a8	50934	14	-	55341051	55400723	heritability (responsiveness)	criterion I-c
Smox	228608	2	+	131317678	131350908	heritability (responsiveness)	criterion I-c
Sp100	20684	1	+	87546624	87606023	heritability (responsiveness)	criterion I-c
Stip1	20867	19	-	7095197	7114433	heritability (responsiveness)	criterion I-c
Stk40	74178	4	+	125781200	125818272	heritability (responsiveness)	criterion I-c
Tgif1	21815	17	-	71193546	71200550	heritability (responsiveness)	criterion I-c
Tjp1	21872	7	-	72441051	72516130	heritability (responsiveness)	criterion I-c
Tlr7	170743	20	-	163742862	163768460	heritability (responsiveness)	criterion I-c
Tnfrsf1b	21938	4	-	144802270	144836773	heritability (responsiveness)	criterion I-c
Tor3a	30935	1	-	158583747	158604470	heritability (responsiveness)	criterion I-c
Trem1	58217	17	+	48371921	48386091	heritability (responsiveness)	criterion I-c
Zbp1	58203	2	-	173039236	173044423	heritability (responsiveness)	criterion I-c
2310014L17	381845	7	+	13512764	13516421	heritability (responsiveness)	criterion I-c
1190002H23	66214	14	-	79688556	79701442	heritability (top in class)	criterion I-a
2010111I01	72061	13	+	63116293	63400964	heritability (top in class)	criterion I-a
2210012G0	66526	4	-	106806766	106850971	heritability (top in class)	criterion I-a

Supplementary Table 2. Nanostring nCounter design (cont)

Symbol	Entrez ID	Chr	Strand	Start	End	Selection criteria	Selection criterion
4631426J05	77590	7	-	139427937	139508838	heritability (top in class)	criterion I-a
5430435G2	226421	1	+	133585271	133610041	heritability (top in class)	criterion I-a
Acox1	11430	11	-	116033201	116060359	heritability (top in class)	criterion I-a
Acss1	68738	2	-	150443846	150493976	heritability (top in class)	criterion I-a
Adcy7	11513	8	+	90812964	90853861	heritability (top in class)	criterion I-a
Adssl1	11565	12	+	113858257	113879566	heritability (top in class)	criterion I-a
Afp	11576	5	+	90919739	90937933	heritability (top in class)	criterion I-a
Akr1b8	14187	6	+	34304163	34318454	heritability (top in class)	criterion I-a
Aldh1a2	19378	9	+	71063595	71144050	heritability (top in class)	criterion I-a
Ap1s2	108012	20	+	160347091	160367478	heritability (top in class)	criterion I-a
Apbb3	225372	18	-	36830812	36839020	heritability (top in class)	criterion I-a
Appl1	72993	14	-	27732173	27783737	heritability (top in class)	criterion I-a
Arhgdib	11857	6	-	136872229	136890238	heritability (top in class)	criterion I-a
Arid5a	214855	1	+	36364577	36380874	heritability (top in class)	criterion I-a
Atad3a	108888	4	-	155114749	155135207	heritability (top in class)	criterion I-a
Batf	53314	12	+	87027669	87050037	heritability (top in class)	criterion I-a
Baz2a	116848	10	+	127529838	127566359	heritability (top in class)	criterion I-a
BC013712	230787	4	-	132338271	132352279	heritability (top in class)	criterion I-a
Bcat2	12036	7	+	52825732	52845078	heritability (top in class)	criterion I-a
Bckdhb	12040	9	+	83842387	84017847	heritability (top in class)	criterion I-a
Bid	12122	6	-	120843136	120866838	heritability (top in class)	criterion I-a
Blvra	109778	2	+	126896392	126922820	heritability (top in class)	criterion I-a
Bub1	12235	2	-	127625935	127657595	heritability (top in class)	criterion I-a
Bxdc1	67239	10	-	39943051	39966785	heritability (top in class)	criterion I-a
C5ar1	12273	7	-	16832091	16844889	heritability (top in class)	criterion I-a
Calcrl	54598	2	-	84170790	84265423	heritability (top in class)	criterion I-a
Cald1	109624	6	+	34659443	34725469	heritability (top in class)	criterion I-a
Cap1	12331	4	-	122536470	122563124	heritability (top in class)	criterion I-a
Carhsp1	52502	16	-	8658679	8672246	heritability (top in class)	criterion I-a
Ccdc58	381045	16	+	36071745	36092204	heritability (top in class)	criterion I-a
Ccl7	20306	11	+	81859213	81861023	heritability (top in class)	criterion I-a
Ccnd1	12443	7	-	152115835	152125830	heritability (top in class)	criterion I-a
Cct6a	12466	5	+	130293260	130322231	heritability (top in class)	criterion I-a
Cd1d1	12479	3	-	86799757	86803262	heritability (top in class)	criterion I-a
Cd33	12489	7	-	50782825	50788541	heritability (top in class)	criterion I-a
Cd72	12517	4	-	43460595	43467498	heritability (top in class)	criterion I-a
Cd93	17064	2	-	148262386	148269271	heritability (top in class)	criterion I-a
Cd97	26364	8	-	86247149	86265210	heritability (top in class)	criterion I-a
Chi3l1	12654	1	+	136078980	136086606	heritability (top in class)	criterion I-a
Chi3l3	12655	3	-	105950472	105970482	heritability (top in class)	criterion I-a
Ciita	12265	16	+	10488371	10527657	heritability (top in class)	criterion I-a
Cited2	17684	10	+	17443033	17445479	heritability (top in class)	criterion I-a
Clcn7	26373	17	+	25270338	25299044	heritability (top in class)	criterion I-a
Clec5a	23845	6	-	40524896	40535804	heritability (top in class)	criterion I-a
Ctla2b	13025	13	-	60996724	60998748	heritability (top in class)	criterion I-a
Ctsk	13038	3	+	95303207	95313284	heritability (top in class)	criterion I-a
Cttn	13043	7	-	151621628	151656646	heritability (top in class)	criterion I-a

Supplementary Table 2. Nanostring nCounter design (cont)

Symbol	Entrez ID	Chr	Strand	Start	End	Selection criteria	Selection criterion
Cxcl9	17329	5	-	92750356	92757105	heritability (top in class)	criterion I-a
Dbi	13167	1	-	122009856	122017496	heritability (top in class)	criterion I-a
Ddx18	66942	1	-	123450413	123464557	heritability (top in class)	criterion I-a
Ddx39	68278	8	+	86239097	86247247	heritability (top in class)	criterion I-a
Dgka	13139	10	-	128157191	128181112	heritability (top in class)	criterion I-a
Dhrs3	20148	4	+	144483039	144517548	heritability (top in class)	criterion I-a
Dhx58	80861	11	-	100556197	100565585	heritability (top in class)	criterion I-a
Dnajb4	67035	3	-	151846918	151856807	heritability (top in class)	criterion I-a
Dtwd1	69185	2	+	125977876	125991012	heritability (top in class)	criterion I-a
Dusp16	70686	6	-	134665490	134742646	heritability (top in class)	criterion I-a
Dusp3	72349	11	-	101835472	101846084	heritability (top in class)	criterion I-a
Egr2	13654	10	+	67000616	67004936	heritability (top in class)	criterion I-a
Ehd1	13660	19	+	6276725	6300096	heritability (top in class)	criterion I-a
Emilin1	100952	5	+	31216158	31223646	heritability (top in class)	criterion I-a
Enah	13800	1	-	183834575	183950111	heritability (top in class)	criterion I-a
Eps8	13860	6	-	137425765	137597641	heritability (top in class)	criterion I-a
Ereg	13874	5	+	91503642	91522675	heritability (top in class)	criterion I-a
Ets2	23872	16	+	95924013	95942654	heritability (top in class)	criterion I-a
Etv3	27049	3	+	87329499	87344078	heritability (top in class)	criterion I-a
Fabp4	11770	3	-	10204342	10208576	heritability (top in class)	criterion I-a
Fam105a	223433	15	-	27586024	27611253	heritability (top in class)	criterion I-a
Flnb	286940	14	+	8650470	8784101	heritability (top in class)	criterion I-a
Ftsj3	56095	11	-	106110457	106117116	heritability (top in class)	criterion I-a
Gdf15	23886	8	-	73153292	73155534	heritability (top in class)	criterion I-a
Gpnmb	93695	6	+	48986516	49008181	heritability (top in class)	criterion I-a
Gpr109a	80885	5	-	124313580	124315518	heritability (top in class)	criterion I-a
Gpr137b-ps	664862	13	-	12706332	12742662	heritability (top in class)	criterion I-a
Gramd4	223752	15	+	85888136	85968064	heritability (top in class)	criterion I-a
Gtf2e2	68153	8	+	34842538	34887645	heritability (top in class)	criterion I-a
Gusb	110006	5	-	130464890	130478698	heritability (top in class)	criterion I-a
Gyk	14933	20	-	82947275	83022158	heritability (top in class)	criterion I-a
Hebp1	15199	6	-	135087536	135118233	heritability (top in class)	criterion I-a
Hfe	15216	13	-	23795709	23802680	heritability (top in class)	criterion I-a
Hice1	76478	8	-	73775023	73796489	heritability (top in class)	criterion I-a
Hmg20a	66867	9	+	56266652	56344743	heritability (top in class)	criterion I-a
Hmgn3	94353	9	-	83003550	83040214	heritability (top in class)	criterion I-a
Ifi44	99899	3	-	151393886	151412923	heritability (top in class)	criterion I-a
Ifna4	15967	4	+	88487719	88488363	heritability (top in class)	criterion I-a
Ifnb1	15977	4	-	88167928	88168698	heritability (top in class)	criterion I-a
Il18	16173	9	+	50373472	50389942	heritability (top in class)	criterion I-a
Il1f6	54448	2	+	24070936	24081221	heritability (top in class)	criterion I-a
Il33	77125	19	+	29999603	30035205	heritability (top in class)	criterion I-a
Il6st	16195	13	+	113254277	113297068	heritability (top in class)	criterion I-a
Il7r	16197	15	-	9435913	9459631	heritability (top in class)	criterion I-a
Inpp5d	16331	1	+	89516886	89617083	heritability (top in class)	criterion I-a
Ints4	101861	7	+	104629465	104689907	heritability (top in class)	criterion I-a
Ipo4	75751	14	-	56244465	56254515	heritability (top in class)	criterion I-a

Supplementary Table 2. Nanostring nCounter design (cont)

Symbol	Entrez ID	Chr	Strand	Start	End	Selection criteria	Selection criterion
Itpr1	16438	6	+	108163089	108501104	heritability (top in class)	criterion I-a
Itpr2	16439	6	-	146060001	146450434	heritability (top in class)	criterion I-a
Jdp2	81703	12	+	86940365	86980828	heritability (top in class)	criterion I-a
Kcnk13	217826	12	+	101202708	101300891	heritability (top in class)	criterion I-a
Kctd14	233529	7	+	104601713	104608066	heritability (top in class)	criterion I-a
Klf7	93691	1	-	64076021	64168856	heritability (top in class)	criterion I-a
Klk1b11	16613	7	+	51251248	51255245	heritability (top in class)	criterion I-a
Klrk1	27007	6	-	129560338	129573859	heritability (top in class)	criterion I-a
Kpnb1	16211	11	-	97021023	97049206	heritability (top in class)	criterion I-a
Lad1	16763	1	+	137715174	137729918	heritability (top in class)	criterion I-a
Lfng	16848	5	+	141083294	141091499	heritability (top in class)	criterion I-a
Lhx2	16870	2	+	38206827	38225248	heritability (top in class)	criterion I-a
Lpgat1	226856	1	+	193542273	193608132	heritability (top in class)	criterion I-a
Lpxn	107321	19	+	12873098	12908298	heritability (top in class)	criterion I-a
Lrrc8c	100604	5	+	105948489	106037973	heritability (top in class)	criterion I-a
Lrrk2	66725	15	+	91503654	91646555	heritability (top in class)	criterion I-a
Lsm10	116748	4	+	125773896	125775827	heritability (top in class)	criterion I-a
Lsr	54135	7	-	31742790	31758488	heritability (top in class)	criterion I-a
Lta	16992	17	-	35340110	35342296	heritability (top in class)	criterion I-a
Ly6i	57248	15	-	74810241	74813860	heritability (top in class)	criterion I-a
Ly96	17087	1	+	16678536	16699686	heritability (top in class)	criterion I-a
Lyl1	17095	8	+	87225355	87228615	heritability (top in class)	criterion I-a
Magohb	66441	6	-	131234406	131243262	heritability (top in class)	criterion I-a
Map4k3	225028	17	-	80979851	81127433	heritability (top in class)	criterion I-a
Med21	108098	6	+	146591100	146599122	heritability (top in class)	criterion I-a
Mfhas1	52065	8	+	36650851	36742503	heritability (top in class)	criterion I-a
Mgl1	17312	11	+	69980275	69984336	heritability (top in class)	criterion I-a
Mgst2	211666	3	+	51465114	51486597	heritability (top in class)	criterion I-a
Mina	67014	16	+	59471600	59492275	heritability (top in class)	criterion I-a
Mmp9	17395	2	+	164773750	164781346	heritability (top in class)	criterion I-a
Mpp6	56524	6	+	50060239	50148597	heritability (top in class)	criterion I-a
Mrpl34	94065	8	+	73988824	73989652	heritability (top in class)	criterion I-a
Mt2	17750	8	+	96696517	96697467	heritability (top in class)	criterion I-a
Mtap	66902	4	+	88783273	88826994	heritability (top in class)	criterion I-a
Myo5a	17918	9	+	74919012	75071494	heritability (top in class)	criterion I-a
Myst3	244349	8	+	23970010	24053734	heritability (top in class)	criterion I-a
Nfe2	18022	15	-	103078648	103085847	heritability (top in class)	criterion I-a
Ngrn	83485	7	+	87406100	87410264	heritability (top in class)	criterion I-a
Nmi	64685	2	-	51804018	51828728	heritability (top in class)	criterion I-a
Nolc1	70769	19	+	46150352	46160020	heritability (top in class)	criterion I-a
Nr2c2ap	75692	8	+	72655231	72657647	heritability (top in class)	criterion I-a
Nts	67405	10	-	101944389	101953052	heritability (top in class)	criterion I-a
Oas1a	246730	5	-	121346267	121357534	heritability (top in class)	criterion I-a
Oas2	246728	5	-	121180342	121199857	heritability (top in class)	criterion I-a
Paip1	218693	13	+	120217406	120249127	heritability (top in class)	criterion I-a
Pak1	18479	7	+	104991448	105060891	heritability (top in class)	criterion I-a
Pde1b	18574	15	+	103333728	103360483	heritability (top in class)	criterion I-a

Supplementary Table 2. Nanostring nCounter design (cont)

Symbol	Entrez ID	Chr	Strand	Start	End	Selection criteria	Selection criterion
Pde8a	18584	7	+	88358689	88478508	heritability (top in class)	criterion I-a
Pdk1	228026	2	+	71711328	71741914	heritability (top in class)	criterion I-a
Pi4k2a	84095	19	+	42164924	42196708	heritability (top in class)	criterion I-a
Piga	18700	20	+	160857718	160871847	heritability (top in class)	criterion I-a
Pigx	72084	16	-	32084501	32099813	heritability (top in class)	criterion I-a
Pik3ap1	83490	19	-	41348707	41459560	heritability (top in class)	criterion I-a
Pla2g4a	18783	1	-	151676751	151808414	heritability (top in class)	criterion I-a
Plod2	26432	9	+	92437060	92503258	heritability (top in class)	criterion I-a
Plscr1	22038	9	+	92145031	92167399	heritability (top in class)	criterion I-a
Pnpla7	241274	2	+	24831552	24909591	heritability (top in class)	criterion I-a
Pon3	269823	6	-	5170851	5206233	heritability (top in class)	criterion I-a
Ppfibp2	19024	7	+	114738564	114888408	heritability (top in class)	criterion I-a
Ppt2	54397	17	-	34753606	34764042	heritability (top in class)	criterion I-a
Prmt3	71974	7	+	57033727	57113635	heritability (top in class)	criterion I-a
Psen2	19165	1	-	182157134	182186431	heritability (top in class)	criterion I-a
Psrc1	56742	3	+	108186760	108191082	heritability (top in class)	criterion I-a
Ptger2	19217	14	+	45607785	45623495	heritability (top in class)	criterion I-a
Ptges	64292	2	-	30744991	30758817	heritability (top in class)	criterion I-a
Ptgir	19222	7	+	17491838	17496254	heritability (top in class)	criterion I-a
Ptgs2	19225	1	+	151947253	151955142	heritability (top in class)	criterion I-a
Ptpn22	19260	3	+	103664214	103716170	heritability (top in class)	criterion I-a
Pvrl2	19294	7	-	20301992	20334922	heritability (top in class)	criterion I-a
Qsox1	104009	1	-	157625284	157660029	heritability (top in class)	criterion I-a
Rbm43	71684	2	-	51779971	51790529	heritability (top in class)	criterion I-a
Rbpms	19663	8	-	34893115	35040313	heritability (top in class)	criterion I-a
Rdh10	98711	1	+	16095962	16122631	heritability (top in class)	criterion I-a
Rere	68703	4	+	149656024	149996075	heritability (top in class)	criterion I-a
Retnla	57262	16	+	48842664	48844574	heritability (top in class)	criterion I-a
Ripk3	56532	14	-	56403832	56407694	heritability (top in class)	criterion I-a
Rnase4	58809	14	+	51710751	51725826	heritability (top in class)	criterion I-a
Rnd3	74194	2	-	50985958	51004631	heritability (top in class)	criterion I-a
Rnh1	107702	7	-	148346225	148354835	heritability (top in class)	criterion I-a
Rps6ka1	20111	4	-	133403205	133443714	heritability (top in class)	criterion I-a
Runx1	12394	16	-	92601710	92826311	heritability (top in class)	criterion I-a
Rusc2	100213	4	+	43394853	43439958	heritability (top in class)	criterion I-a
Ryr1	20190	7	-	29788358	29910170	heritability (top in class)	criterion I-a
Sc5d	235293	9	-	42062259	42072383	heritability (top in class)	criterion I-a
Sdc1	20969	12	+	8778201	8800493	heritability (top in class)	criterion I-a
Sdcbp2	228765	2	+	151398367	151415735	heritability (top in class)	criterion I-a
Sfmbt2	353282	2	+	10294208	10516787	heritability (top in class)	criterion I-a
Six1	20471	12	-	74142813	74147699	heritability (top in class)	criterion I-a
Slamf7	75345	1	-	173562533	173583168	heritability (top in class)	criterion I-a
Slc15a2	57738	16	-	36750249	36785048	heritability (top in class)	criterion I-a
Slc24a6	170756	5	+	120961200	120984033	heritability (top in class)	criterion I-a
Slc25a37	67712	14	-	69859907	69903160	heritability (top in class)	criterion I-a
Slc29a3	71279	10	-	60174819	60215530	heritability (top in class)	criterion I-a
Slc2a1	20525	4	+	118781349	118809934	heritability (top in class)	criterion I-a

Supplementary Table 2. Nanostring nCounter design (cont)

Symbol	Entrez ID	Chr	Strand	Start	End	Selection criteria	Selection criterion
Slc30a1	22782	1	+	193730659	193737126	heritability (top in class)	criterion I-a
Slc33a1	11416	3	-	63746257	63768655	heritability (top in class)	criterion I-a
Slc35a3	229782	3	-	116373715	116415198	heritability (top in class)	criterion I-a
Slc41a2	338365	10	-	82693883	82800562	heritability (top in class)	criterion I-a
Slc6a4	15567	11	+	76812098	76845845	heritability (top in class)	criterion I-a
Slfn1	20555	11	+	82930346	82936161	heritability (top in class)	criterion I-a
Slfn8	276950	11	-	82815659	82834312	heritability (top in class)	criterion I-a
Smc5	226026	19	-	23283221	23348367	heritability (top in class)	criterion I-a
Smpdl3b	100340	4	-	132288880	132313086	heritability (top in class)	criterion I-a
Snapc3	77634	4	+	83063647	83099244	heritability (top in class)	criterion I-a
Spata13	219140	14	+	61252838	61383386	heritability (top in class)	criterion I-a
Spint1	20732	2	+	119063095	119075249	heritability (top in class)	criterion I-a
Spred1	114715	2	+	116947185	117005072	heritability (top in class)	criterion I-a
Spsb4	211949	9	-	96843900	96918774	heritability (top in class)	criterion I-a
St3gal3	20441	4	-	117604757	117807495	heritability (top in class)	criterion I-a
St3gal5	20454	6	+	72047606	72104564	heritability (top in class)	criterion I-a
Stk25	59041	1	-	95517327	95532304	heritability (top in class)	criterion I-a
Syngr1	20972	15	+	79921763	79943870	heritability (top in class)	criterion I-a
Tcf19	106795	17	-	35649679	35653769	heritability (top in class)	criterion I-a
Tef	21685	15	+	81641843	81657291	heritability (top in class)	criterion I-a
Tgfb1	21803	7	+	26472020	26490015	heritability (top in class)	criterion I-a
Thbs4	21828	13	-	93521541	93564773	heritability (top in class)	criterion I-a
Tlcd2	380712	11	+	75281580	75284146	heritability (top in class)	criterion I-a
Tlr3	142980	8	-	46481018	46495893	heritability (top in class)	criterion I-a
Tnip1	57783	11	-	54724288	54776440	heritability (top in class)	criterion I-a
Trf	22041	9	-	103111205	103132616	heritability (top in class)	criterion I-a
Trim12	76681	7	-	111448410	111464009	heritability (top in class)	criterion I-a
Trim25	217069	11	+	88860716	88881607	heritability (top in class)	criterion I-a
Trim34	94094	7	+	111392970	111410750	heritability (top in class)	criterion I-a
Tsc22d3	14605	20	-	137074067	137135061	heritability (top in class)	criterion I-a
Tspan14	52588	14	-	41719732	41780096	heritability (top in class)	criterion I-a
Tuba4a	22145	1	-	75211548	75215828	heritability (top in class)	criterion I-a
Uap1l1	227620	2	-	25217011	25221146	heritability (top in class)	criterion I-a
Ube2m	22192	7	-	13620587	13623327	heritability (top in class)	criterion I-a
Uchl1	22223	5	+	67067359	67078473	heritability (top in class)	criterion I-a
Ugcg	22234	4	+	59202421	59235705	heritability (top in class)	criterion I-a
Upf3b	68134	20	-	34631828	34650317	heritability (top in class)	criterion I-a
Vcan	13003	13	-	89794914	89882117	heritability (top in class)	criterion I-a
Vwf	22371	6	+	125502980	125636695	heritability (top in class)	criterion I-a
Wdfy1	69368	1	-	79698836	79758344	heritability (top in class)	criterion I-a
Ypel3	66090	7	+	133920488	133924028	heritability (top in class)	criterion I-a
7530420F21	320019	1	-	151923791	151946896	Biological relevance	criterion II
Glb1	12091	9	+	114310236	114383495	Biological relevance	criterion II
Ahr	11622	12	-	36182650	36219661	Biological relevance	criterion II
Bcl3	12051	7	-	20393810	20408104	Biological relevance	criterion II
Btg2	12227	1	-	135971441	135975732	Biological relevance	criterion II
Cbx4	12418	11	-	118938884	118947551	Biological relevance	criterion II
Cebpd	12609	16	+	15887378	15889638	Biological relevance	criterion II
Crkl	12929	16	+	17452079	17486348	Biological relevance	criterion II

Supplementary Table 2. Nanostring nCounter design (cont)

Symbol	Entrez ID	Chr	Strand	Start	End	Selection criteria	Selection criterion
Cd70	21948	17	-	57285419	57289200	Biological relevance	criterion II
Cd80	12519	16	+	38459012	38487014	Biological relevance	criterion II
Csf1	12977	3	-	107543965	107563387	Biological relevance	criterion II
Cxcl1	14825	5	+	91320270	91322139	Biological relevance	criterion II
Daxx	13163	17	+	34046442	34052534	Biological relevance	criterion II
Dnmt3a	13435	12	+	3806979	3914443	Biological relevance	criterion II
Egr1	13653	18	+	35020860	35024610	Biological relevance	criterion II
Etv6	14011	6	+	133985724	134220165	Biological relevance	criterion II
Fos	14281	12	+	86814850	86818219	Biological relevance	criterion II
Hhex	15242	19	+	37509330	37515221	Biological relevance	criterion II
Hmga1	15361	17	+	27693518	27700617	Biological relevance	criterion II
Ifit2	15958	19	+	34625183	34651024	Biological relevance	criterion II
Ifit3	15959	19	+	34658018	34663472	Biological relevance	criterion II
Ifna2	15965	4	-	88329110	88329683	Biological relevance	criterion II
Ifnar2	15976	16	+	91373027	91394288	Biological relevance	criterion II
Ifngr2	15980	16	+	91547338	91564252	Biological relevance	criterion II
Igf1	16000	10	+	87323855	87399792	Biological relevance	criterion II
Iigp1	60440	18	+	60535682	60552281	Biological relevance	criterion II
Iigp2	54396	11	+	58028478	58036282	Biological relevance	criterion II
Il12a	16159	3	+	68495345	68502469	Biological relevance	criterion II
Il15ra	16169	2	+	11627474	11654876	Biological relevance	criterion II
Il1rl1	17082	1	+	40497472	40522259	Biological relevance	criterion II
Il23a	83430	10	-	127733195	127735140	Biological relevance	criterion II
Irf2	16363	8	+	47825098	47932812	Biological relevance	criterion II
Irf4	16364	13	+	30841126	30858796	Biological relevance	criterion II
Irf7	54123	7	-	148449087	148452300	Biological relevance	criterion II
Irf8	15900	8	+	123260275	123280592	Biological relevance	criterion II
Isg20	57444	7	+	86059120	86065282	Biological relevance	criterion II
Jhdm1d	338523	6	-	39086618	39156772	Biological relevance	criterion II
Jun	16476	4	-	94715726	94718913	Biological relevance	criterion II
Mbnl1	56758	3	+	60305173	60433670	Biological relevance	criterion II
Myd116	17872	7	-	52778289	52781638	Biological relevance	criterion II
Myd88	17874	9	-	119245105	119249158	Biological relevance	criterion II
Nfkb1	18033	3	-	135247618	135354511	Biological relevance	criterion II
Nfkb2	18034	19	+	46380107	46386580	Biological relevance	criterion II
Nfkbiz	80859	16	-	55811490	55838754	Biological relevance	criterion II
Rbl1	19650	2	-	157000732	157030270	Biological relevance	criterion II
Rel	19696	11	-	23641728	23670970	Biological relevance	criterion II
Relb	19698	7	-	20191570	20214787	Biological relevance	criterion II
Stat2	20847	10	+	127707631	127729905	Biological relevance	criterion II
Stat4	20849	1	+	52065087	52164028	Biological relevance	criterion II
Timeless	21853	10	+	127669118	127689988	Biological relevance	criterion II
Tlr2	24088	3	-	83640193	83645530	Biological relevance	criterion II
Tlr4	21898	4	+	66488844	66503830	Biological relevance	criterion II
Tnfsf8	21949	4	-	63493857	63522318	Biological relevance	criterion II
Tsc22d1	21807	14	+	76904371	76907568	Biological relevance	criterion II
Trim21	20821	7	-	109706435	109713983	Biological relevance	criterion II
Usp9x	22284	20	+	12648623	12750453	Biological relevance	criterion II
Zc3h12a	230738	4	-	124795657	124805125	Biological relevance	criterion II

Supplementary Table 2. Nanostring nCounter design (cont)

Symbol	Entrez ID	Chr	Strand	Start	End	Selection criteria	Selection criterion
Tnfsf9	21950	17	+	57244807	57247180	Biological relevance	criterion II
U90926	57425	5	-	92638960	92644434	Biological relevance	criterion II
Zfp36	22695	7	-	29161802	29164247	Biological relevance	criterion II
Zfp36l1	12192	12	-	81208746	81214000	Biological relevance	criterion II
Tmcc3	319880	10	+	93977601	94053699	responsiveness	criterion III
Ms4a7	109225	19	-	11395902	11410606	responsiveness	criterion III
Znhit3	448850	11	-	84724456	84729858	responsiveness	criterion III
Adcy6	11512	15	-	98420420	98438064	responsiveness	criterion III
AI451617	209387	7	-	111618530	111656363	responsiveness	criterion III
Areg	11839	5	+	91568641	91577458	responsiveness	criterion III
D6Mm5e	110958	6	+	82896915	82980303	responsiveness	criterion III
Dusp1	19252	17	-	26642536	26645417	responsiveness	criterion III
Gadd45a	13197	6	-	66985089	66987401	responsiveness	criterion III
Hmgcr	15357	13	-	97418918	97440891	responsiveness	criterion III
Lox	16948	18	*	52679571	52689357	responsiveness	criterion III
Net1	56349	13	-	3881808	3892824	responsiveness	criterion III
Ngp	18054	9	+	110322311	110325516	responsiveness	criterion III
Pfkfb3	170768	2	-	11393061	11423694	responsiveness	criterion III
Rrp15	67223	1	-	188544857	188573237	responsiveness	criterion III
S100a9	20202	3	-	90496554	90499613	responsiveness	criterion III
Slamf7	18173	1	+	74421776	74432625	responsiveness	criterion III
Spry1	24063	2	+	116947110	117008015	responsiveness	criterion III
Zbtb46	72147	2	-	181122467	181194131	responsiveness	criterion III
Shfm1	20422	6	-	:6508283	6528652	responsiveness	criterion III
Arcn1	213827	9	-	44550227	44575891	negative control	criterion IV
Arfgap1	228998	2	+	180701930	180717231	negative control	criterion IV
Bat3	224727	17	+	35272187	35284181	negative control	criterion IV
Capg	12332	1	+	72499442	72512974	negative control	criterion IV
Eif4h	22384	5	-	135095746	135115198	negative control	criterion IV
Hnrnpa2b1	53379	6	-	51410433	51419893	negative control	criterion IV
Ireb2	64602	9	+	54711561	54760341	negative control	criterion IV
Mea1	17256	17	+	46818085	46820054	negative control	criterion IV
Metap2	56307	10	-	93321234	93353947	negative control	criterion IV
Mkln1	27418	6	+	31348827	31459477	negative control	criterion IV
Ppig	228005	2	+	69561144	69592116	negative control	criterion IV
Ppp1r7	66385	1	+	95240221	95264195	negative control	criterion IV
Psmd4	19185	3	-	94836626	94846467	negative control	criterion IV
Saps3	52036	19	-	3454927	3575749	negative control	criterion IV
Sf3b4	107701	3	+	95976472	95981487	negative control	criterion IV
Sla	20491	15	-	66612438	66663391	negative control	criterion IV
Tbca	21371	13	+	95558897	95612854	negative control	criterion IV
Tomm7	66169	5	-	23344761	23349963	negative control	criterion IV
Trappc10	216131	10	-	77649470	77707387	negative control	criterion IV
Ube2i	22196	17	-	25397456	25410336	negative control	criterion IV
Ubl5	66177	9	+	20447322	20451584	negative control	criterion IV

Supplementary Table 2 - Experimental design - nCounter genes. Shown are gene symbols (column 1), entrez ID (column 2), and their genomic position (columns 3-6).
Columns 7-8 provide information about the selection criteria for these genes.

Selection criterion	Selection criterion name	Number of genes	Fraction of genes	Number of *cis* and *trans* genes
I	**Heritability** (InSignature)	322	0.76	264 (*trans*), 58 (*cis*)
I-a	Top in class	232	0.55	184 (*trans*), 48(*cis*)
I-b	Biological relevance	20	0.05	18 (*trans*), 2 (*cis*)
I-c	Responsiveness	35	0.08	31 (*trans*), 4(*cis*)
I-d	Random selection	35	0.08	31 (*trans*), 4(*cis*)
II	**Biological relevance**	61	0.14	
III	**Responsiveness**	20	0.05	
IV	**Negative control**	21	0.05	

Supplementary Table 3. **The variation signature genes.** Shown are the four main selection criteria I-IV (column 1). Genes selected based on a genetic criterion (I, using InSignature) are subdivided based on the criteria that was applied to choose genes within the InSignature classes (Ia-Id; column 1). For each criterion, shown are its name (column 2), the number of genes in the variation signature that were selected based on this criterion (column 3) and their fraction of the signature (column 4). For genes selected by criterion I, InSignature also predicts *cis*- and *trans*-association, as detailed in column 5.

Strain Name	# individuals	Litter	comment
BXD1/TyJ	2	2 different litters	
BXD2/TyJ	2	2 different litters	
BXD5/TyJ	2	2 different litters	
BXD6/TyJ	2	2 different litters	
BXD8/TyJ	2	2 different litters	1 sample was destroyed
BXD9/TyJ	2	2 different litters	
BXD11/TyJ	2	2 different litters	
BXD12/TyJ	2	2 different litters	
BXD13/TyJ	2	2 different litters	
BXD14/TyJ	2	2 different litters	
BXD15/TyJ	2	2 different litters	
BXD16/TyJ	2	2 different litters	
BXD18/TyJ	2	2 different litters	
BXD19/TyJ	2	2 different litters	
BXD20/TyJ	2	2 different litters	
BXD22/TyJ	2	2 different litters	
BXD27/TyJ	2	2 different litters	
BXD28/TyJ	2	2 different litters	
BXD29/TyJ	2	2 different litters	
BXD29-Tlr4	2	2 different litters	
BXD32/TyJ	2	2 different litters	
BXD34/TyJ	2	2 different litters	
BXD39/TyJ	2	2 different litters	
BXD40/TyJ	2	2 different litters	
BXD42/TyJ	2	2 different litters	
BXD43/RwwJ	2	same litter	
BXD44/RwwJ	2	same litter	
BXD48/RwwJ	2	same litter	
BXD50/RwwJ	2	same litter	
BXD51/RwwJ	2	same litter	
BXD55/RwwJ	2	2 different litters	
BXD60/RwwJ	2	same litter	
BXD64/RwwJ	2	same litter	
BXD68/RwwJ	2	2 different litters	
BXD69/RwwJ	2	2 different litters	
BXD70/RwwJ	1	2 different litters	1 sample was destroyed
BXD73/RwwJ	2	2 different litters	
BXD75/RwwJ	2	same litter	
BXD79/RwwJ	2	same litter	
BXD83/RwwJ	2	same litter	
BXD86/RwwJ	2	same litter	
BXD89/RwwJ	2	same litter	
BXD96/RwwJ	2	2 different litters	
BXD100/RwwJ	2	same litter	
B6	5	different litters	
D2	4	different litters	
total	96 mice		

Supplementary Table 4. Mouse strains for nCounter assays. Shown are the mouse strains (column 1), number of individuals from each strain (column 2) and their litter (column 3). Column 4 provides additional information when available.

Supplementary Table 5

module identifier	module trait		module reQTL		optimal variant	
	gene symbol	stimulation	chromosome	position (Mb)	chromosome	position
#1	Mtap	LPS	19	39682640	19	39682640
#1	Kcnk13	poly IC	19	39682640	19	39682640
#1	Isg20	PAM	19	39682640	19	39682640
#1	Oas1a	PAM	19	39682640	19	39682640
#1	Oasl2	PAM	19	39682640	19	39682640
#1	Iigp2	PAM	19	39682640	19	38242986
#1	Slfn8	PAM	19	39682640	19	39682640
#1	Ifi44	PAM	19	39682640	19	39682640
#1	Ddx60	PAM	19	39682640	19	39682640
#1	Ifit2	PAM	19	39682640	19	39682640
#1	Ifit3	PAM	19	39682640	19	39682640
#1	Irf7	PAM	19	39682640	19	39682640
#1	Stat2	PAM	19	39682640	19	39682640
#1	Dhx58	PAM	19	39682640	19	39682640
#2	Lamc1	poly IC	1	160302634	12	26992470
#2	Iigp2	poly IC	1	160302634	1	159872935
#2	Slfn8	poly IC	1	160302634	1	156052564
#2	Ifi44	poly IC	1	160302634	1	160302634
#2	Ddx60	poly IC	1	160302634	1	160302634
#2	Ifit2	poly IC	1	160302634	1	159872935
#2	Ifit3	poly IC	1	160302634	1	159872935
#2	Irf7	poly IC	1	160302634	1	159872935
#2	Stat2	poly IC	1	160302634	1	159872935
#2	Dhx58	poly IC	1	160302634	1	159872935
#2	Cox18	poly IC	1	160302634	1	159872935
#2	Nmi	poly IC	1	160302634	1	148717645
#2	Sp100	poly IC	1	160302634	1	160302634
#2	Daxx	poly IC	1	160302634	1	155319104
#2	Arid5a	poly IC	1	160302634	1	156052564
#2	Iigp1	poly IC	1	160302634	1	159872935
#2	Irf2	poly IC	1	160302634	1	155319104
#2	Trim21	poly IC	1	160302634	1	159872935
#2	Ints4	poly IC	1	160302634	1	160302634
#2	Csf1	poly IC	1	160302634	1	160302634
#2	Timeless	poly IC	1	160302634	1	159872935
#2	Rbm43	poly IC	1	160302634	1	159872935
#2	Tgif1	poly IC	1	160302634	1	155319104
#2	Myd88	poly IC	1	160302634	1	155319104
#2	Tlr2	poly IC	1	160302634	1	148385403
#2	Smpdl3b	poly IC	1	160302634	1	148385403
#2	Vwf	poly IC	1	160302634	1	148385403
#2	Tnf	poly IC	1	160302634	1	148717645
#2	Clec5a	poly IC	1	160302634	1	148385403
#2	Hdac5	poly IC	1	160302634	1	148385403
#2	Rusc2	poly IC	1	160302634	1	148385403
#2	Cd70	PAM	1	160302634	1	159872935
#2	Lox	LPS	1	160302634	1	156456243
#2	Cxcl1	PAM	1	160302634	1	160302634
#2	Bcl3	PAM	1	160302634	1	155319104
#2	Fam105a	PAM	1	160302634	1	160302634
#2	Nfkbiz	PAM	1	160302634	1	160302634

Supplementary Table 5 – cont.

module identifier	module trait		module reQTL		optimal variant	
	gene symbol	stimulation	chromosome	position (Mb)	chromosome	position
#3	Apbb3	poly IC	18	9902165	6	97878025
#3	Socs2	poly IC	18	9902165	18	9489145
#3	Acox1	poly IC	18	9902165	18	9902165
#3	Med21	poly IC	18	9902165	18	9902165
#3	Cd1d1	poly IC	18	9902165	18	9902165
#3	Ypel3	poly IC	18	9902165	18	9902165
#3	Ccl7	poly IC	18	9902165	18	9902165
#3	Ifna2	poly IC	18	9902165	18	9902165
#3	BC013712	poly IC	18	9902165	18	9902165
#3	Ifna4	poly IC	18	9902165	8	28002388
#3	Cxcl9	poly IC	18	9902165	18	9902165
#3	Hmgn3	poly IC	18	9902165	18	9902165
#3	Idi1	poly IC	18	9902165	18	11633352
#3	Plscr1	poly IC	18	9902165	18	11633352
#3	Ifnb1	poly IC	18	9902165	18	9902165
#3	Pmvk	poly IC	18	9902165	15	87908143
#3	Il12rb2	poly IC	18	9902165	18	9902165
#3	Ptger4	poly IC	18	9902165	10	75305586
#3	Dusp16	poly IC	18	9902165	18	9902165
#3	Clcn7	poly IC	18	9902165	18	9902165
#3	Kctd14	poly IC	18	9902165	18	9902165
#3	Gpr109a	poly IC	18	9902165	18	9902165
#3	Cd1d2	poly IC, LPS	18	9902165	18	9902165
#3	7530420F21Rik	LPS	18	9902165	18	14271308
#3	Fam105a	poly IC	18	9902165	18	5041117
#3	Nfkbiz	poly IC	18	9902165	18	9902165
#4	Tlr7	poly IC	6	99053858	6	99053858
#4	Trim25	poly IC	6	99053858	6	99053858
#4	Atad3a	poly IC	6	99053858	6	99053858
#4	Ddx18	poly IC,PAM	6	99053858	6	99053858
#4	Ftsj3	poly IC	6	99053858	6	99053858
#4	Bysl	poly IC	6	99053858	6	99053858
#4	Irf8	poly IC	6	99053858	6	99053858
#4	Prmt3	poly IC	6	99053858	6	99053858
#4	Pdk1	poly IC	6	99053858	6	99053858
#4	Ikbke	poly IC,PAM	6	99053858	6	99053858
#4	Slc6a4	poly IC	6	99053858	6	99053858
#4	Exosc5	poly IC	6	99053858	6	99053858
#4	Egln3	poly IC	6	99053858	6	99053858
#4	Zmat3	poly IC	6	99053858	6	99053858

Supplementary Table 5– cont.

module identifier	module trait		module reQTL		optimal variant*	
	gene symbol	stimulation	chromosome	position (Mb)	chromosome	position
#5	Nlrp3	PAM, LPS	9	122834340	9	122834340
#5	Ehd1	PAM, LPS	9	122834340	9	122834340
#5	Cxcr4	PAM	9	122834340	9	122834340
#5	Gadd45a	PAM	9	122834340	9	122834340
#5	Spred1	LPS	9	122834340	9	122834340
#5	Dhrs3	LPS	9	122834340	9	122834340
#5	Six1	PAM	9	122834340	9	122834340
#5	Eps8	PAM	9	122834340	9	122834340
#5	Rasgrp1	PAM	9	122834340	9	122834340
#5	Nfkb2	LPS	9	122834340	9	122834340
#5	Tsc22d3	PAM, LPS	9	122834340	9	122834340
#5	Lfng	PAM, LPS	9	122834340	9	122834340
#5	Tef	PAM	9	122834340	9	122834340
#5	Socs6	PAM	9	122834340	9	122834340
#5	E2f5	LPS	9	122834340	9	122834340
#5	Gtf2e2	LPS	9	122834340	9	122834340
#5	Fam107b	LPS	9	122834340	9	122834340
#5	Net1	LPS	9	122834340	9	122834340
#5	Irf4	poly IC	9	122834340	9	122834340
#5	Ube2m	poly IC	9	122834340	9	122834340
#5	Ets2	LPS	9	122834340	9	122834340
#5	Fam105a	LPS	9	122834340	9	122834340
#6	Areg	PAM, LPS	18	86749671	18	86553541
#6	Ereg	PAM, LPS	18	86749671	18	86553541
#6	Ripk3	PAM	18	86749671	18	86553541
#6	Ptgs1	PAM	18	86749671	18	86553541
#6	Nfe2	LPS	18	86749671	18	86749671
#6	Batf	LPS	18	86749671	18	86749671
#6	Rnh1	PAM, LPS	18	86749671	18	86553541
#6	Ugcg	LPS	18	86749671	18	86553541
#6	Trem1	PAM	18	86749671	18	86553541
#6	Spry1	PAM	18	86749671	3	37339254
#6	C5ar1	LPS	18	86749671	18	86553541
#6	Il15ra	LPS	18	86749671	18	86553541
#6	Appl1	poly IC	18	86749671	18	86749671
#6	Lamc1	LPS	18	86749671	18	86553541
#6	Ets2	PAM	18	86749671	18	86553541

Supplementary Table 5. **Co-variation modules.** Shown are module identifier (column 1), module's traits – gene (column 2) and condition (column 3) – the genomic position of the reQTL (columns 4 and 5) and the best-scoring marker for each trait independently (columns 6 and 7).

Module ID	Myeloid cells Gerrits *et al.* 2009	Progenitor cells Gerrits *et al.* 2009	DCs This study
#1	Pdlim1	Pdlim1	Myof*
#2	Tor1aip2, Lamc1	Tor1aip2, Lamc1,	Glul*, Pla2g4a
#3			
#4			Frmd4b*
#5	Sec22c, Acaa1, Eif1b	Acaa1, Eif1b	
#6			

Supplementary Table 6. *Cis*-associated genes that lie in the genetic intervals associated with the co-variation modules from **Fig. 4b** in *trans*. For each module (column 1), the table provides *cis*-associated genes based on previously published data in bone marrow derived myeloid cells (Gerrits et al. 2009) (column 2), progenitor cells (Gerrites et al. 2009) (column 3), and our own DC data (column 4). In module #2, only *cis*-associated genes at the peak of the linkage interval (chr1: 140-157Mb) are presented. In column 4 (DCs), the prediction is based on both results of our meso-scale profiling (using only the relevant stimulation for a module), as well as the InSignature predictions using our microarray genome-wide dataset (marked with *). Presented are genes whose best-scored linked variant lies in *cis*, regardless the LR score. For example, the genes Pla2g4a is best associated in *cis*, although with an insignificant LR score (and thus is not included in **Fig. 3a**). Predictions using InSignature (Myof, Glul and Frmd4b) for modules #1, #2, and #4 are using the genome-wide profiling of a limited number of strains in LPS only. InSignature's predictions, therefore, are not at the relevant conditions for the module (#1 – PAM; #2, #4 - Poly IC).