Figure S1. A network approach to expression filtering

a. A Pearson correlation co-expression network of the genes FCs is constructed. Links with absolute value smaller than a given cutoff are eliminated, and the Largest Connected Component (LCC) size is computed. A strong LCC size decrease is observed around a cutoff of 0.4.
b. The derivative of the previous plot is shown. The cutoff of 0.5 corresponding to the end of the drop-off is selected to define 11,279 genes in the LCC.
c. Examples of cardiac functionally relevant genes in and out of the LCC. Genes left out have either low expression (*Calm4*) or saturation issues (*Tnnc1*) which introduce noise in the correlation process.
d. Effect of thresholding on network clustering. We computed the number of nodes in every connected component in the co-expression networks and ranked them by decreasing size. We show the connected component size as a function of their rank. The LCC is chosen as the filtered set of genes. The second largest connected component is of size 4. We see that there is no "competing" connected component that could contain other genes of interest.

Figure S2. Effect of the pre-filtering on FC genes

Same plots than Figure 2a, using the filtered set of genes (a), or the genes filtered out by the method from Figure S1 (b). This shows that the genes highly correlated to hypertrophy are extracted during the filtering process, while genes with low correlations are filtered out.

Figure S3 Replicability of individual fold-changes

a. Heatmap showing the fold-changes of the 36 hypertrophic genes for pairs of mice from 9 replicated strains.

b. The quality of replication is assessed by computing the Spearman correlation between the fold-changes of the 36 genes between replicated strains (red) and for random pairs of non-replicated strains (gray). The average correlation is 0.76, which is significantly higher than between two distinct strains where it is 0.14 (p=1.6e-7, Wilcoxon test).

c. Scatterplot corresponding to the data from the heatmap in a. Points correspond to personal FCs in a given strain between two replicates. We found a Spearman correlation of rho=0.53, highly significant (p<1e-16).

Figure S4 Pathway enrichment of neighbor genes in the interactome

a,b. Pathway enrichment was assessed on first neighbor genes of the FC (a) and SAM (b) genes in the human Protein-Protein Interactome [33]. The 10 most enriched pathways are shown. FC neighbors are seen to be highly enriched in a previously published Cardiac Hypertrophy Signaling Network or CHSN [20].

Figure S5. FC genes interaction with the CHSN

Network visualization of the CHSN (gray nodes) and their first neighbors in the FC set (red) in the interactome [33]. Darker nodes from CHSN indicate interaction with a FC protein.

Figure S6. Microscopic images of *Hes1* siRNA assays in neonatal rat ventricular myocytes size

Microscopic images of neonatal rat cardiomyocytes following transfection with either control or Hes1 siRNAs and a 48 hour treatment with control or isoproterenol or phenylepherine containing media. Scale bars show 100 μm.

Figure S7. *Hes1* in the HMDP

Barplots comparing Heart mass (a) and *Hes1* (b) fold-changes across HMDP strains as in Figure 1h,k. Strains with no or mild hypertrophy show a negative fold-change of *Hes1*, an effect consistent with the *Hes1* siRNA assay in neonatal rat cells of Figure 4c.

Table S1. List of 104 strains and numbers of untreated control animals and ISO treated animals used for each strain for cardiac hypertrophy measurements.

Table S2. Number of qPCR replicate experiments following *Hes1* or control siRNA transfection in neonatal rat ventricular myocytes.

Table S3. qPCR data for Hes1 and Hes1 targets corresponding to Figure 4a,b.

Table S4. Cell cross-sectional area corresponding to Figure 4c.

Figure S1

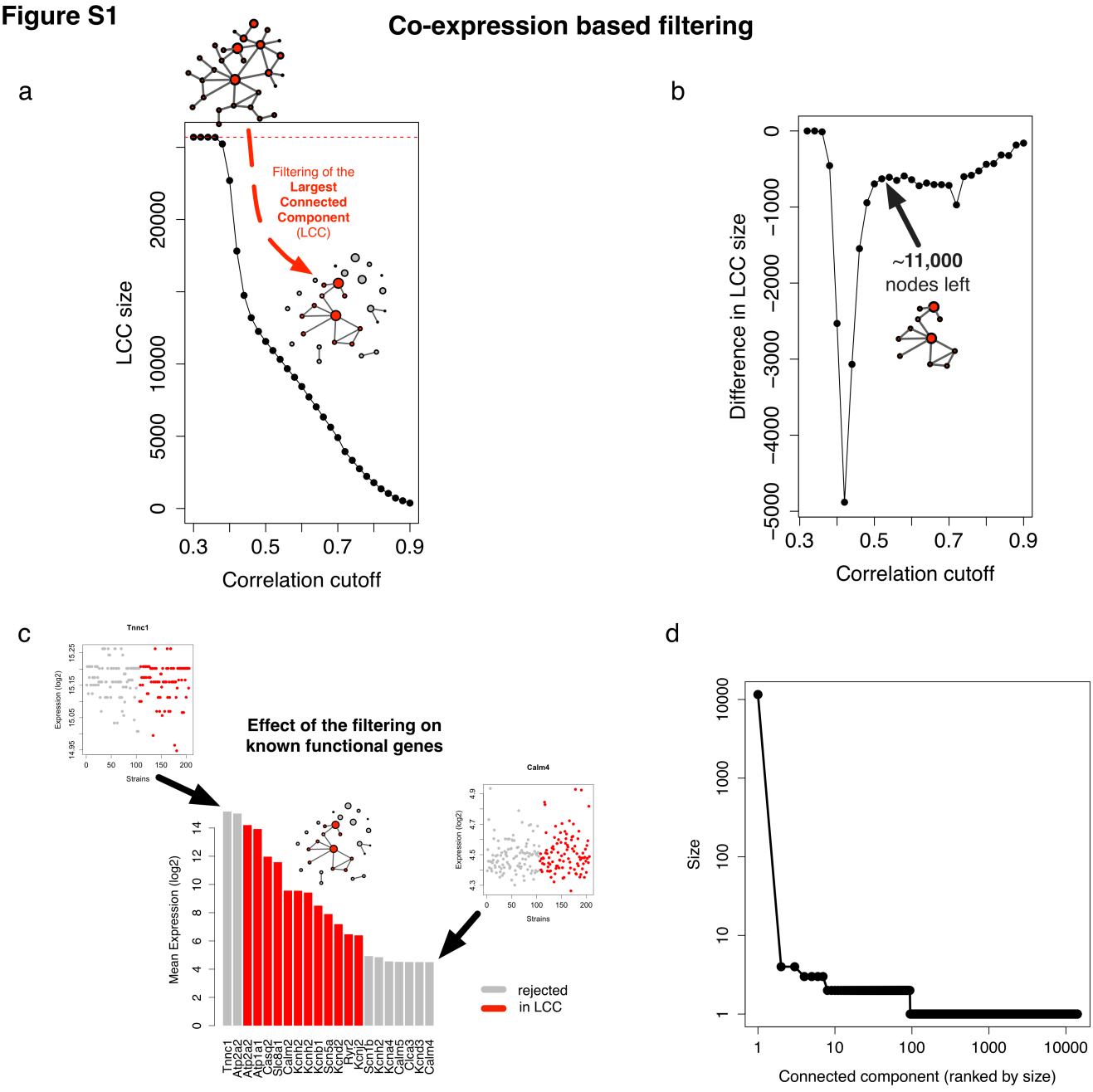
Co-expression based filtering
a
Filtering of the
Largest
Connected
Component
(LCC)
LCC size
0
5000
10000
20000
0.3
0.5
0.7
0.9
Correlation cutoff
b
~11,000
nodes left
Difference in LCC size
0
−1000
−2000
−3000
−4000
−5000
0.3
0.5
0.7
0.9
Correlation cutoff
c
Tnnc1
Expression (log2)
Strains
Effect of the filtering on
known functional genes
Calm4
Mean Expression (log2)
rejected
in LCC
Tnnc1
Atp2a2
Atp2a2
Atp1a1
Casq2
Slc8a1
Calm2
Kcnh2
Kcnb1
Scn5a
Kcnd2
Ryr2
Kcnj2
Scn1b
Kcna4
Calm5
Clca3
Kcnd3
Calm4
d
Size
1
10
100
1000
10000
Connected component (ranked by size)

Figure S2

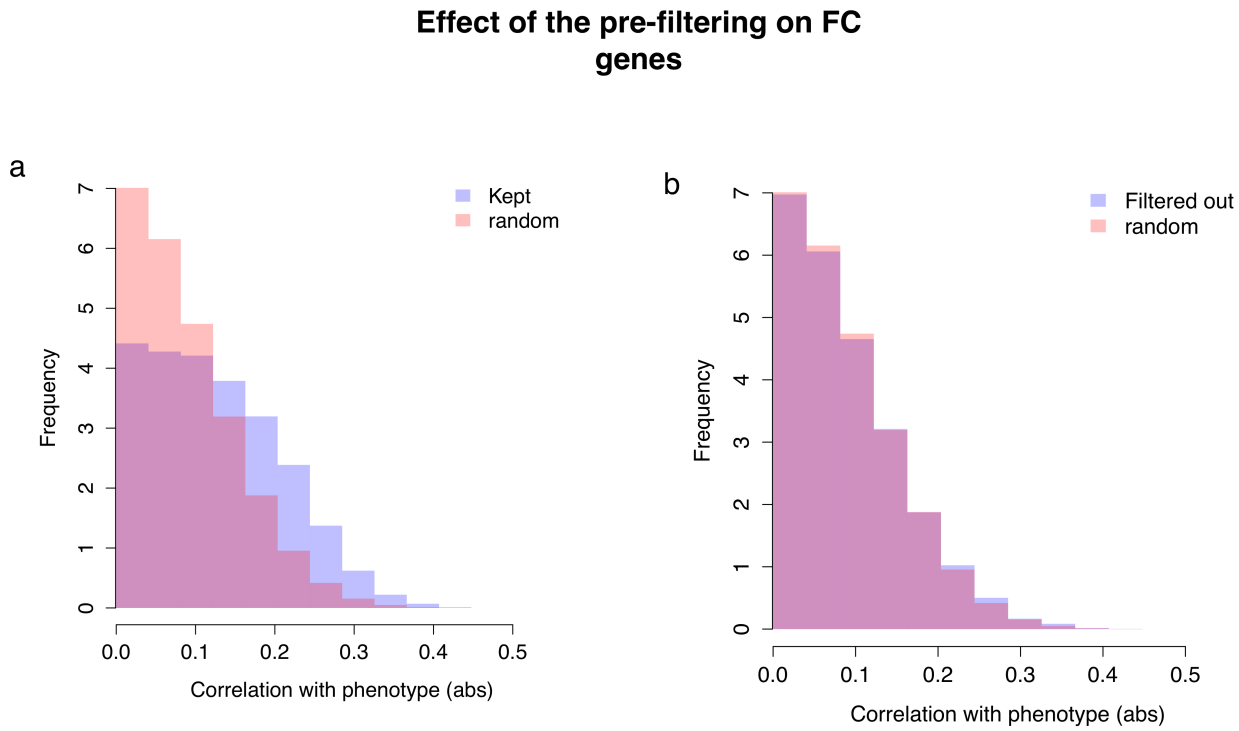
Effect of the pre-filtering on FC genes
a
Kept
random
Frequency
0
1
2
3
4
5
6
7
0.0
0.1
0.2
0.3
0.4
0.5
Correlation with phenotype (abs)
b
Filtered out
random
Frequency
0
1
2
3
4
5
6
7
0.0
0.1
0.2
0.3
0.4
0.5
Correlation with phenotype (abs)

Figure S3

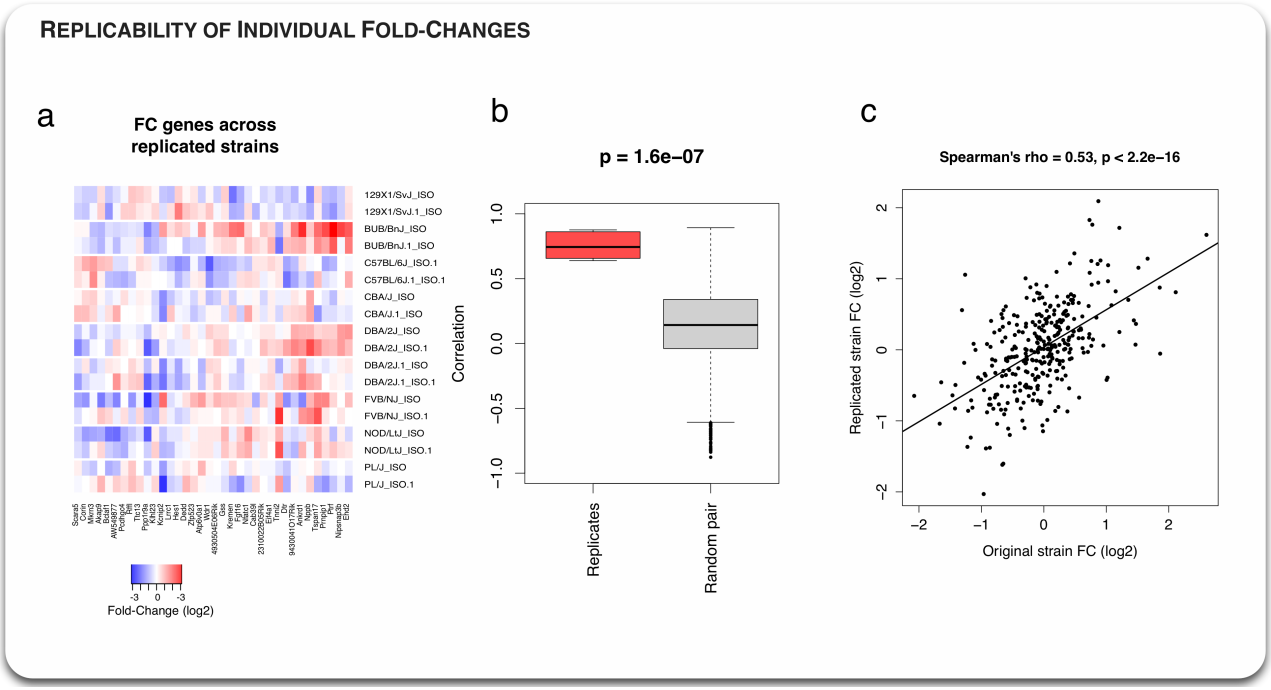
REPLICABILITY OF INDIVIDUAL FOLD-CHANGES
a
FC genes across replicated strains
129X1/SvJ_ISO
129X1/SvJ.1_ISO
BUB/BnJ_ISO
BUB/BnJ.1_ISO
C57BL/6J_ISO.1
C57BL/6J.1_ISO.1
CBA/J_ISO
CBA/J.1_ISO
DBA/2J_ISO
DBA/2J_ISO.1
DBA/2J.1_ISO
DBA/2J.1_ISO.1
FVB/NJ_ISO
FVB/NJ_ISO.1
NOD/LtJ_ISO
NOD/LtJ_ISO.1
PL/J_ISO
PL/J_ISO.1
Fold-Change (log2)
b
p = 1.6e−07
Correlation
Replicates
Random pair
c
Spearman's rho = 0.53, p < 2.2e−16
Replicated strain FC (log2)
Original strain FC (log2)

Figure S4

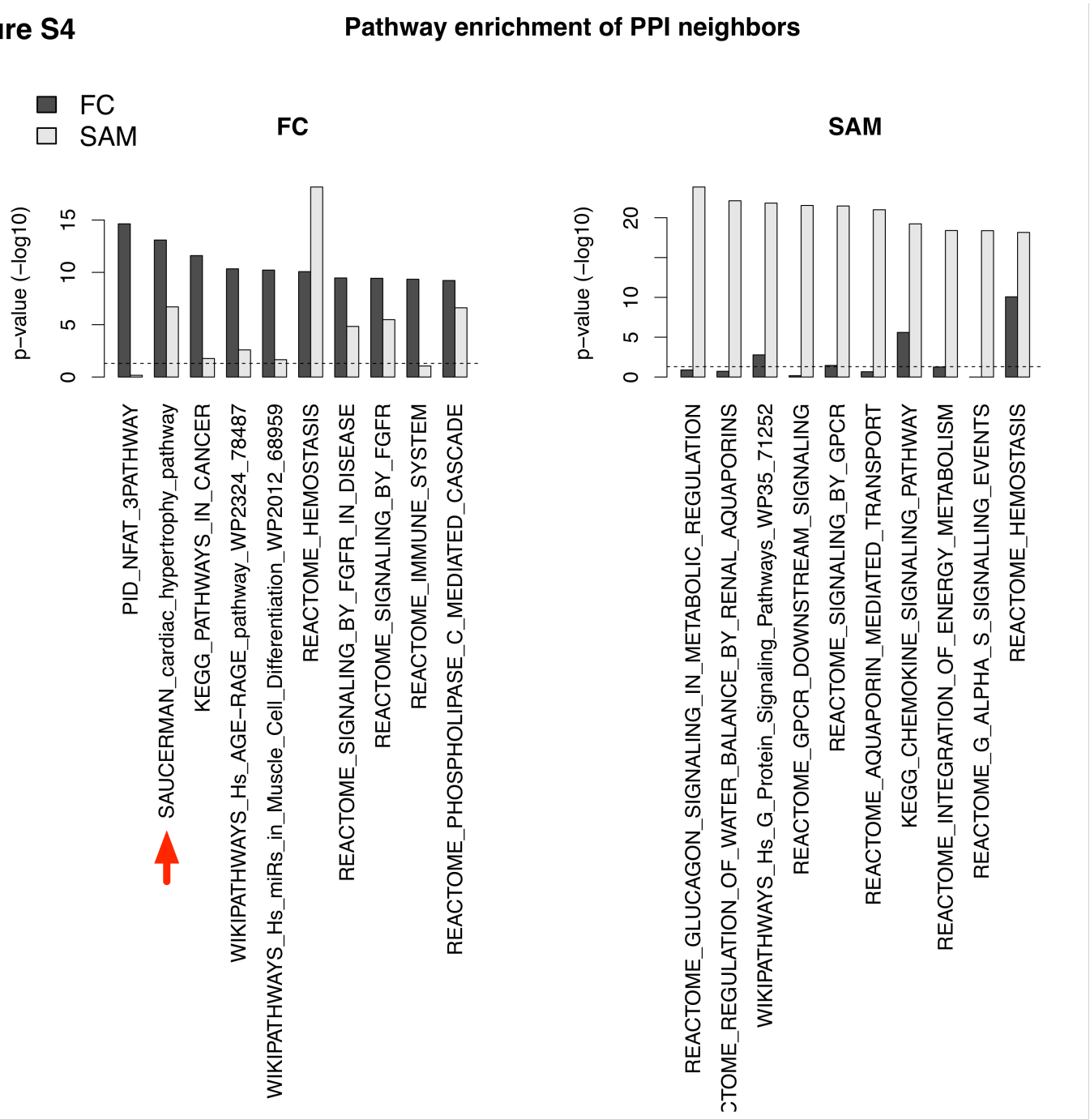
Pathway enrichment of PPI neighbors
FC
SAM
FC
SAM
p−value (−log10)
0
5
10
15
20
PID_NFAT_3PATHWAY
SAUCERMAN_cardiac_hypertrophy_pathway
KEGG_PATHWAYS_IN_CANCER
WIKIPATHWAYS_Hs_AGE−RAGE_pathway_WP2324_78487
WIKIPATHWAYS_Hs_miRs_in_Muscle_Cell_Differentiation_WP2012_68959
REACTOME_HEMOSTASIS
REACTOME_SIGNALING_BY_FGFR_IN_DISEASE
REACTOME_SIGNALING_BY_FGFR
REACTOME_IMMUNE_SYSTEM
REACTOME_PHOSPHOLIPASE_C_MEDIATED_CASCADE
REACTOME_GLUCAGON_SIGNALING_IN_METABOLIC_REGULATION
CTOME_REGULATION_OF_WATER_BALANCE_BY_RENAL_AQUAPORINS
WIKIPATHWAYS_Hs_G_Protein_Signaling_Pathways_WP35_71252
REACTOME_GPCR_DOWNSTREAM_SIGNALING
REACTOME_SIGNALING_BY_GPCR
REACTOME_AQUAPORIN_MEDIATED_TRANSPORT
KEGG_CHEMOKINE_SIGNALING_PATHWAY
REACTOME_INTEGRATION_OF_ENERGY_METABOLISM
REACTOME_G_ALPHA_S_SIGNALLING_EVENTS
REACTOME_HEMOSTASIS

Figure S5

FC genes interaction with the CHSN

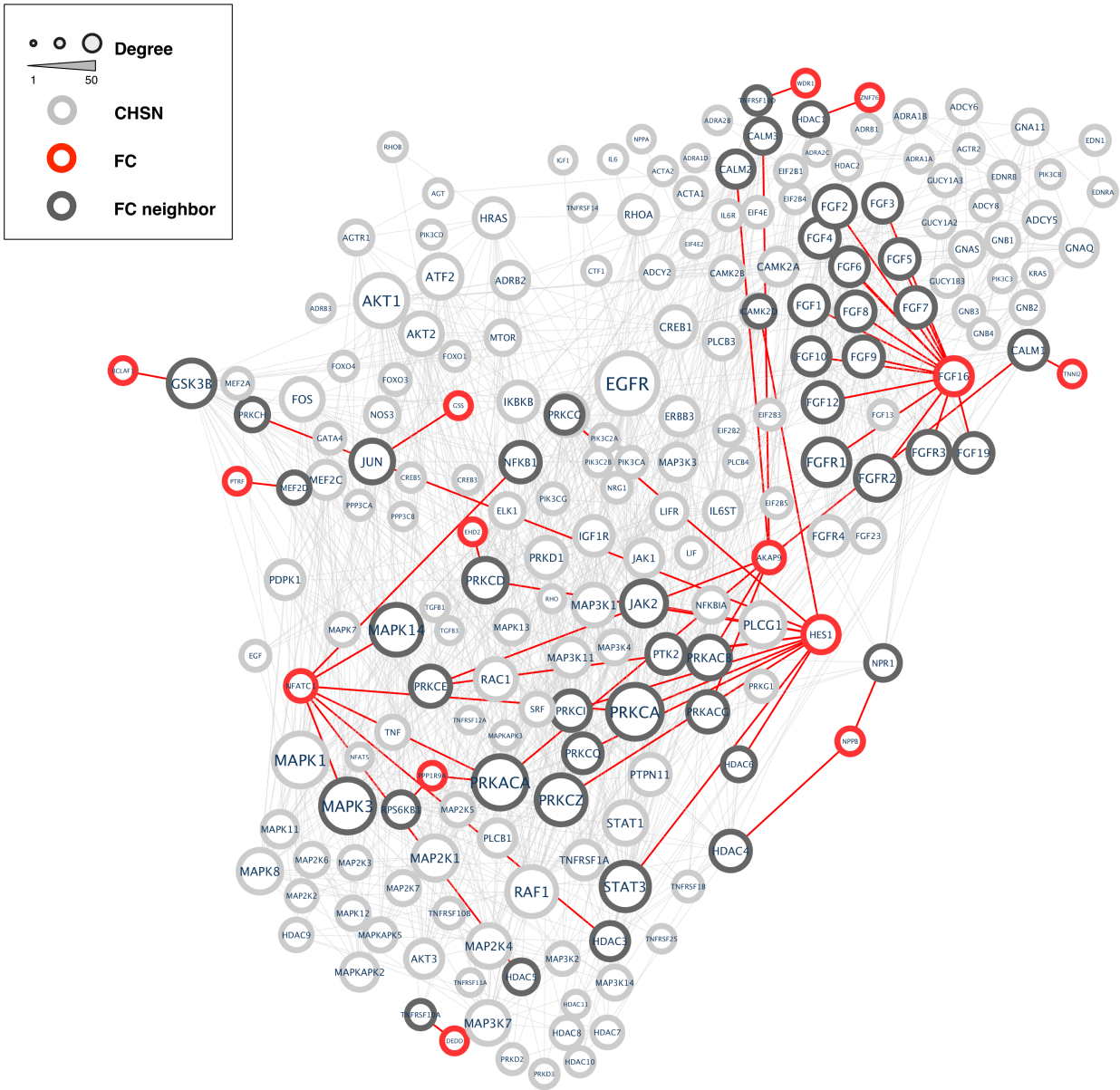

Figure S6

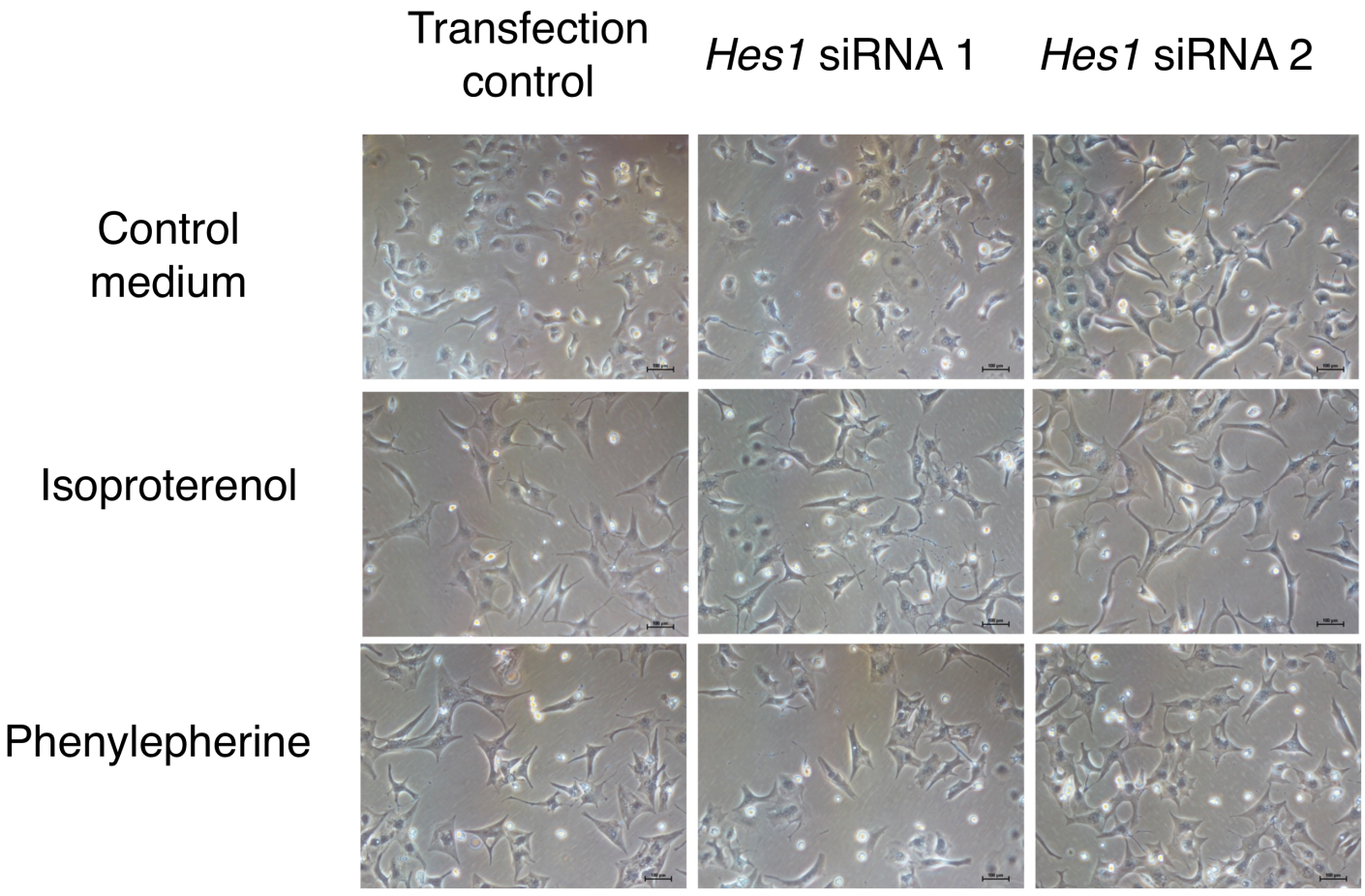
Transfection control
Hes1 siRNA 1
Hes1 siRNA 2
Control medium
Isoproterenol
Phenylepherine

Figure S7 ***Hes1*** **expression FC in the HMDP**