Cross-talk between AMPK and EGFR dependent Signaling in Non-Small Cell Lung Cancer (Supplement)

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1 Sources of prior knowledge

The approaches presented here primary consider the following sources of biological knowledge.

Protein-Protein Interactions database

Protein-protein interaction (PPI) data present the current knowledge about pairs of proteins that interact in living system and hence can be an important source of information as a network prior. Such knowledge resides in various databases, like IntAct, HPRD *etc*. Here we use interaction data from the PathwaysCommons database; a collection of publicly available pathway information [1]. To compute a confidence value for each interaction between a pair of genes/proteins we look at the shortest path distance between the two entities. To calculate the shortest path distance between two nodes the function *sp.between* function based on Dijkstra's algorithm is used from R-package RBGL. The edge confidence is then computed as the inverse shortest path distance.

KEGG pathway

KEGG pathways [5] is a knowledge base representing our knowledge on the molecular interaction and reaction networks. It includes various kinds of pathways e.g. metabolic pathways, disease related pathways etc. We compiled a comprehensive network from KEGG with ∼3776 nodes and ∼29878 edges by merging ∼80 KEGG graphs. The Dijkastra algorithm was executed on this graph to compute scores similar to those obtained for PPI databases.

Gene Ontology

The Gene Ontology (GO) offers controlled vocabularies for aiding the annotation of biomolecules. Interacting proteins often function in the same biological process. This implies that two proteins acting in the same biological process are more likely to interact than two proteins involved in different processes. Here we use this information based on GO *BiologicalProcess* (BP) annotations.Therefore, exploring the knowledge buried in GO annotations seems a promising approach to map relations among genes. To do this mapping of relations comparison of individual GO terms was performed via Lin's similarity measure [6] via the default method in GOSim [3, 10].

Protein Domain Annotation

It has been found that found that proteins in distinct KEGG pathways are enriched for certain protein domains, i.e. proteins with similar domains are more likely to act in similar biological pathways [4, 2]. Therefore, the confidence for interaction between two proteins can thus be seen as a function of the similarity of the inter-pro domain annotations [7] of proteins. For each protein we constructed a binary vector, where each component represents one Inter-Pro domain. A "1" in a component thus indicates that the protein is annotated with the corresponding domain. Otherwise a "0" is filled in. The similarity between two binary vectors u, v (domain signatures) is presented in terms of the cosine similarity

$$S_{domain} = \frac{\langle u, v \rangle}{\|u\| \|v\|} \tag{1}$$

Domain-Domain Interactions

Two proteins are more likely to interact if they contain domains, which can potentially interact. The DOMINE database collates known and predicted domain–domain interactions [9]. Calculation for edge confidence (I_{AB}) based on the DOMINE database is done as

$$I_{AB} = \frac{H}{D_A . D_B} \tag{2}$$

where H is the number of hit pairs found in the DOMINE database and D_A and D_B are the the number of domains in proteins A and B, respectively.

2 Methods to compute priors

The Noisy-OR model (NOM) [8] to compute consensus probabilistic prior from the sources described above. Here we describe the NOM approach: The Noisy-OR represents a non-deterministic disjunctive relation between an effect and its possible causes and has been extensively used in artificial intelligence. The Noisy-OR model assumes that the relation among the causes and the effect is non-deterministic, allowing the presence of the effect in absence of any of the modeled causes. The Noisy-OR principle is governed by two hallmarks: First, each cause has a probability to produce the effect and second, the probability of each cause being sufficient to produce the effect is independent of the presence of other causes .

In our case $X_{ij}^{(1)}$, $X_{ij}^{(2)}$, ..., $X_{ij}^{(n)}$ are interpreted as causes and $\hat{\Phi}_{ij}$ as effect. The link between both is given by

$$\hat{\Phi}_{ij} = 1 - \prod_k (1 - X_{ij}^{(k)}) \tag{3}$$

In consequence $\hat{\Phi}_{ij}$ becomes close to 1, if the edge $i \rightarrow j$ has a high confidence in at least one knowledge source, because then the product gets close to 0. Hence, in the Noisy-OR model high edge confidences in one information source can overrule low confidences in other information sources. For a detailed description please see Praveen et al. 2013 [8]
This prior was percieved as the S-gene prior for the NEM algorithm together with the data.

References

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[10] Andreas Schlicker, Francisco S Domingues, Jörg Rahnenführer, and Thomas Lengauer. A new measure for functional similarity of gene products based on gene ontology. *BMC Bioinformatics*, 7:302, 2006.

Cross-talk between AMPK and EGFR dependent Signaling in Non-Small Cell Lung Cancer (Supplementary Figures)

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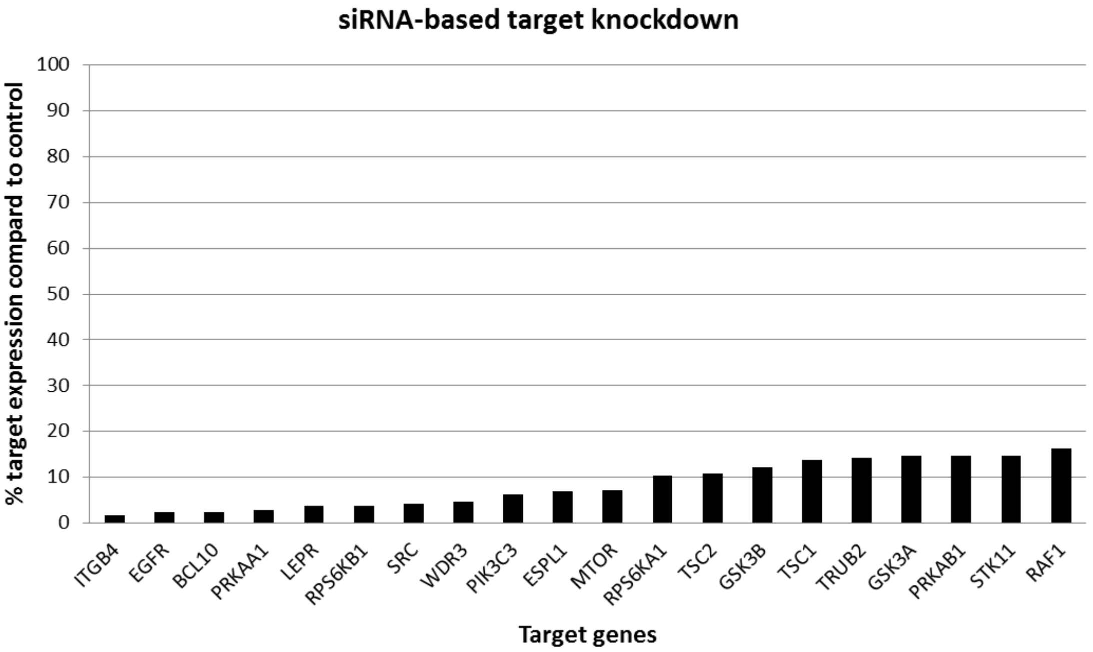
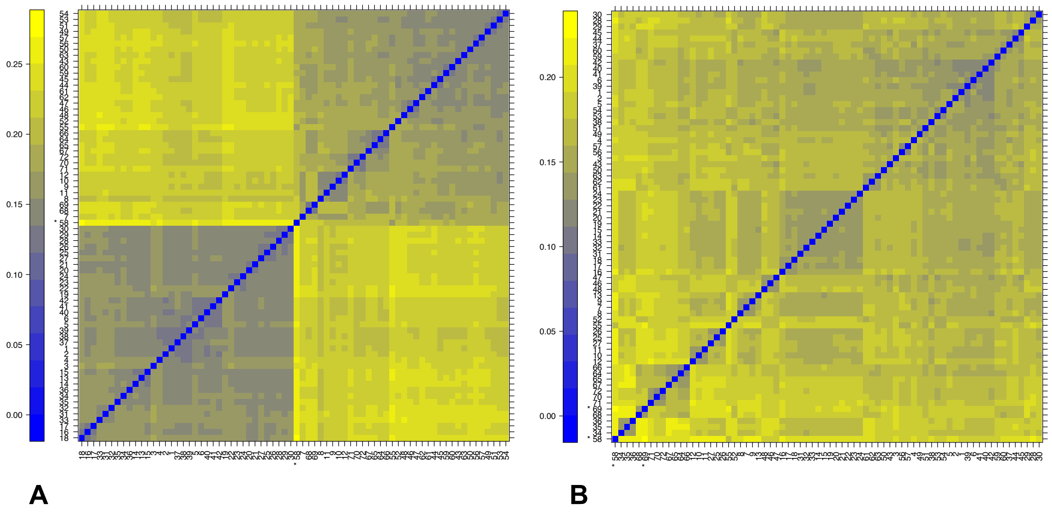
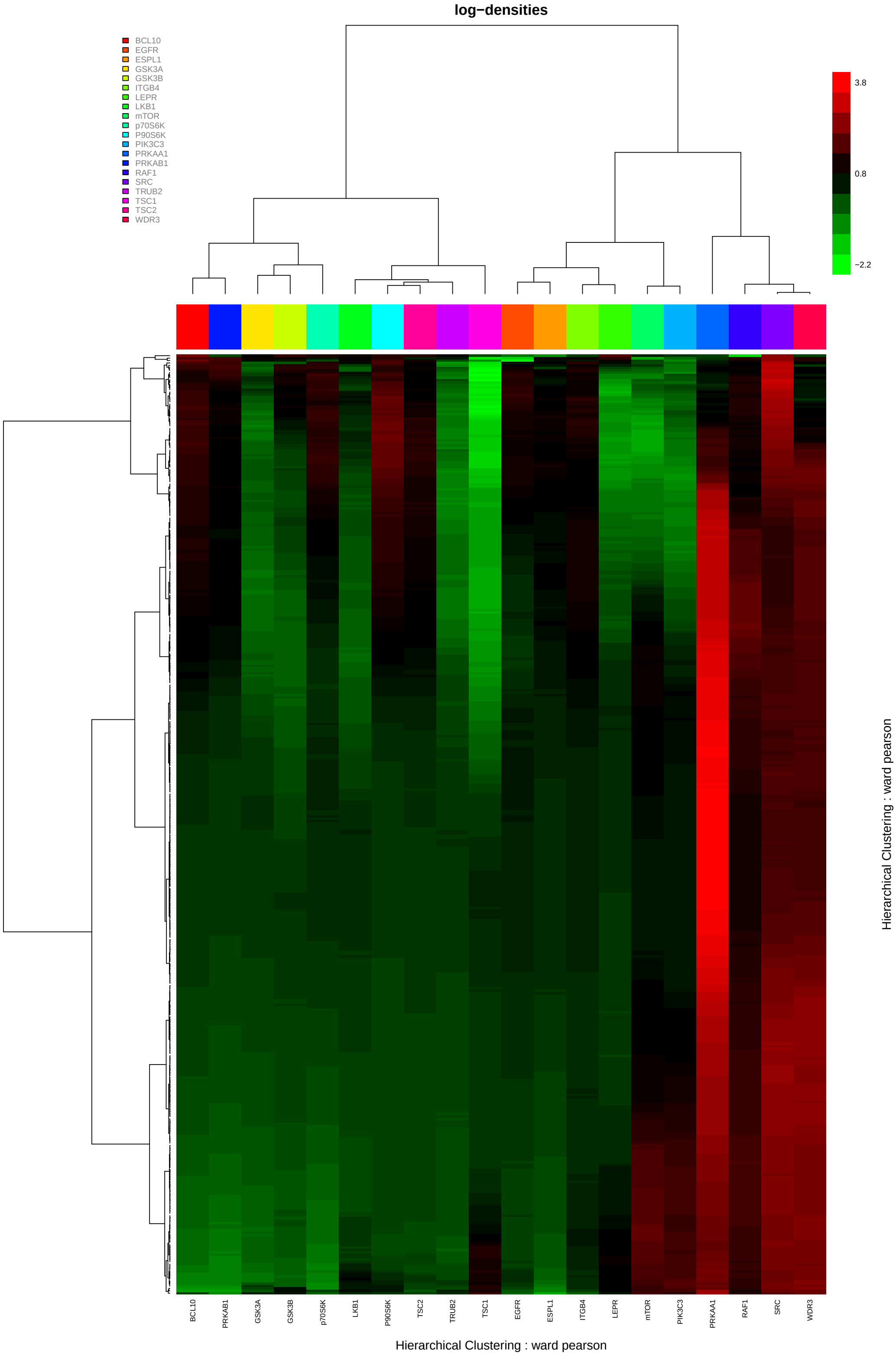


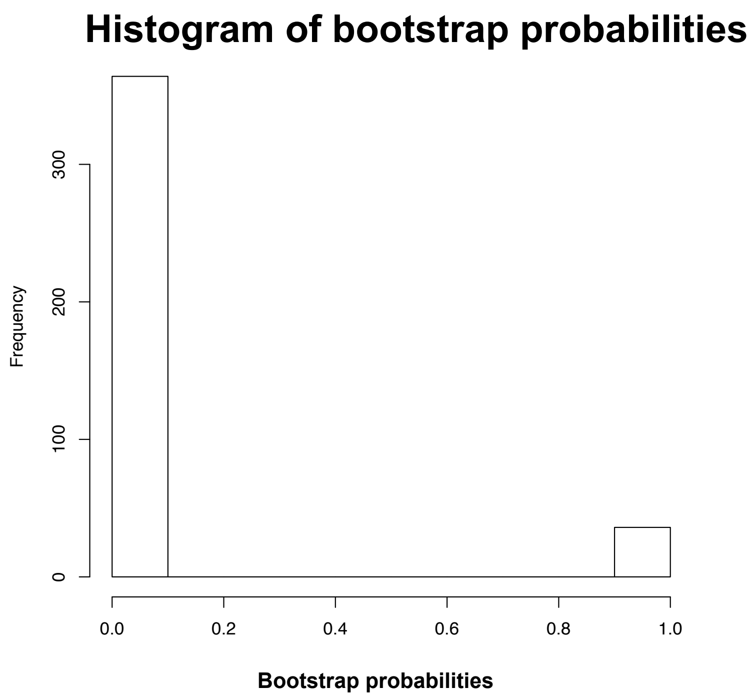
SF1: Target gene expression upon siRNA-based knockdown experiment in H1650 cells. Gene expression was measured by qPCR. Relative expression decrease upon knockdown was calculated in comparison to non-template controls (100%).



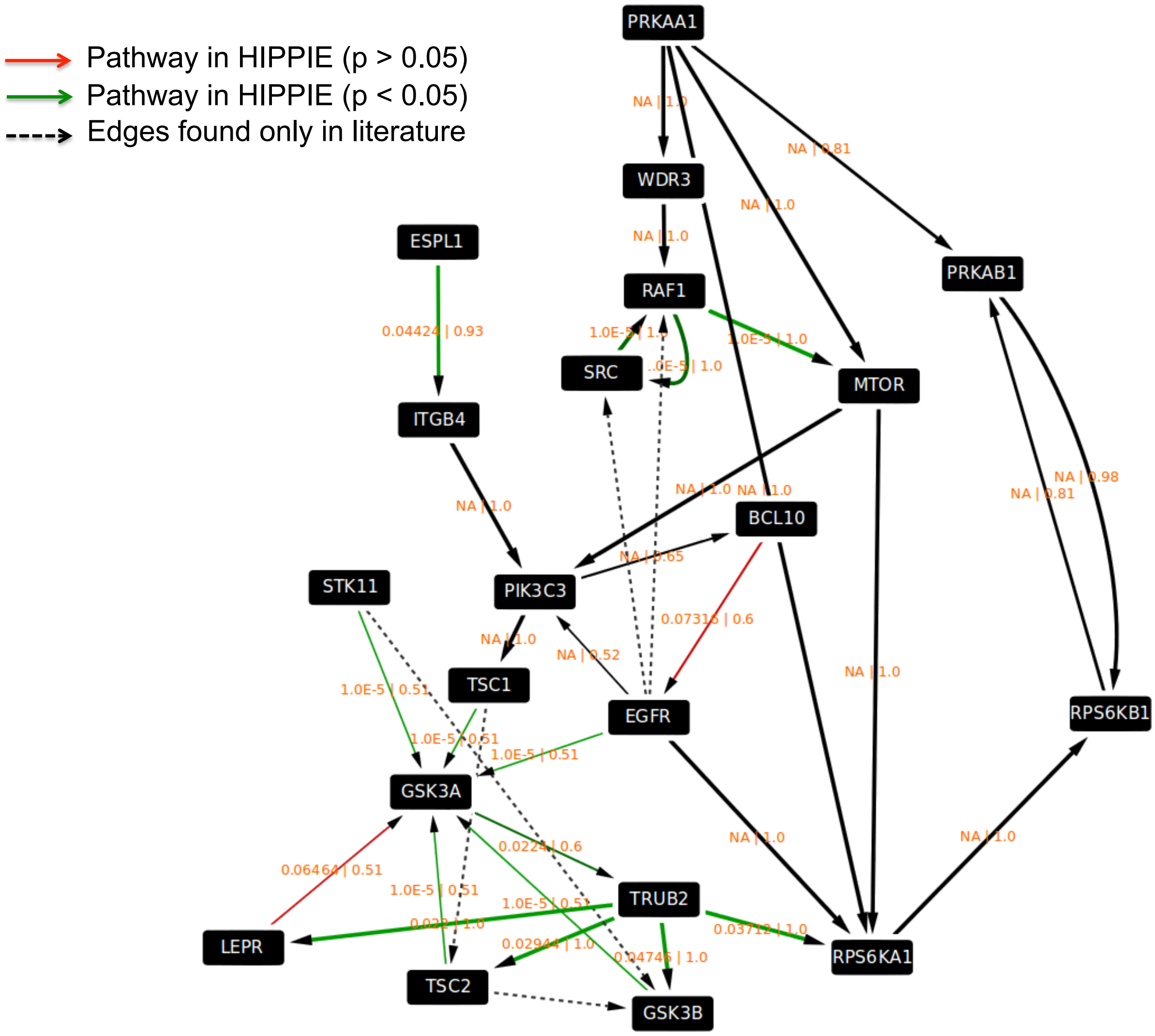
SF2: Batch effect removal from data (A) Heat for the mRNA data before removing the batch effect (B) After removing the batch effect



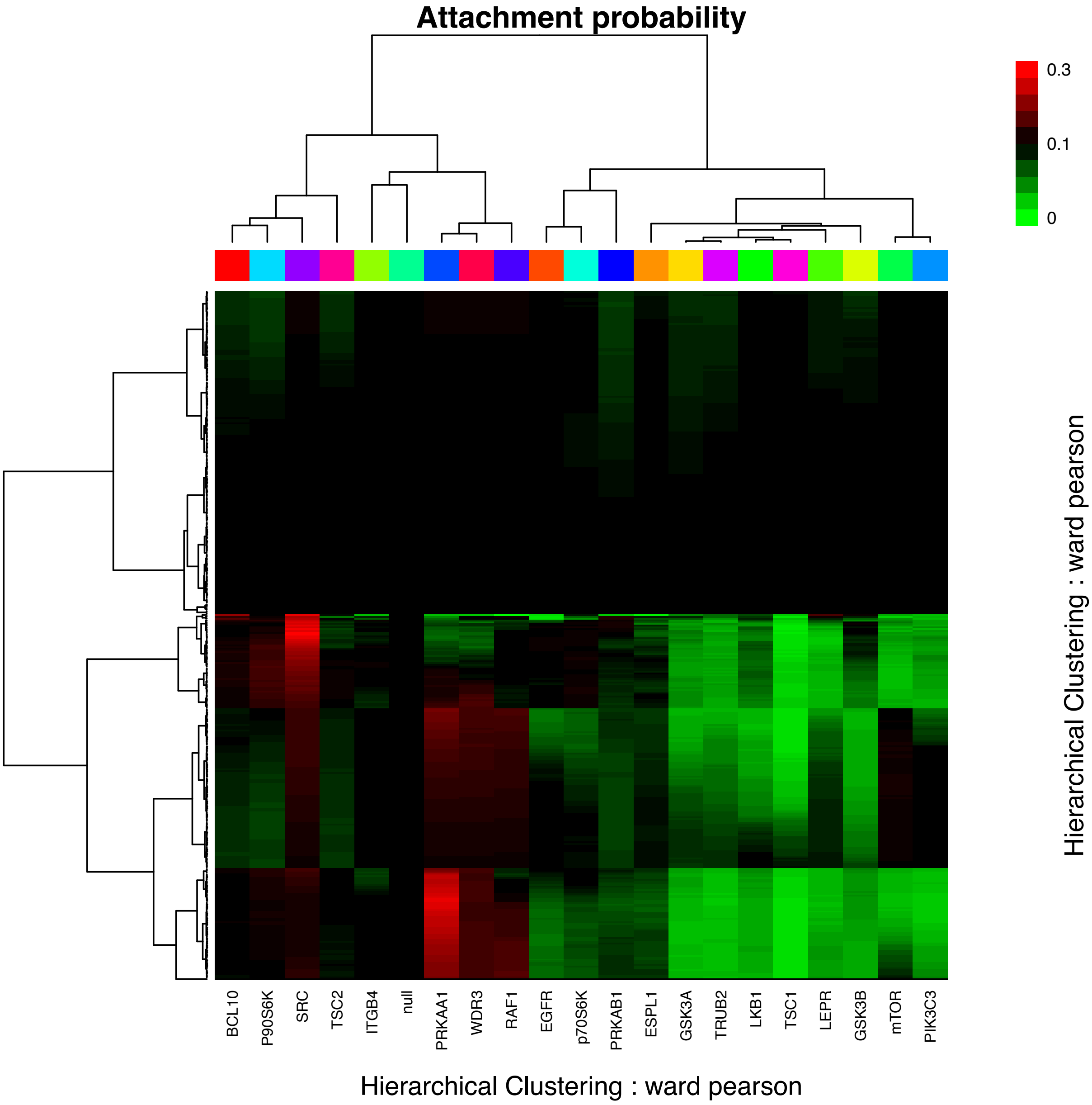
SF3: Heatmap for the log p-value density in mRNA perturbation data



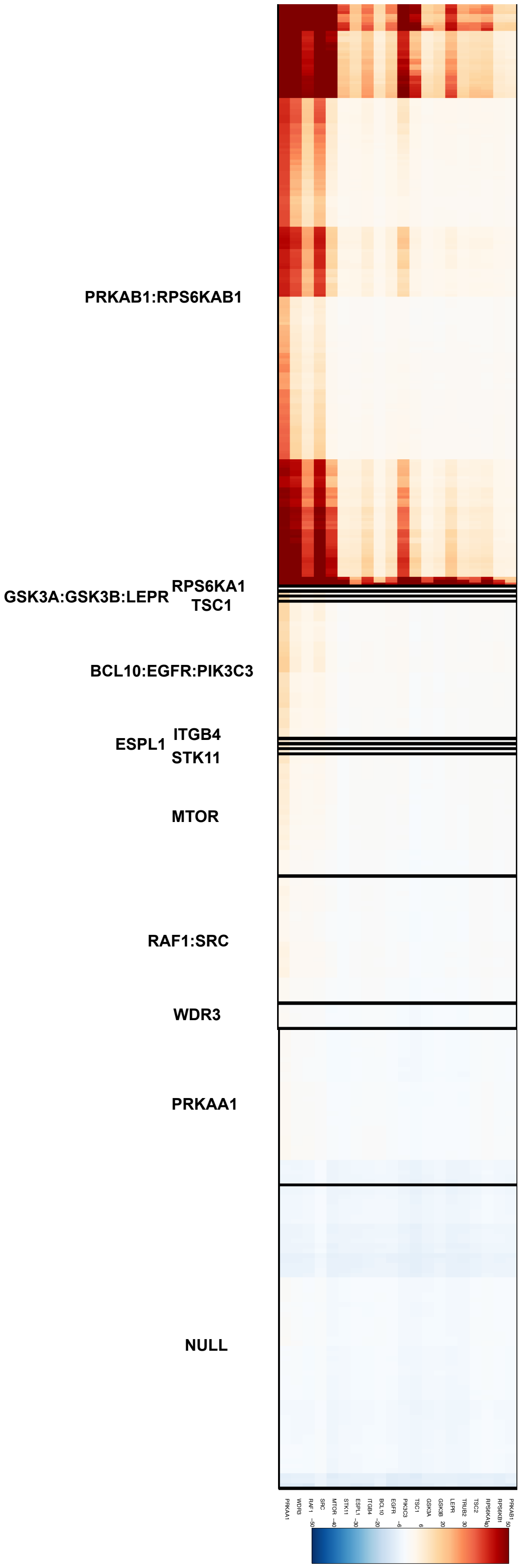
SF4: Histogram for the bootstrap confidence in the inferred bootstrapped network



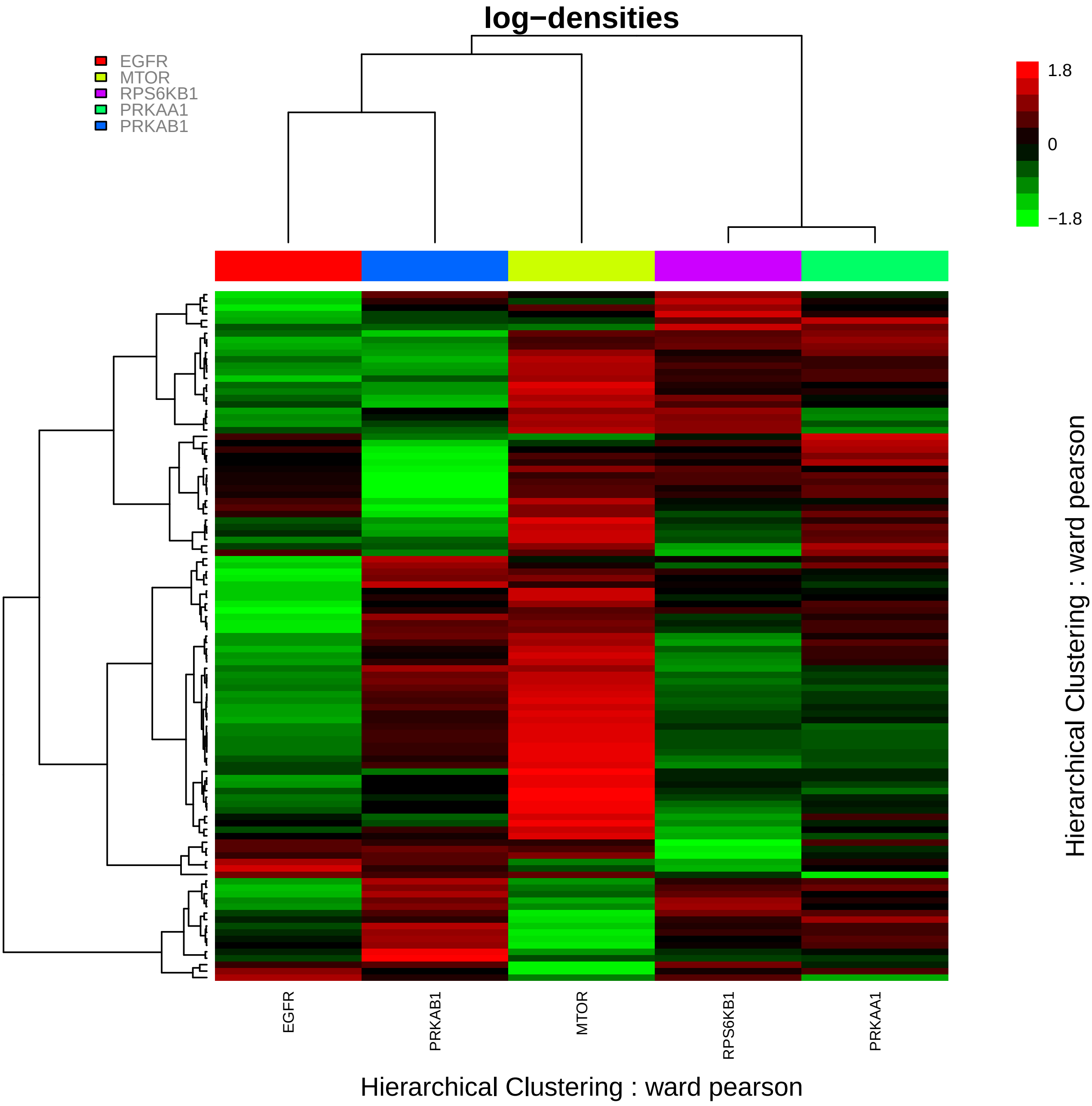
SF5: Comparison of inferred network with HIPPIE



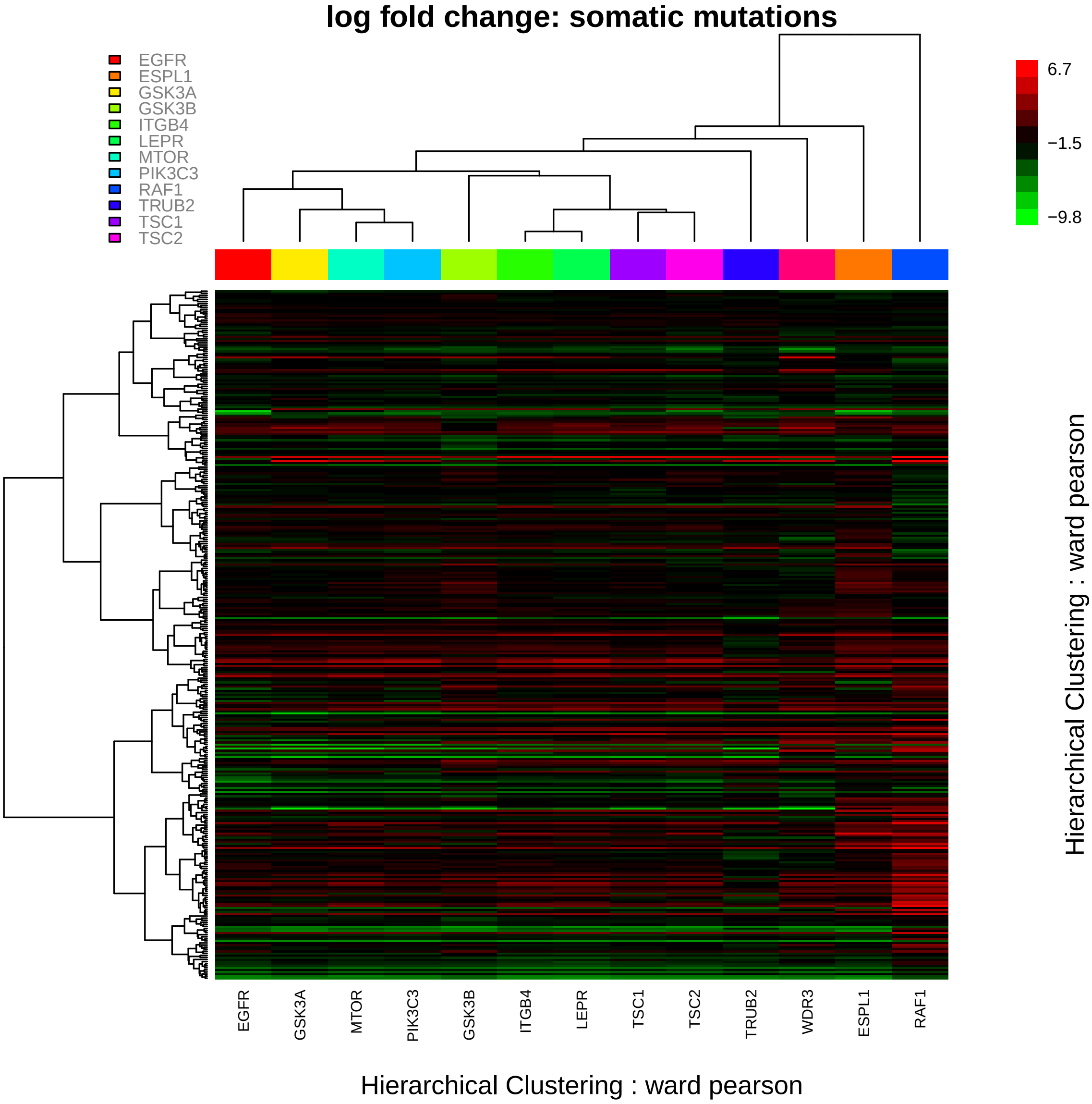
SF6: Heatmap of attachment probabilities of reporter genes



SF7: Heatmap of perturbation effects grouped by mostlikely S-gene attachments.



SF8: Heatmap showing effect on proteins for knocking down 5 genes



SF9: Heatmap of log fold changes for genes showing differential expression between patients with and without the somatic mutation shown in columns.

Table 1: Inferred network edges explained by STRING paths

Network Path	Explained by (String)
PRKAA1→ PRKAB1	PRKAA1→PRKAB1
PRKAA1→MTOR	PRKAA1→MTOR
PRKAA1→RPS6KA1	PRKAA1→RPS6KA1
PRKAB1→WDR3	PRKAB1→RPS6→WDR3
PRKAB1→RPS6KB1	PRKAB1→RPS6KB1
ESPL1→ITGB4	ESPL1→CDKN2A→ITGB4
WDR3→RAF1	WDR3→GNB2L1→RAF1
RAF1→SRC	RAF1→SRC
RAF1→MTOR	RAF1→MTOR
ITGB4→PIK3C3	ITGB4→CDKN2A→PIK3C3
SRC→RAF1	SRC→RAF1
MTOR→PIK3C3	MTOR→PIK3C3
MTOR→RPS6KA1	MTOR→RPS6KA1
PIK3C3→TSC1	PIK3C3→TSC1
TSC1→GSK3A	TSC1→GSK3A
TSC2→GSK3A	TSC2→GSK3A
BCL10→EGFR	BCL10→CDKN2A→EGFR
BCL10→RPS6KA1	BCL10→RPS6KA1
EGFR→PIK3C3	EGFR→PIK3C3
EGFR→GSK3A	EGFR→GSK3A
STK11→GSK3A	STK11→GSK3A
GSK3A→TRUB2	GSK3A→PRKAG2→TRUB2
TRUB2→TSC2	TRUB2→PRKAG2→TSC2
TRUB2→GSK3B	TRUB2→PRKAG2→GSK3B
TRUB2→LEPR	TRUB2→PRKAG2→LEPR
TRUB2→RPS6KA1	TRUB2→UBC→RPS6KA1
LEPR→GSK3A	LEPR→STAT1→GSK3A
RPS6KA1→RPS6KB1	RPS6KA1→CREB1→RPS6KB1

Table 2: Inferred network edges explained by HIPPIE paths

Network Path	Explained by (Hippie)
PRKAA1→ PRKAB1	NA
PRKAA1→MTOR	NA
PRKAA1→RPS6KA1	NA
PRKAB1→WDR3	NA
PRKAB1→RPS6KB1	NA
ESPL1→ITGB4	NA
WDR3→RAF1	NA
RAF1→SRC	RAF1→ARRB2→SRC
RAF1→MTOR	RAF1→HSP74→MTOR
ITGB4→PIK3C3	NA
SRC→RAF1	SRC→RAF1
MTOR→PIK3C3	NA
MTOR→RPS6KA1	NA
PIK3C3→TSC1	NA
TSC1→GSK3A	TSC1→AKT1→GSK3A
TSC2→GSK3A	TSC2→RRAGB→A4→GSK3A
BCL10→EGFR	BCL10→UB2V2→EGFR
BCL10→RPS6KA1	NA
EGFR→PIK3C3	NA
EGFR→GSK3A	EGFR→AKT1→GSK3A
STK11→GSK3A	STK11→A4→GSK3A
GSK3A→TRUB2	GSK3A→EBP2→H11→TRUB2
TRUB2→TSC2	TRUB2→FYCO1→KINH→1433G→TSC2
TRUB2→GSK3B	TRUB2→FYCO1→LMNA→TOP2A→GSK3B
TRUB2→LEPR	TRUB2→FYCO1→RFA1→XRN1→ LEPR
TRUB2→RPS6KA1	NA
LEPR→GSK3A	LEPR→GRB2→FCG2B→GSK3A
RPS6KA1→RPS6KB1	NA