Combining transcriptional and post-transcriptional regulation to predict mutations altering the gene regulatory program in cancer

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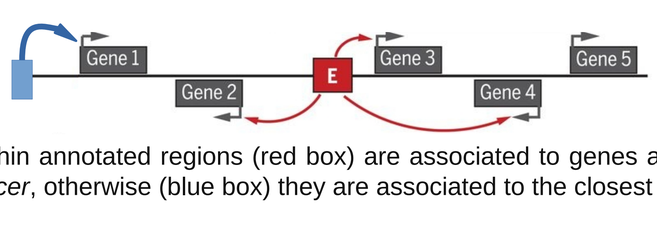
TFBS mutations with a cascading effect on miRNA-target expression

- Most somatic mutations are non-coding, a small fraction occurs at transcription factor binding sites (TFBSs).
- Interpretation of the effect of TFBS mutations can be eased by using expression data.
- Most of the known cancer drivers genes are protein-coding, but non-coding genes may also be cancer drivers.
- We mapped somatic mutations to TFBS with experimental and computational evidence derived from *UniBind*[1].
- Each TFBS was associated to its potential targets by combining the annotations from geneHancer[2] and associations to the closest TSS.

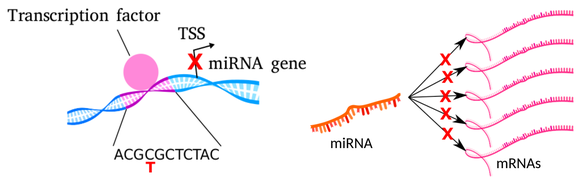


TFBS within annotated regions (red box) are associated to genes according to *geneHancer*, otherwise (blue box) they are associated to the closest TSS.

1. Gheorghe et al, NAR 2018
2. Fishilevich et al, Database 2017

- We adapted *xseq*[3], a bayesian probabilistic framework, to assess the likely association between mutated miRNA-associated TFBSs with dysregulation (cascading effect) in miRNA networks.

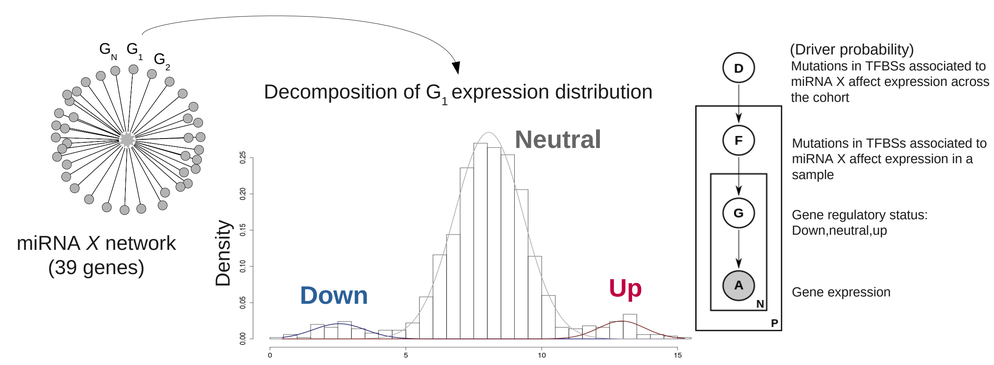
3. Ding et al, Nat Commun 2015



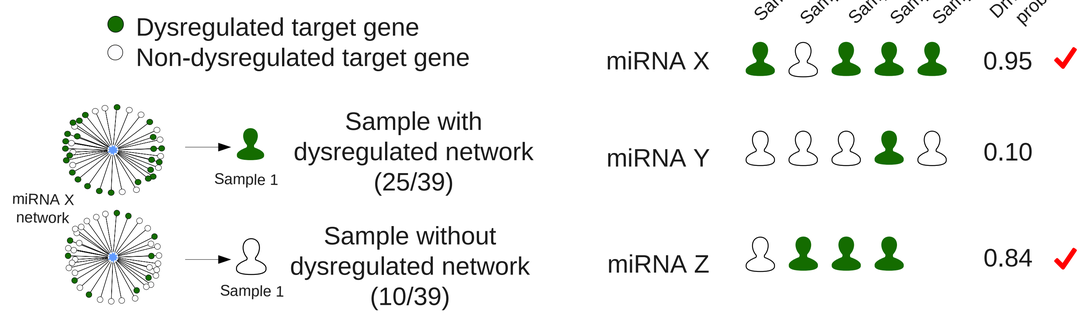
- We combined transcriptional (TFBS mutations) and post-transcriptional (miRNA networks) information to highlight cancer driver miRNAs across 7 TCGA[4] cohorts .

4. Zhang et al, Database 2011

Associating mutations with gene dysregulation



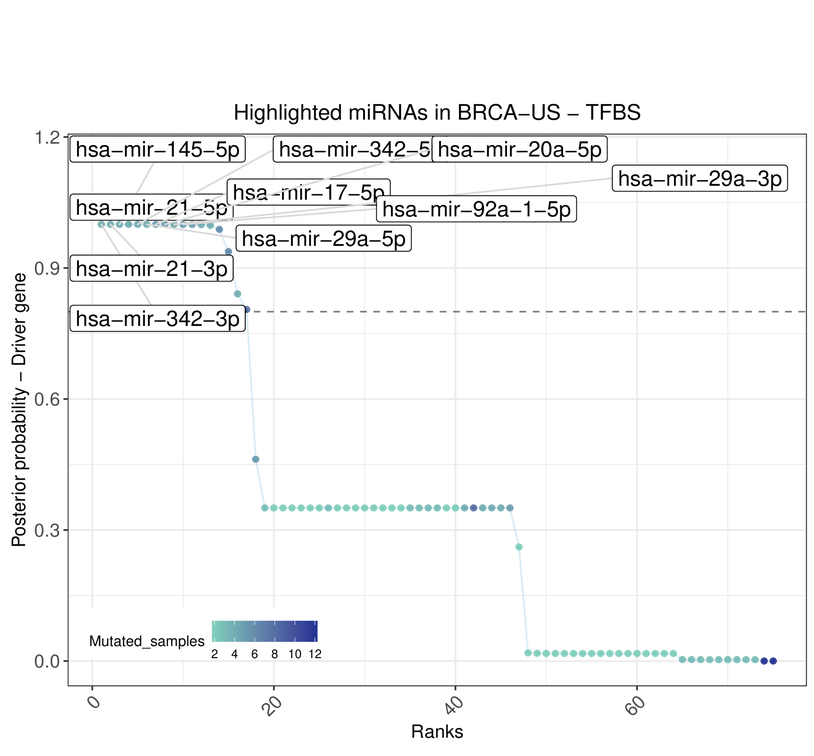
On each sample, we infer the regulatory status (down,neutral,up) of each gene within a miRNA network.



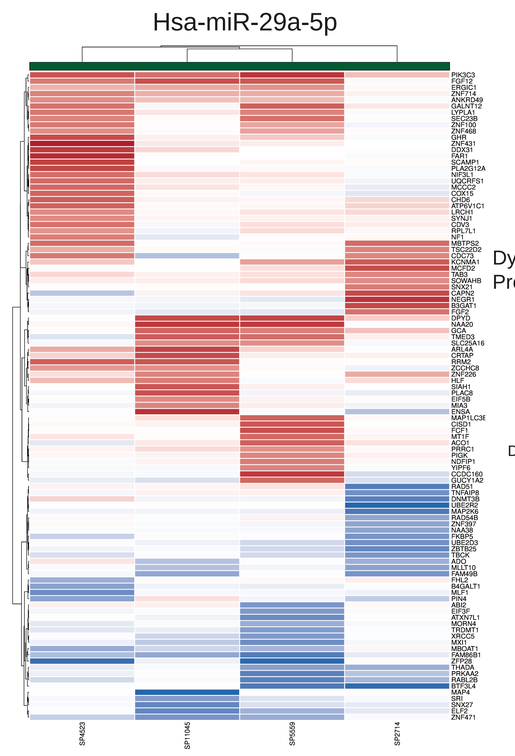
miRNA X mutations are associated with dysregulation in the network (Sample 1).

Mutations in miRNAs X and Z, are recurrently associated with dysregulation across the cohort.

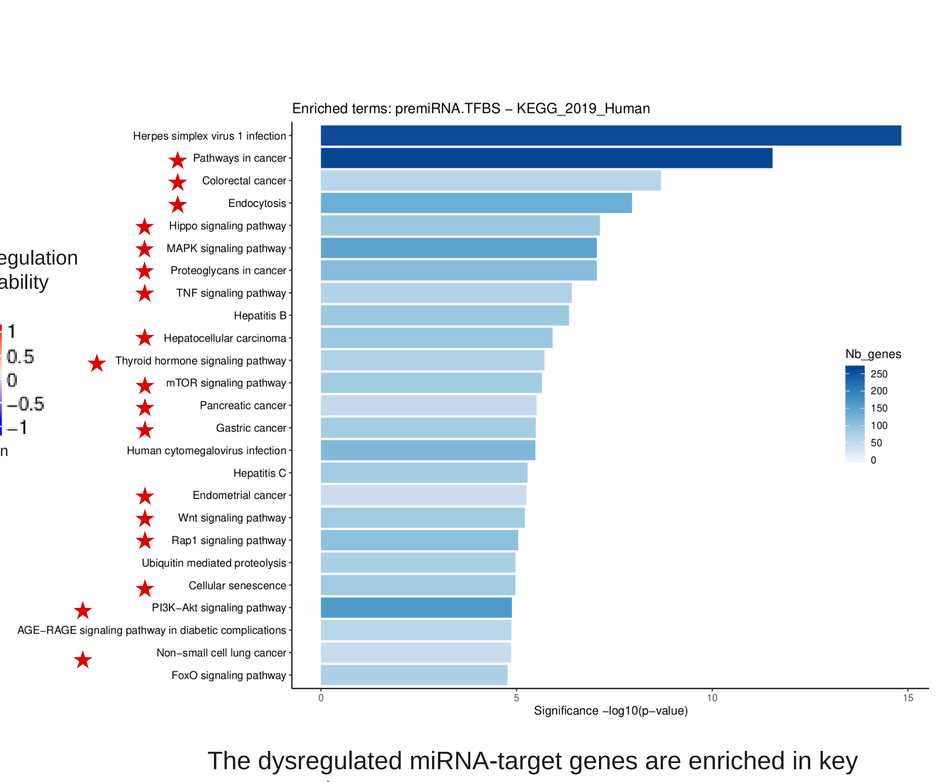
Dysregulated miRNA-target genes are enriched in key cancer pathways



For each cohort, we selected the miRNAs with high *Driver posterior probability.*

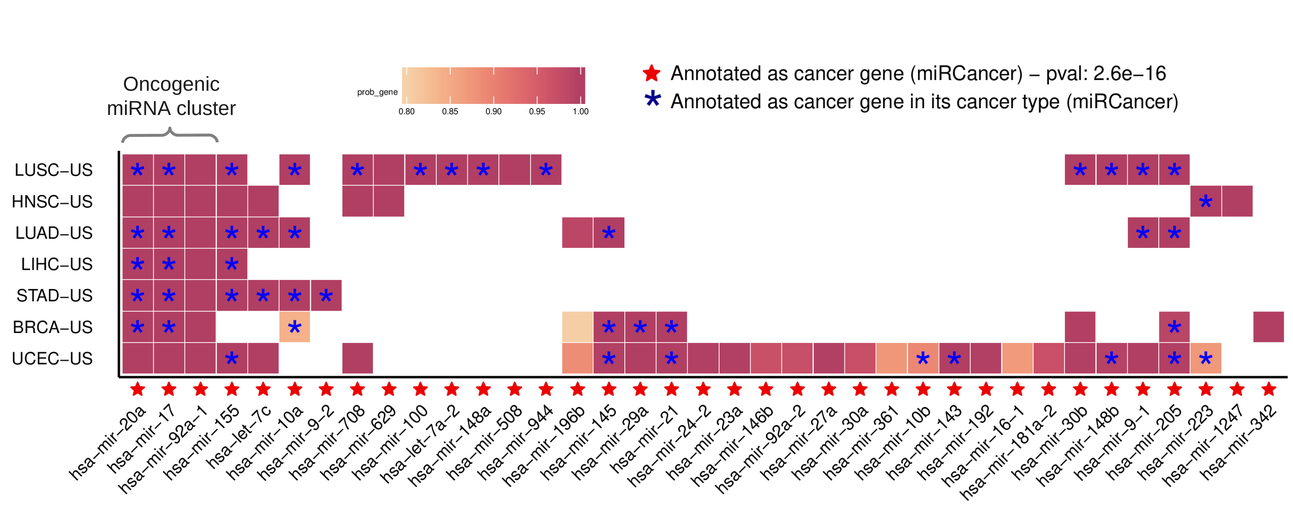


For each mutated sample (columns), we selected the dysregulated target genes (rows) of the highlighted miRNAs.



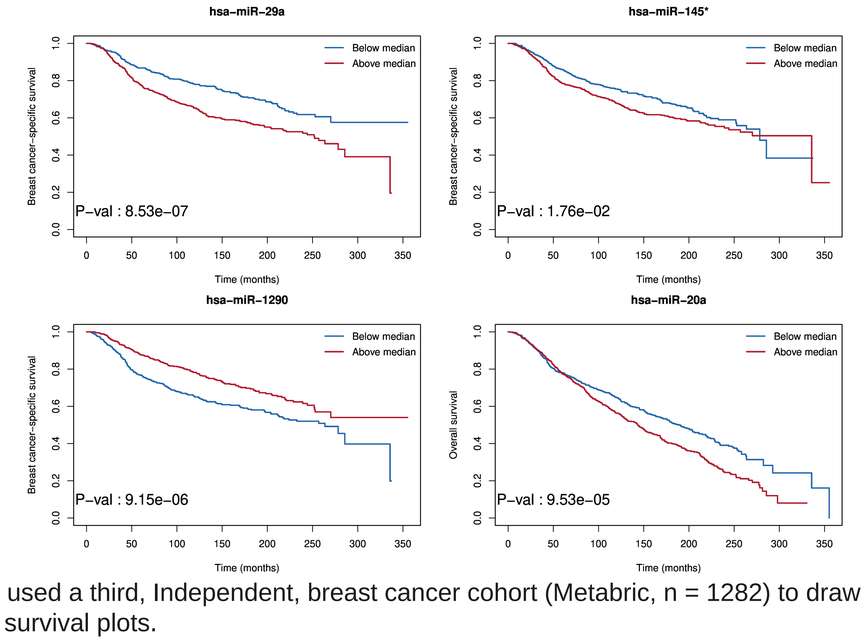
The dysregulated miRNA-target genes are enriched in key cancer pathways.

Pan-cancer predicted cancer driver miRNAs



We predicted 38 miRNAs in 7 TCGA cohorts. Three well known oncogenic miRNAs (miR-20a, miR-17, miR-92a) were predicted independently in the 7 cohorts. All the predicted miRNAs are annotated as cancer miRNAs in miRCancer.

Predicted cancer driver miRNAs are associated to prognosis



We used a third, Independent, breast cancer cohort (Metabric, n = 1282) to draw the survival plots.

Conclusions

- By combining transcriptional and post-transcriptional information we highlighted potential cancer driver miRNAs (with mutations at their TFBSs) likely associated to a cascading effect on the miRNA networks.
- Non-coding mutations coupled with gene expression can be explored to highlight cancer driver genes.
- The same methodology also works in TFBS mutations associated to protein coding genes, and could be adapted for other genes such as lncRNAs.