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H19, a Long Non-coding RNA, Mediates Transcription Factors and Target Genes through Interference of MicroRNAs in Pan-Cancer

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Long non-coding RNAs (lncRNAs) have recently been found to be important in gene regulation. lncRNA H19 has been reported to play an oncogenic role in many human cancers. Its specific regulatory role is still elusive. In this study, we developed a novel analytic approach by integrating the synergistic regulation among lncRNAs (e.g., H19), transcription factors (TFs), target genes, and microRNAs (miRNAs) and then applied it to the pan-cancer expression datasets from The Cancer Genome Atlas (TCGA). Using linear regression models, we identified 88 H19-TF-gene co-regulatory triplets, in which 93% of the TF-gene pairs were related to cancer, indicating that our approach was effective to identify disease-related lncRNA-TF-gene co-regulation mechanisms. lncRNAs can function as miRNA sponges. Our further experiments found that H19 might regulate SP1-*TGFBR2* through let-7b and miR-200b, ETS1-*TGFBR2* through miR-29a and miR-200b, and STAT3-*KLF11* through miR-17 in breast cancer cell lines. Our work suggests that miRNA-mediated lncRNA-TF-gene co-regulation is complicated yet important in cancer.

INTRODUCTION

Long non-coding RNA (lncRNA) refers to a class of transcripts that are longer than 200 nt (bp) and are not translated to protein.[1] lncRNA has been recently found to have many biological functions such as transcriptional regulation, epigenetic modification, and cell fate determination.[2] It has been involved in many diseases, including cancer.[3] For example, oncogenic lncRNAs may downregulate cancer cell antigen presentation and intrinsic tumor suppression,[4] and they can serve as potential biomarkers for cancer diagnosis and therapeutic strategy development.[5,6] Among thousands of lncRNA molecules discovered so far, H19 is one that is highly expressed.[7–9] Accumulating data have suggested that lncRNA H19 plays a critical role in tumor initiation, progression, and recurrence in various human cancers.[10] H19 has been reported to control cell cycle progression through regulating RB-E2F signaling in colorectal cancer.[11] It plays an essential role in the exosome-mediated phenotype of endothelial liver cancer cells.[12] H19 competitively binds a microRNA, miR-17-5p, to regulate *YES1* gene expression in thyroid cancer.[13] Moreover, H19-derived miR-675 contributes to bladder cancer cell proliferation through regulating p53 activity.[14]

lncRNA can act as a competing endogenous RNA (ceRNA) to interact with other protein-coding RNA transcripts, both transcription factor (TF) and non-TF genes.[15,16] Hereafter, we refer to genes as protein-coding genes to separate them from non-coding genes. By sharing the common miRNA-binding sites with mRNAs or directing miRNA degradation, lncRNA competes with the miRNA target genes (TFs or non-TF genes) through interacting with miRNA; consequently, the expression of miRNA-targeted genes will be upregulated. This type of lncRNA-miRNA-gene competing co-regulation (triplets) has been discovered in humans and several other species.[17] lncRNA may also interfere with the classic TF-gene regulation by acting as a ceRNA.

Although lncRNA is important in cancer, how it plays its regulatory roles in the complex and dynamic cellular systems remains largely unknown, especially at the pan-cancer level. In this work, we developed

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an analytical strategy to explore the synergistic regulation among lncRNAs, miRNAs, TFs, and genes. We applied this approach to The Cancer Genome Atlas (TCGA) pan-cancer datasets. We specifically examined H19, one of the highly expressed lncRNAs in cancer (Figure S1). Among the 24 cancer types we examined, we found that H19 was highly expressed in 21 cancer types, although not in the other three types (lower grade glioma [LGG], prostate adenocarcinoma [PRAD], and thyroid carcinoma [THCA]). As mentioned above, lncRNA might act as miRNA sponges to play roles in TF-gene regulation. Thus, we hypothesized that H19 could mediate TF-gene regulation through controlling miRNAs. After investigating the regulatory relationship among H19, miRNAs, TFs, and genes, we pinpointed three co-regulation triplets (H19-SP1-*TGFBR2*, H19-ETS1-*TGFBR2*, and H19-STAT3-*KLF11*) to validate our hypothesis in breast cancer cell lines. Our experimental results revealed that H19 might mediate (1) SP1-*TGFBR2* (TF-gene) interaction through let-7b and miR-200b, (2) ETS1-*TGFBR2* (TF-gene) interaction through miR-29a and miR-200b, and (3) STAT3-*KLF11* (TF-gene) interaction through miR-17. Such regulatory triplets can be used to predict the potential function of lncRNAs and miRNAs in cancer. Our study showed that lncRNA could interfere with miRNA-mediated TF-gene interactions. This critical regulation, if universal in various cancer types, will be important for understanding the molecular mechanisms of cancer initiation and progression, and the molecules included in the interaction can serve as biomarkers for cancer diagnosis, drug development, and therapeutic strategy development.

RESULTS

Classifying Samples by H19 Expression Level

lncRNA H19 is highly expressed in many cancer types and is actively involved in all stages of tumorigenesis.[10] To better understand the role of H19 in cancer, we analyzed the expression level of H19 in TCGA pan-cancer datasets and grouped the samples into "low," "middle," and "high" by H19 expression level. For instance, in breast invasive carcinoma (BRCA) samples, we reordered all of the samples by H19 expression and named the top 25% as the high group and the bottom 25% as the low group of H19 expression (Figure 1A). Taking the same criterion, we evaluated the H19 expression level in the remaining 23 cancer types and found that 25% is an appropriate percentage to set as the threshold (Table S1; Figure 2). In most of these 24 cancer types, the H19 expression profile within the middle 50% of samples showed a steady line with a mild slope. This indicated that these samples had similar and stable levels of H19 expression. However, outside the middle section, the profile lines showed significant change at the inflection points. As shown in Figure 2, samples falling into the zone from zero to the end point of rapid increases (the red vertical solid line) are considered as the H19 low group, whereas samples with the H19 level in the top section, from the start of dramatic increases (the blue vertical dashed line) to the end, are designated as the H19 high group. Interestingly, in a previous study, Li et al.[18] also used the 25th percentile as the threshold for dividing the top and bottom samples in their study. After having these cutoff thresholds, we further identified the H19 class labels of samples for BRCA TF expression data.

Identification of H19-TF-Gene Triplets

We first focused on explaining the results from TCGA BRCA samples; the results of other cancer types are provided in Table S1. Based on the FPKM (fragments per kilobase of exon per million mapped reads) score, we filtered out 694 TFs and 11,867 non-TF genes from TCGA BRCA dataset. Using two databases, TRANSFAC (release 2016.4)[19] and TRRUST (version 2.0),[20] we obtained a total of 13,263 TF-target gene pairs (interactions), of which 8,181 TF-target gene pairs (interactions) were found to be expressed (FPKM score of at least 50% of samples was greater than 1) in these samples, corresponding to 625 unique TFs and 2,198 unique non-TF genes.

To evaluate the impact of H19 on TF-gene regulation, we used linear regression to obtain the expression profile of TFs and genes after excluding the effect of copy number variations (CNVs) on their expression (Figure 1B; Equation 1). Next, these new expression profiles were fed to the second linear regression model (Figure 1B; Equation 2) to assess the effect of H19 on TF or gene expression. In BRCA, 679 TF-gene regulation interactions were found to be affected by H19 (required both false discovery rate $[FDR]_{EXPTF,\xi:GroupH19} < 0.05$ and $p_{EXPTF,\xi} < 0.05$) (Table 1). Of note, to reduce the false-positive rate (FDR), we required that these significant H19-TF-gene triplets should present in at least two TCGA cancer types. By following the analysis procedure above, we obtained a total of 88 triplets (Table S2). Figure 3 demonstrates the four most significant triplets ($-\log_{10}(p_{EXPTF,\xi}) > 9$) whose TF-gene regulation was affected by the change of H19 expression. The remaining triplets are presented in Figure S2. In Figure 3, all TF-gene regulations affected by the change of H19 expression were statistically significant (FDR < 0.05). For instance, in the presence of high H19 expression, the correlation between MYBL2 and *COL1A1* was significantly changed (positive correlation with $p = 3.31 \times 10^{-3}$ to negative correlation with $p = 2.74 \times 10^{-10}$).

We found that 173 of 186 (93%) TF-gene pairs had direct or indirect evidence to support their relationship to cancer (Table S3). According to this high rate, we thought that the remaining 13 TF-gene pairs might play roles in cancer as well and warrant further studies. These 13 TF-gene pairs are as follows: LUAD, CTCF-*IPO13*; KIRC, SP3-*EDF1*; PAAD, USF1-*FMR1*; STAD, EZH2-*DACT3*; TGCT, FOXO1-*HYOU1*; THCA, CTCF-*IPO13*, NFKB1-*CHUK*, NFYB-*EDF1*, RELA-*BGN*, RUNX1-*SYMPK*, SP1-*ME1*, SP1-*SIGIRR*, and SP3-*EDF1*. Interestingly, most of them (8 out of 13) were found in THCA, suggesting that this cancer type might have additional regulatory roles. These results indicate that our approach is effective in identifying TFs or genes that are related to cancer.

H19 Regulates TF-Gene Function through the Related miRNAs

Given that one of the important lncRNA functions is modulating miRNAs, we speculated that H19 might mediate TF-gene interactions through the regulation of miRNAs. Through a comprehensive literature search (Table S4), we identified 29 miRNAs (let-7a, let-7b, let-7g, let-7i, miR-106a, miR-130b-3p, miR-138-5p, miR-139, miR-141, miR-152-3p, miR-152-5p, miR-17-5p, miR-181d-3p, miR-181d-5p,

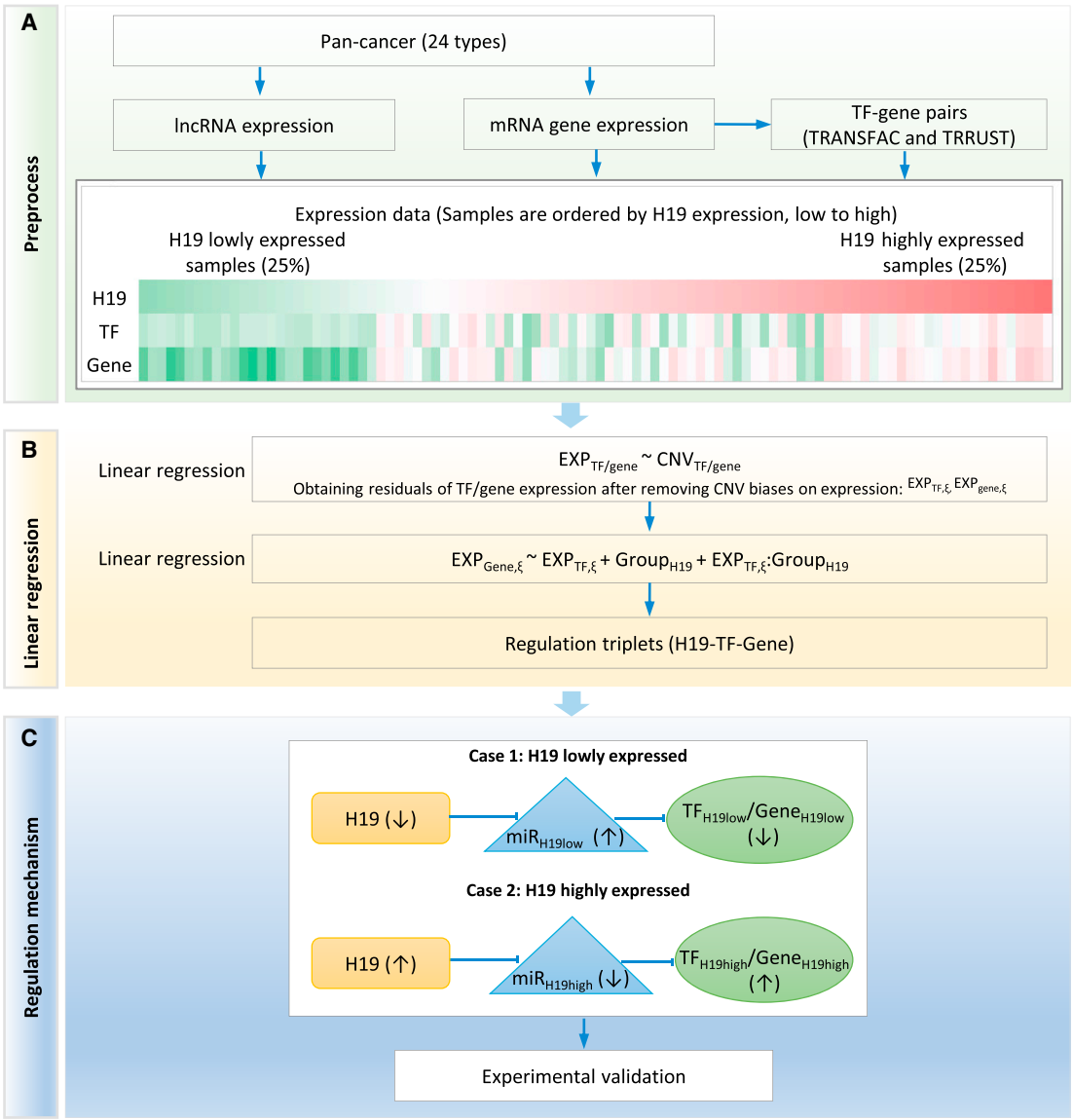

Figure 1. Analytical Pipeline for Identification of lncRNA-TF-Gene Triplets and H19 Is Used as an Example

(A) Analysis of lncRNA, TF and gene expression, followed by ordering the samples according to H19 expression. Expression data for lncRNAs, TFs, and genes in 24 cancer types were extracted from TCGA. TF-gene interaction pairs were retrieved from two databases, TRANSFAC and TRRUST. On each plot, samples were ordered by H19 expression from low to high. Samples that were within 25% of the lowly (highly) expressed samples were considered as a lowly (highly) expressed group. (B) Linear regression analysis of H19 expression with the TF-gene pairs, leading to H19-TF-gene triplets. The effect of copy number variation (CNV) on gene expression was filtered out. (C) Test of the hypothesis that H19 may act as a miRNA sponge in lncRNA-TF-gene triplet regulation. In the low expression H19 case, loss of H19 weakens the inhibition of miRNAs, leading to the downregulation of miRNA target TFs and/or genes; in the high expression H19 case, enhanced H19 inhibits miRNA expression, leading to upregulation of miRNA target TFs and/or genes. ↑, Upregulated; ↓, downregulated.

miR-18a, miR-194-5p, miR-196a, miR-19a, miR-19b-1, miR-200b, miR-200c, miR-20a, miR-22, miR-29a, miR-29b, miR-342-3p, miR-630, miR-874, and miR-92a-1) that were targeted by H19 (Table S4). Next, miRNA target genes of these 29 miRNAs were collected from the miRNA target prediction databases using the SpidermiR R tool.[21] Among these target genes, 85 overlaid with the H19-TF-gene triplets that we identified in the earlier regression analysis. We selected eight triplets (H19-ETS1-*TGFBR2*, H19-FLI1-*TGFBR2*, H19-FOXO1-*TXNIP*, H19-KLF6-*TXNIP*, H19-NFYB-*SP3*, H19-PPARA-*KLF11*, H19-SP1-*TGFBR2*, and H19-STAT3-*KLF11*) and investigated the impact of these 29 miRNAs on them (Table S5). After having confirmed the target TF and non-TF genes of the H19-mediated miRNAs, we mainly focused on two cases (cases 1 and 2) in BRCA (Figure 1C).

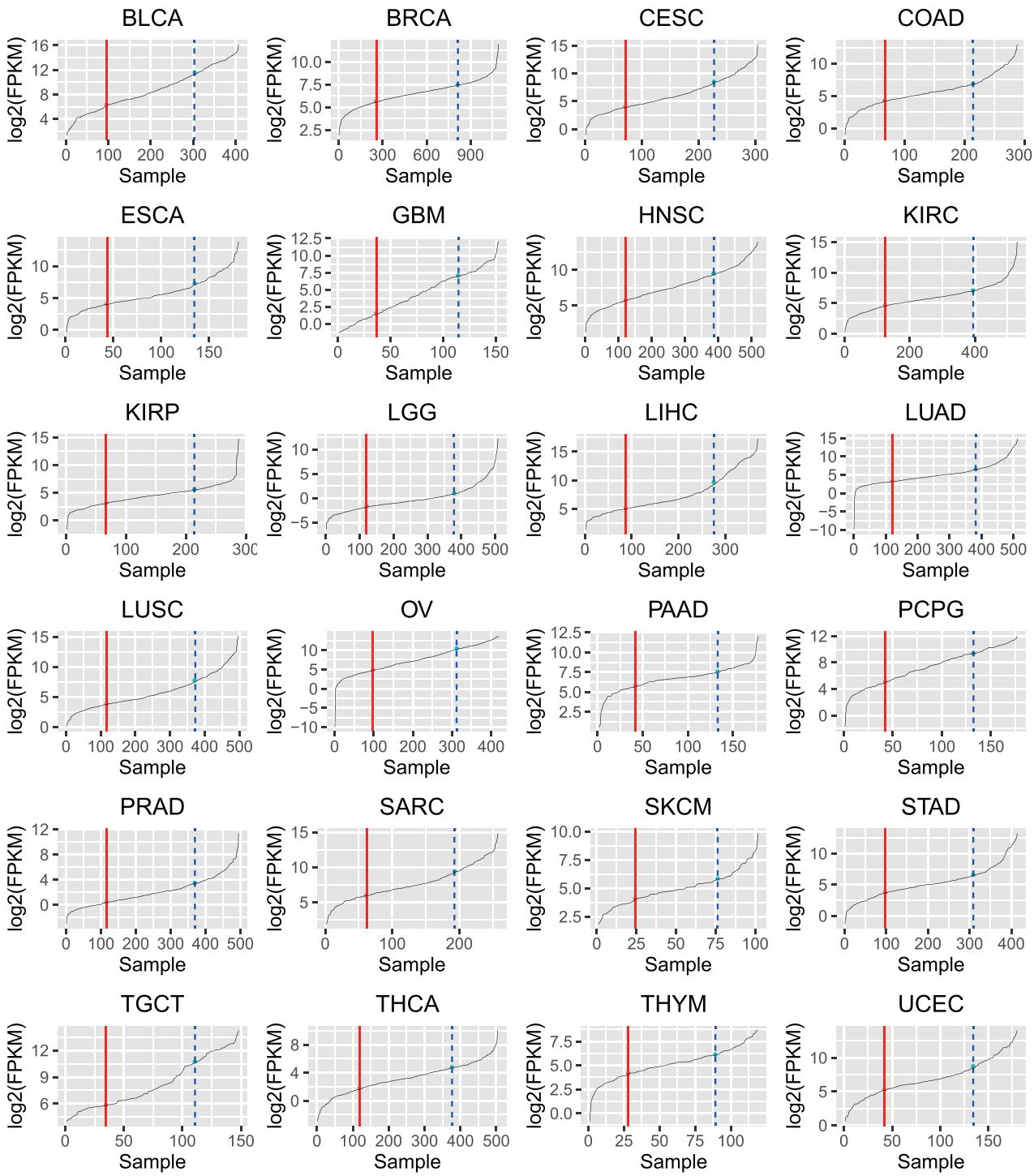

Figure 2. All Tested Cancer Types, with Samples Classified into Low, Moderate, and High Expression Groups by H19 Level

Twenty-four cancer types are represented. Classifications of samples are shown as low (left of the solid line), moderate (middle), and high (right of the dotted line).

Table 1. TF-gene Regulation Interactions Significantly Affected by the Expression Alteration of H19

	Number				
Cancer Type	TFs	Genes	TF-Gene Pairs	TF-Gene Pairs (FDR < 0.05)[a]	Triplets[b]
BLCA	607	2,103	7,723	1	0
BRCA	625	2,198	8,181	874	679
CESC	634	2,161	8,057	0	0
COAD	631	2,187	8,123	148	123
ESCA	655	2,205	8,277	3	1
GBM	636	2,156	7,755	2	0
HNSC	621	2,140	7,866	78	49
KIRC	628	2,172	7,889	246	160
KIRP	591	2,030	7,130	12	5
LGG	589	1,996	6,837	179	112
LIHC	546	1,964	6,988	2	1
LUAD	621	2,233	8,223	610	462
LUSC	653	2,281	8,444	0	0
OV	622	2,159	8,030	0	0
PAAD	651	2,369	8,758	1,165	945
PCPG	562	1,896	6,438	1	0
PRAD	624	2,170	7,889	1	0
SARC	602	2,053	7,353	24	13
SKCM	585	1,982	7,055	0	0
STAD	648	2,252	8,460	207	159
TGCT	620	2,202	8,042	574	466
THCA	587	2,020	7,284	1,095	916
THYM	602	2,055	7,270	0	0
UCEC	625	2152	8,092	0	0

[a]Number of TF-gene pairs with regression FDR <0.05.
[b]Number of triplets after CNV filtration.

Case 1

First, we chose 56 matched (common) H19 low expression group samples along with the corresponding 56 matched normal samples from TCGA BRCA miRNA/TF/non-TF gene expression database. Next, we applied the limma-voom R statistical tool[22] and obtained the lists of upregulated (UPR) and downregulated (DWR) miRNAs/TFs/non-TF genes from this pool. As the result (i.e., for the H19 low expression group samples), we identified five cases as $UPRmiR_{H19low}$ (let-7b, $p = 1.51 \times 10^{-6}$; miR-29a, $p = 6.77 \times 10^{-6}$; miR-200b, $p = 2.67 \times 10^{-3}$; miR-17, $p = 1.42 \times 10^{-2}$; and miR-29b, $p = 4.49 \times 10^{-2}$), one case as $DWRmiR_{H19low}$ (miR-130b, $p = 4.60 \times 10^{-4}$), five cases as $DWRTF_{H19low}$ (ETS1, $p = 8.40 \times 10^{-4}$; PPARA, $p = 8.16 \times 10^{-4}$; STAT3, $p = 3.29 \times 10^{-8}$; NFYB, $p = 4.58 \times 10^{-8}$; and SP1, $p = 4.63 \times 10^{-3}$), and two cases as $DWRGene_{H19low}$ (SP3, $p = 2.84 \times 10^{-14}$; and *TGFBR2*, $p = 2.99 \times 10^{-3}$). Neither TFs nor genes were found as $UPRTF_{H19low}$ or $UPRGene_{H19low}$, respectively (Table 2). The specific definitions of the terms such as $UPRmiR_{H19low}$ and $DWRmiR_{H19low}$ are provided in Materials and Methods.

Case 2

Similarly, we selected 40 matched cancer and normal samples in the H19 high expression group from TCGA BRCA miRNA/TF/non-TF gene expression database. The limma-voom tool was utilized to identify the upregulated and downregulated miRNAs/TFs/non-TF genes in this set. For this H19 high expression group samples, we identified two cases as $UPRmiR_{H19high}$ (miR-141, $p = 5.86 \times 10^{-5}$; and miR-29b, $p = 1.42 \times 10^{-2}$), one case as $DWRmiR_{H19high}$ (miR-200b, $p = 4.45 \times 10^{-3}$), and four cases as $DWRTF_{H19high}$ (SP1, $p = 2.06 \times 10^{-5}$; FL11, $p = 5.65 \times 10^{-4}$; STAT3, $p = 2.86 \times 10^{-3}$; and NFYB, $p = 1.24 \times 10^{-2}$). Neither TFs nor genes were found as $UPRTF_{H19high}$, $UPRGene_{H19high}$, or $DWRGene_{H19high}$ (Table 2).

Statistically Evaluated Interesting Gene Regulation Cascades of Triplets

We proposed two scenarios to explain the regulation between every pair of two participating biomolecules within a triplet under different conditions, as follows: (1) H19 (↓)-$UPRmiR_{H19low}$ (↑)-$DWRTF_{H19low}$/$DWRGene_{H19low}$ (↓): the downregulated expression of H19 causes the upregulation of its target miRNAs, which results in the downregulated expression of their target TFs or genes. (2) H19 (↑)-$DWRmiR_{H19low}$ (↓)-$UPRTF_{H19low}$/$UPRGene_{H19low}$ (↑): the upregulated expression of H19 causes the downregulation of its target miRNAs, which in turn causes upregulated expression of their target TFs or genes. Accordingly, we found five triplets that met the regulation scenarios above: (1) H19 (↓)-let-7b (↑)-SP1 (↓)-*TGFBR2* (↓); (2) H19 (↓)-miR-29a (↑)-ETS1 (↓)-*TGFBR2* (↓); (3) H19 (↓)-miR-200b (↑)-ETS1 (↓)-*TGFBR2* (↓); (4) H19 (↓)-miR-200b (↑)-SP1 (↓)-*TGFBR2* (↓); and (5) H19 (↓)-miR-17 (↑)-STAT3 (↓)-*KLF11* (↓). If we could prove that the status changes met our prediction, it would be helpful to improve the network validation and understanding the overall effect on expression patterns of the miRNAs/TFs/genes due to different expression levels of H19.

Experimental Validation

In order to examine whether H19 serves as a mRNA sponge to regulate the expression of TFs and their downstream targets through antagonizing let-7b, miR-17, miR-200b, and miR-29a,[13,23–28] breast cancer cell lines BT-549, HCC38, MCF7, and MDA-MB-231 were used with ectopically expressing inducible H19.[29] Compared to the control cells, the overexpression of H19 could upregulate the distinct levels of mRNA expression of let-7b/miR-200b-regulated SP1, miR-29a/miR-200b-regulated ETS1, and miR-17-regualted STAT3 in the breast cancer cell lines (Figures 4A–4D). Consequently, the expression of the SP1/ETS1 transcriptional target *TGFBR2* and STAT3 target *KLF11* was also increased to different extents upon H19 induction. However, there was no obvious induction of *TGFBR2* detected in BT549 or MD-MB231 cells, which could be due to the low expression of SP1 and ETS in such cells or dysregulation of other transcriptional co-regulators (Figures 4A and 4C). Taken together, these lines of experimental evidence support our notion of miRNA-mediated

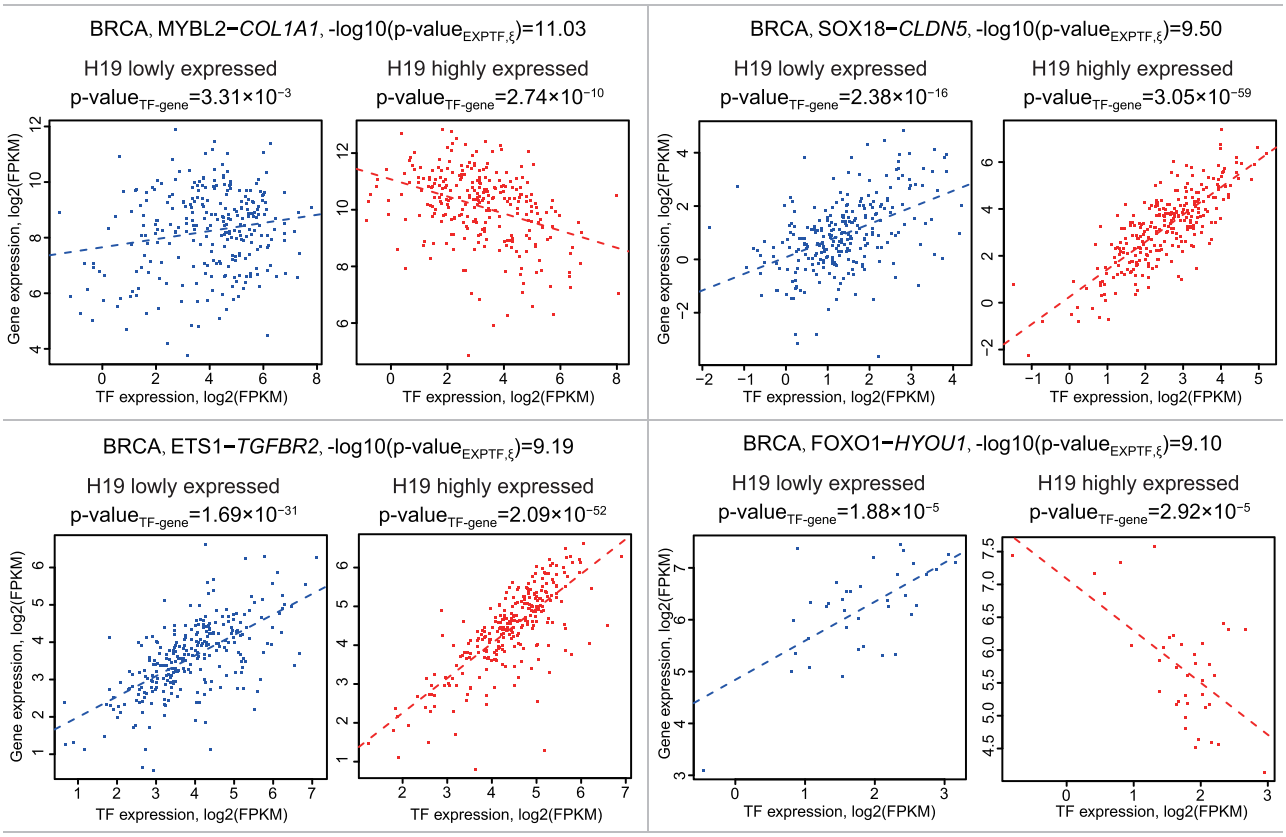

Figure 3. TF-Gene Regulation as Affected by H19 Expression Level

Linear regression was used to evaluate the association between TF expression and its target gene expression.

H19-TF-gene triplet regulation, indicating that H19 upregulates transcription factors and their downstream effects by sequestering miRNAs in cancer.

DISCUSSION

Identification of cancer-associated lncRNAs and uncovering their molecular mechanisms are currently challenging but important tasks. Traditionally, studies of gene expression deregulation and alterations in genomic sequences in tumor cells have led to the identification of cancer-associated lncRNAs.[5,30] Subsequent *in vitro* and *in vivo* studies have directly associated some of the identified lncRNAs with specific cancer phenotypes. In this study, we identified 88 H19-TF-gene triplets based on TCGA pan-cancer data using linear regression models. Most of these TF-gene pairs (93%) had direct or indirect evidence to support their relationship to cancer (Table S3). The remaining TF-gene pairs could serve as potential candidates and warrant further investigation. Our results demonstrate that this analytical, co-regulation-based approach is promising to identify TFs or genes related to cancer. To investigate the potential regulatory mechanism, we hypothesized that H19 acts as a miRNA sponge to diminish certain miRNAs, which in turn preserves the corresponding TF-gene function. Our quantitative real-time PCR experimental results suggest that H19 mediates SP1-*TGFBR2* (TF-gene) regulation through let-7b and miR-200b (miRNA), ETS1-*TGFBR2* regulation through miR-29a and miR-200b, and STAT3-*KLF11* regulation through miR-17 in BT-549, HCC38, MCF7, and MDA-MB-231 breast cancer cell lines. Our approach can help identify lncRNAs, miRNAs, TFs, and genes that are potentially cancer associated and uncover their complex regulatory mechanisms. This approach effectively extends the previous miRNA-TF-gene co-regulation approach that has been well studied in various cancer types or other disease.[31–33]

TRANSFAC and TRRUST are representative databases for annotations of TF-target gene pairs. The annotations are based on stringent criteria, including both experimental evidence and statistical tests. After filtration, we obtained 13,263 TF-target gene pairs from these two databases. Although the number of TF-gene pairs is smaller than that from other databases, such as ENCODE,[34] we decided to use them for reducing false-positive results. For the large-scale data analysis, false-positive data would have more potential problems than false-negative data, while our goal is to find those enriched signals (e.g., regulatory networks) that have reliable evidence.

The samples studied were classified into three groups by H19 expression, that is, low, middle, and high. In such a way, we could

Table 2. Genes, TFs, and miRNAs Were Upregulated or Downregulated.

Group	Molecule		Log_2FC	p	Regulation
H19 lowly expressed	miRNA	let-7b	0.92885	1.51×10^{-6}	upregulated
		miR-130b	−3.6149	4.60×10^{-4}	downregulated
		miR-17	0.90485	1.42×10^{-2}	upregulated
		miR-200b	2.54065	2.67×10^{-3}	upregulated
		miR-29a	1.903	6.78×10^{-6}	upregulated
		miR-29b-2	2.4692	4.49×10^{-2}	upregulated
	TF	ETS1	−1.66925	8.41×10^{-4}	downregulated
		NFYB	−2.8769	4.58×10^{-8}	downregulated
		PPARA	−2.2694	8.16×10^{-4}	downregulated
		SP1	−0.89175	4.64×10^{-3}	downregulated
		SP3	−1.1854	2.85×10^{-14}	downregulated
		STAT3	−1.9026	3.29×10^{-8}	downregulated
	gene	*TGFBR2*	−2.41715	3.00×10^{-3}	downregulated
H19 highly expressed	miRNA	miR-141	1.12925	5.86×10^{-5}	upregulated
		miR-200b	−2.5865	4.46×10^{-3}	downregulated
		miR-29b-2	1.13575	1.42×10^{-2}	upregulated
	TF	NFYB	−1.8413	1.25×10^{-2}	downregulated
		SP1	−0.9865	2.07×10^{-5}	downregulated
		SP3	0.0436	6.47×10^{-8}	upregulated
		STAT3	−1.3972	2.86×10^{-3}	downregulated
	gene	*KFLI1*	−0.992	5.65×10^{-4}	downregulated

FC, fold change.

observe the TF-gene status change along with the changes of H19 expression. For example, we used linear regression to describe the association between ETS1 (TF) expression and *TGFBR2* expression. The p values of linear regression were 1.69×10^{-31} in the H19 low expression group and 2.09×10^{-52} in the H19 high expression group. Additionally, this classification method significantly improved ETS1-*TGFBR2* regulation ($p < 10^{-9}$). This suggests that such an integrative grouping approach is effective in investigating the relationship between variation of lncRNA expression and TF-gene regulation.

Figure 2 shows a smooth slope of the curves for the patients with intermediate levels of H19 expression. This is because all of the samples were ordered by their H19 expression, and most of these samples had H19 expression without large fluctuation. For the H19 highly or lowly expressed groups, the curves displayed sharp slopes. These sharp slopes suggested that H19 was expressed with strong variation in these two groups, which is biologically useful to investigate the effect of H19 expression changes on TF-gene regulation.

Linear regression is a widely used approach to predict the output values of a biological process under specific conditions.[35,36] Some studies use linear regression to predict the expression of genes.[37] However, to our knowledge, there are few studies that use linear regression to investigate the effect of lncRNAs on TF-gene regulation.

In this study, we used a linear regression model that was fit on non-TF gene expression changes in tumor samples as the response variable using a linear combination of the input variables, including TF expression, sample groups distinguished by H19 expression level, and interaction between TF and group (Equation 2). Within a H19-TF-gene triplet, this requires the TF to regulate the target gene, and H19 to affect TF expression and consequently regulate the target gene. Therefore, we required that such triplets should satisfy both $FDR_{EXPTF,\xi:GroupH19} < 0.05$ and $p_{EXPTF,\xi} < 0.05$.

CNVs contribute largely to gene expression.[38] Structural variants, including CNVs, in cancer genomes can lead to significantly reduced or increased gene expression in cancer cells.[39] Therefore, we removed the effect of CNVs on gene expression and reconsidered the mediation of H19 on the TF-gene regulation relationship.

The H19-let7b-SP1-*TGFBR2* interaction we identified by our bioinformatics approach was supported by actual biological experiments (Figure 4E). The lncRNA H19 can act as a sponge to bind let-7b to mediate breast cancer cell plasticity.[28] The let7b-SP1 interaction was verified from chimeric reads.[40] DNA precipitation, electrophoretic mobility shift assays, and promoter analysis confirmed that the *TGFBR2* promoter was bound by SP1.[41]

We observed the expression variation of SP1 and *TFFBR2* in the presence of a high level of H19 in breast cancer cell lines. The H19-let7b-SP1-*TGFBR2* interaction can be used to elucidate such a correlation. The abnormal expression of H19 and let-7b might lead to abnormal expression of SP1 and *TGFBR2* and, consequently, lead to the development of breast cancer. The molecules included in the interaction can provide candidate diagnosis biomarkers and targets for therapy.

The synergistic regulatory relationship between lncRNAs, miRNAs, and protein-coding RNAs implemented in our approach can better infer the potential function of non-coding RNAs. The H19-let7b-SP1-*TGFBR2* interaction can be used to interpret the potential functions of lncRNAs and miRNAs (Figure 4E). In mice, an overexpression of SP1 has been reported to suppress migratory and invasive abilities of breast cancer cells.[42] *TGFBR2* is upregulated in basal-like breast cancer cell lines.[43] The minor allele homozygote (GG) of rs1078985, an intronic single nucleotide polymorphism (SNP) in *TGFBR2*, had a 24% lower risk of having breast cancer compared with major allele carriers (AG or AA).[44] H19 and let-7b interact with SP1 and *TGFBR2*. Therefore, H19 and let-7b might be involved in breast cancer in terms of cell migratory and invasive abilities, and they could serve as potential biomarkers. This regulation can also be verified by the following evidence in literature: (1) H19 enhances breast cancer cell proliferation through positive control by E2F1;[45] (2) overexpression of an ectopic H19 gene promotes the tumorigenic properties of breast cancer cells;[46] and (3) let-7b expression in breast cancer patients was inversely associated with tumor lymph node metastasis and patient overall survival.[47]

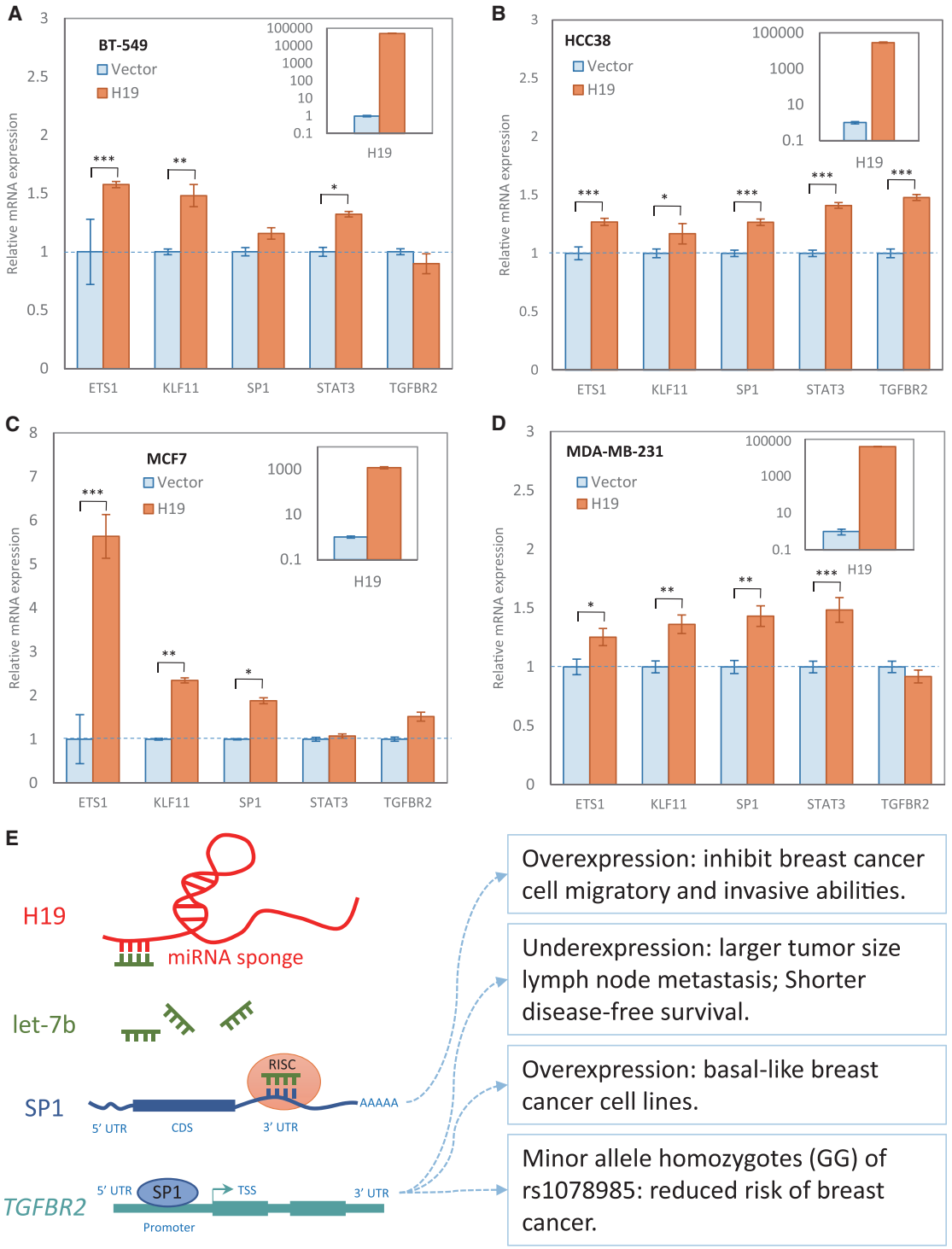

Figure 4. H19 Functions as a miRNA Sponge to Relieve miRNA-Mediated Suppression of Transcription Factors and Their Targets

Transcription factor targets included H19-SP1-*TGFBR2*, H19-ETS1-*TGFBR2*, and H19-STAT3-*KLF11*. (A–D) H19 led to an upregulated expression of let-7b/miR-17/miR-29a/miR-200b-controlled *SP1*, *ETS1* and *STAT3* (three TF genes), and their transcriptional targets *TGFBR2* and *KLF11* in four breast cancer cell lines (A, BT-549; B, HCC38; C, MCF7; and D, MDA-MB-231). All samples were analyzed in triplicate and normalized to GAPDH expression. The top-right panel shows relative H19 expression. Quantitative real-time PCR data are presented as mean ± SE (standard error). *p < 0.05, **p < 0.01, ***p < 0.001. (E) The H19-let7b-SP1-*TGFBR2* interaction and its

(legend continued on next page)

The study has several limitations, and there is scope for future work to be carried out. For instance, the current work only focused on one lncRNA, H19. In fact, our approach can be applied to any other lncRNAs. We focused on H19 in this study because it is one of the most promising lncRNAs and is highly expressed in most of the cancer types we examined. Moreover, this study cannot exclude false-positive results: some H19-TF-gene triplets are possibly not the real or impactful regulatory correlations, and some TFs or genes may not directly cause or be related to the specific cancer under investigation. To address this problem, we can use a lower FDR threshold to minimize a false-positive rate or validate them using various biological experiments. Finally, cancer is highly heterogeneous, and its development is dynamic in the cellular system. Our approach, like many others, cannot consider real-time or dynamic regulation in cancer and matched normal cells. However, our approach of uncovering lncRNA molecular functions contributes to identify and functionally annotate these cancer related genes, making these genes the attractive targets. These regulatory units can also better explain cancer biology. Finally, in this study, we first examined lncRNA (H19) expression in pan-cancer and then explored how it potentially regulated genes, including TF genes. Alternatively, we may analyze H19-miRNA pairs first and examine which miRNAs might be altered by H19 in the datasets. We will explore this analytical approach in the future.

MATERIALS AND METHODS

Data Collection

TCGA pan-cancer data consisting of 24 cancer types such as BLCA, BRCA, CESC, COAD, ESCA, GBM, HNSC, KIRC, KIRP, LGG, LIHC, LUAD, LUSC, OV, PAAD, PCPG, PRAD, SARC, SKCM, STAD, TGCT, THCA, THYM, and UCEC (full names are summarized in Table S1), whose numbers of samples were at least 90, were used for this study (Figure 1A). Tissue-specific data contained RSEM[48] gene FPKM data that included the lncRNA expression profile, TF expression profile, and gene (non-TF) expression profile. The data were collected through the UCSC (University of California, Santa Cruz) Xena database (https://xenabrowser.net/). The BRCA RSEM gene FPKM expression data contained a total of 60,499 genes and a total of 1,212 samples. For the remaining tissue-specific data, such information was provided in the UCSC Xena database (Table S1). An expression dataset of miRNAs was also collected from the UCSC Xena database. It consisted of 744 miRNAs and 10,818 samples. The curated clinical (phenotype) data that provided the list of the primary tumor samples were collected from the UCSC Xena database. In addition, the interactions between TFs and genes were collected from TRANSFAC (release 2016.4)[19] and TRRUST (version 2.0).[20] Furthermore, the interactions between miRNAs and (validated or predicted) target genes were obtained from the SpidermiR R tool[21] by using six target prediction databases. Among these databases, the miRTar[49] and miRWalk[50] databases provided only validated target genes, whereas the DIANA,[51] miRanda,[52] PicTar,[53] and TargetScan[54] databases supplied predicted target genes. H19-targeted miRNAs were identified from the published literature. The detailed descriptions regarding the association of H19 and its targeted miRNAs are demonstrated in Table S4.

Data Preprocessing

First, the biomolecules (lncRNAs, TFs, and genes) whose FPKM score of at least 50% of samples was greater than 1 were selected, whereas the remaining biomolecules were excluded from further analyses (Figure 1A). After this step, we partitioned the whole gene expression data into several subparts according to the category of the genes such as filtered TF expression data, filtered non-TF gene expression data, and filtered lncRNA (H19) expression data. The interactions between TFs and target genes were determined from two well-known databases, TRANSFAC (release 2016.4)[19] and TRRUST (version 2.0).[20] We first obtained 800 TFs and 3,470 genes from the TRANSFAC and TRRUST databases and then applied these TFs and genes to filter results from these databases and obtained 13,263 TF-target gene pairs. Using the resultant interactions, we further filtered the TF expression data in a way such that the participating (interacting) TFs belonging to the TF-gene interactions (obtained by TRANSFAC and TRRUST), which were listed in the TF expression data, were only considered in the resultant filtered TF expression data. Similarly, we again filtered the non-TF gene expression data in a way such that the target genes belonging to the TF-gene interactions that were mentioned in the non-TF gene expression data were only selected in the resultant filtered non-TF gene expression data. Next, to determine the type of expression of existing samples, we ordered the expression data of H19 underlying all of these samples based on the expression values from low to high. Here, a certain percentage of the lowly expressed samples was considered as the first group (lowly expressed group), whereas the same percentage of the highly expressed samples was treated as the second group (highly expressed group). The remaining samples were used as the third group ("middle" group). According to the resultant class labels of H19 samples, the samples of the other molecules such as gene and TF had been classified.

Linear Regression and Copy Number Variation Factor

CNVs contribute largely to gene expression.[38] We removed the effect of CNVs on gene expression and then reconsidered the mediation of H19 on the TF-gene regulation relationship (Figure 1B). First, we obtained the residuals of expression of the TF and genes through the linear regression ("Stats" R tool)[55] using Equation 1, and then used the residuals of expression of the TF and genes to evaluate the mediation of H19 on the TF-gene regulation relationship through Equation 2 as follows:

$$EXP_{TF/Non-TF\ Gene} \sim CNV_{TF/Non-TF\ Gene}, \quad (1)$$

involvement with breast cancer. H19 acts as a miRNA sponge for let-7b that targets TF gene *SP1*. Let-7b inhibits the expression of *SP1*, whose overexpression inhibits breast cancer cell migratory and invasive abilities. SP1 regulates *TGFBR2*, whose abnormal expression or mutation is related to breast cancer. CDS, coding DNA sequence; RISC, RNA-induced silencing complex; TSS, transcription start site; UTR, untranslated region.

where $EXP_{TF/Gene}$ symbolizes the expression data of TF or gene, and $CNV_{TF/Gene}$ denotes the CNV data of the TF or gene; and

$$EXP_{Non-TF\ Gene,\xi} \sim EXP_{TF,\xi} + Group_{H19} + EXP_{TF,\xi} : Group_{H19}, \quad (2)$$

where $EXP_{Gene,\xi}$ refers to the expression data of the gene after removing the effect of CNVs, $EXP_{TF,\xi}$ denotes the expression data of TF after removing the effect of CNVs, and $Group_{H19}$ symbolizes the class labels of samples (low, middle, and high), whereas $EXP_{TF,\xi}$:$Group_{H19}$ refers to the interaction effect between the TF and the group. Finally, we determined the triplets using the criteria (1) the adjusted p value should be less than 0.05 ($FDR_{EXPTF,\xi:GroupH19} < 0.05$), and (2) the p value corresponding to coefficient of $EXP_{TF,\xi}$ should be less than 0.05 ($p_{EXPTF,\xi} < 0.05$).

Regulatory Mechanism

After obtaining the triplets (H19-TF-gene) through linear regression, we conducted an extensive literature search to determine the interactions between H19 and miRNAs. We identified target miRNAs that interacted with H19. Next, the target genes (including TFs as well as non-TF genes) of the employing miRNAs had been identified using the SpidermiR R tool.[21] After finding the target genes of the H19-mediated miRNAs, we had mainly focused on two cases (Figure 1C), that is, cases 1 and 2.

Case 1

First we chose the matched (common) H19 lowly expressed group samples along with the matched normal samples from TCGA BRCA miRNA/TF/non-TF gene expression data. Then, we applied the limma-voom R statistical tool[22] to determine which miRNAs/TFs/non-TF genes were upregulated (denoted as $UPRmiR_{H19low}$, $UPRTFH_{19low}$, and $UPRGene_{H19low}$, respectively), downregulated (denoted as $DWRmiR_{H19low}$, $DWRTF_{H19low}$, and $DWRGene_{H19low}$, respectively), or not differentially expressed.

Case 2

Similarly, we selected the matched (common) H19 highly expressed group samples along with the matched normal samples from TCGA BRCA miRNA or gene expression data. Then, we used the limma-voom R statistical tool[22] to determine which miRNAs or genes were upregulated ($UPRMiR_{H19high}$, $UPRTF_{H19high}$, and $UPRGene_{H19lhigh}$, respectively), downregulated ($DWRMiR_{H19high}$, $DWRTF_{H19high}$, and $DWRGene_{H19high}$, respectively), or not differentially expressed.

Cell Lines

All cell lines were obtained from the American Type Culture Collection (Manassas, VA, USA), independently validated by STR DNA fingerprinting at the University of Texas MD Anderson Cancer Center (Houston, TX, USA) and determined to be negative for mycoplasma contamination. HEK293T (RRID:CVCL_0063) cells and human breast cancer cell lines BT-549 (RRID:CVCL_1092), HCC38 (RRID:CVCL_1267), MCF7 (RRID:CVCL_0031), and MDA-MB-231 (RRID:CVCL_0062) were cultured in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum (FBS) supplemented with 100 IU/mL penicillin and 100 μg/mL streptomycin. Cells were maintained at 37°C in a humidified 5% CO_2 incubator.

Generation of H19 Lentivirus and Infection

2×10^6 HEK293T cells were seeded in 10-cm tissue culture plates and maintained in DMEM complete medium for 20 h. Media were discarded and replaced with 3 mL of Opti-MEM. 6 μg of pCMV-dR8.2-dvpr, 2 μg of pCMV-VSV-dvpr, 8 μg of TetO-FUW H19[29] or rtTA, and 32 μg of polyethyleneimine (PEI) were added into 400 μL of Opti-MEM. The transfection mixture was incubated at room temperature for 15 min and then added into HEK293T cells. After a 3-h incubation, 3 mL of DMEM complete medium was added. After overnight incubation, the medium was replaced with 6 mL of DMEM complete medium. The viruses were collected at 48–72 h after transfection and concentrated by Amicon Ultra-15 (Millipore). For viral infection, BT-549, HCC38, MCF7, and MDA-MB-231 cells were seeded, respectively, in six-well plates and infected with either control or H19 lentivirus. One μg/mL doxycycline was used to turn on the expression of H19. After 48–72 h of induction, cells were collected to examine H19, *ETS1*, *KLF11*, *SP1*, *STAT3*, and *TGFBR2* gene expression for quantitative real-time PCR.

Quantitative Real-Time PCR

Total RNA was extracted using TRIzol reagent (Thermo Fisher Scientific, CA, USA) following the manufacturer's instructions. The RNA samples were qualified using a NanoDrop spectrophotometer (Thermo Fisher Scientific, CA, USA). 1 μg of mRNA was used for reverse transcription using the iScript cDNA synthesis kit (Bio-Rad, CA, USA). A 20-μL quantitative real-time PCR reaction solution was composed of 1 μL of cDNA, 1 μL each of 10 μM forward and reverse qPCR primers, 10 μL of SYBR Green PCR master mix (Bio-Rad, CA, USA), and 7 μL of RT-PCR-grade water. qPCR reactions were performed on a CFX96 machine (Bio-Rad). All reactions were run in triplicate. The relative ETS1, KLF11, SP1, STAT3, and TGFBR2 mRNA expression levels were normalized to their corresponding GAPDH mRNA expression. Primers used for quantitative real-time PCR detection are listed in Table S6.

Statistical Analysis

The limma-voom R statistical tool[22] using an empirical Bayes statistical test was applied to identify the differentially expressed miRNAs, TFs, and non-TFs in the (common) H19 lowly or highly expressed group samples versus the matched normal samples using TCGA breast cancer gene miRNA and mRNA expression datasets. For quantitative real-time PCR, all grouped data are presented as mean ± SE (standard error). A Student's t test was used to assess statistical significance between the two groups.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.omtn.2020.05.028.

AUTHOR CONTRIBUTIONS

Z.Z. and P.J. conceived the study. A.L. and S.M. collected the data and conducted the bioinformatics analysis. H.L. and D.-F.L. conducted laboratory experiments. A.L., S.M., H.L., D.-F.L., and Z.Z. verified the results and wrote the manuscript. All authors revised and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no competing interests.

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Supplemental Information

H19, a Long Non-coding RNA, Mediates Transcription Factors and Target Genes through Interference of MicroRNAs in Pan-Cancer

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SUPPLEMENTARY FILES

Figure S1. H19 highly expressed across pan-cancer except for brain lower grade glioma (LGG), prostate adenocarcinoma (PRAD), and thyroid carcinoma (THCA).

Figure S2. TF-gene regulation was affected by H19 expression level.

Table S1. Number of samples and genes across the 24 cancer types based on TCGA data.

Table S2. Eighty-eight H19-TF-gene regulation triplets identified in at least two cancer types.

Table S3. 173 of 186 (93%) TF-gene pairs had direct or indirect evidence to support their relation to cancer (Table S3). The remaining 13 TF-gene pairs might be potential candidates for cancer research.

Table S4. The list of 29 H19 target miRNAs with evidence in literature.

Table S5. Regulation of 29 miRNAs in eight triplets. In the H19-ETS1-*TGFBR2* sheet, we list all the 29 miRNAs and their targets (TFs and genes). Some of the targets were predicted and then verified. In the H19-ETS1-*TGFBR2* table, TFs are marked in yellow if miRNAs target them, and genes are marked in red if miRNAs target them.

Table S6. Primers for qRT-PCR.

Figure S1. H19 highly expressed across pan-cancer except for brain lower grade glioma (LGG), prostate adenocarcinoma (PRAD), and thyroid carcinoma (THCA).

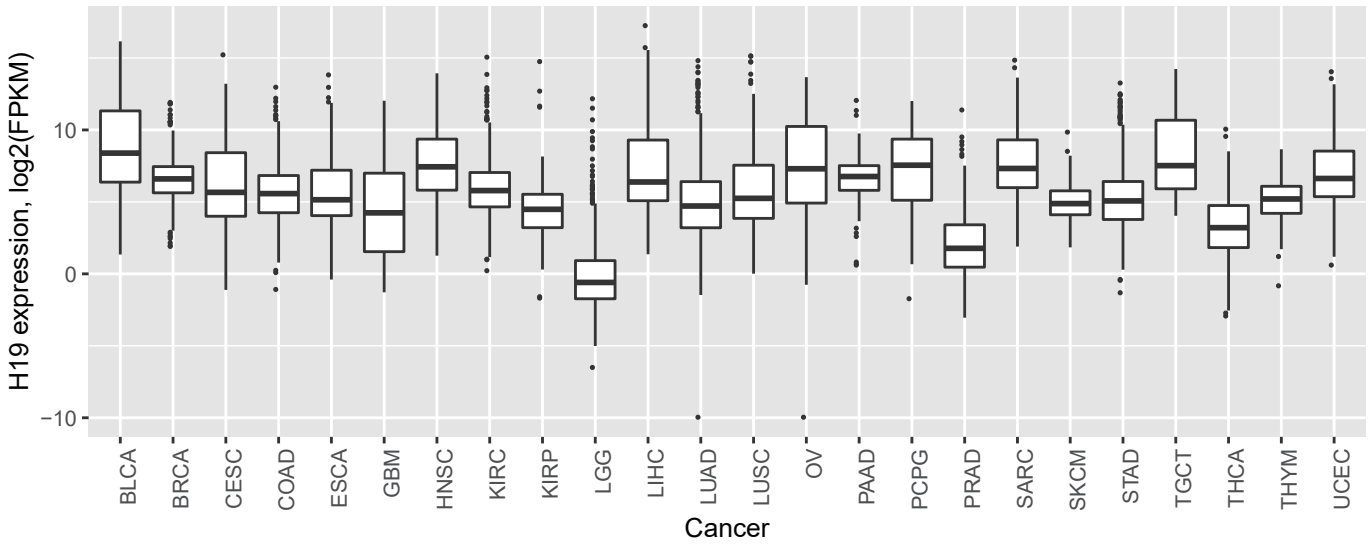
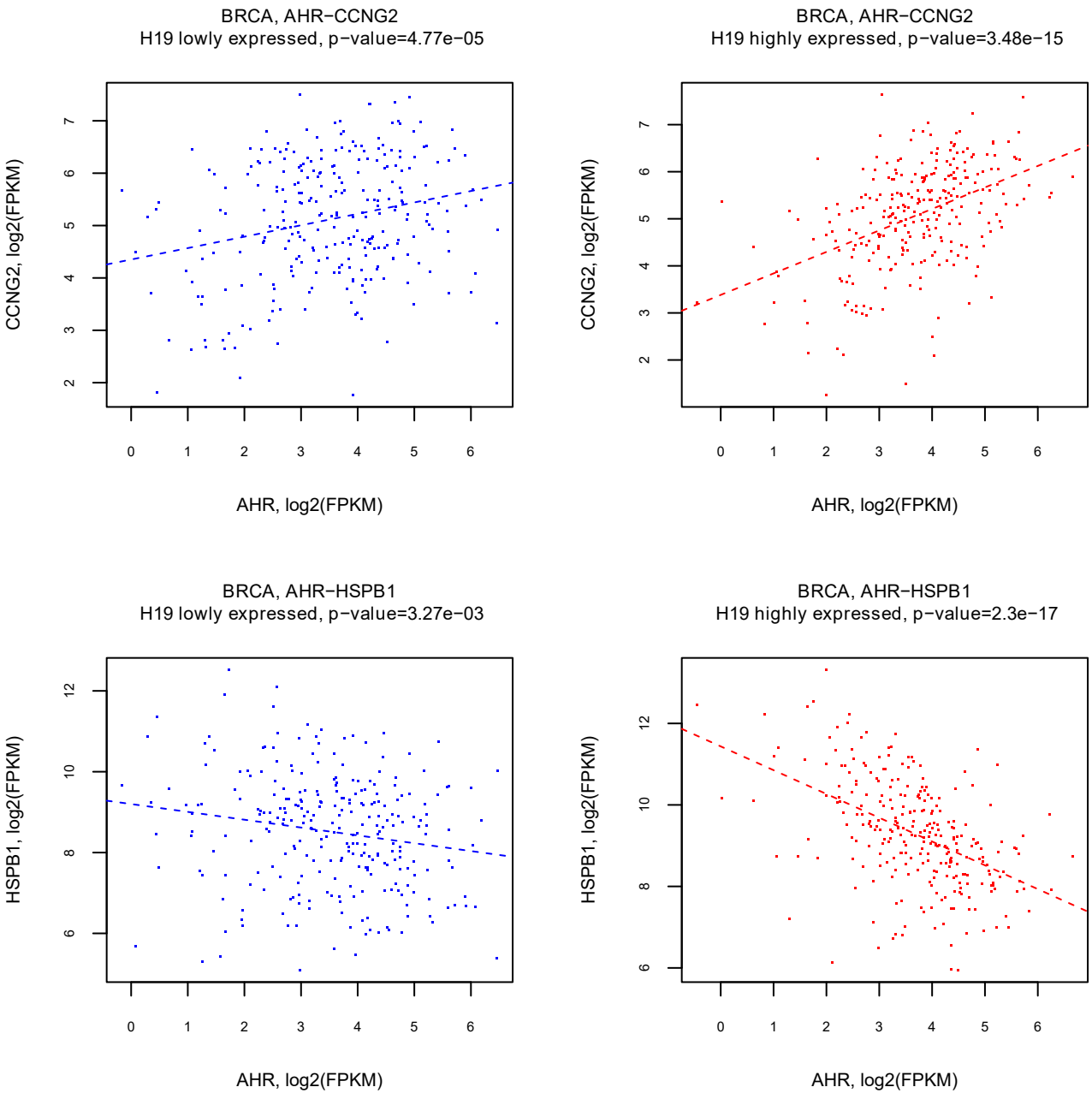
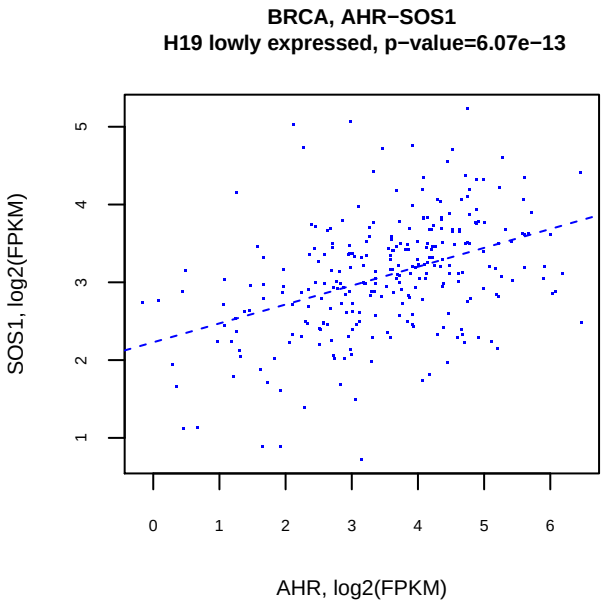
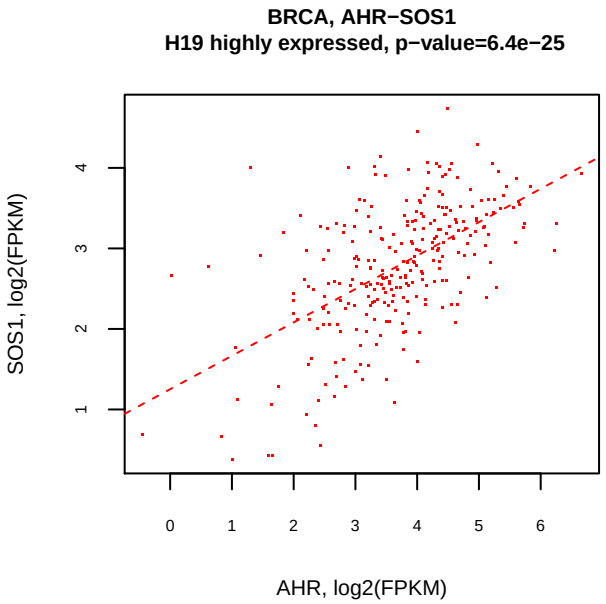
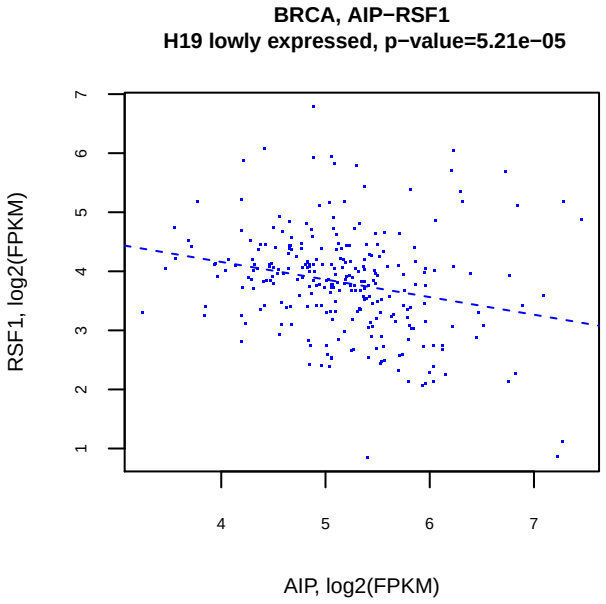


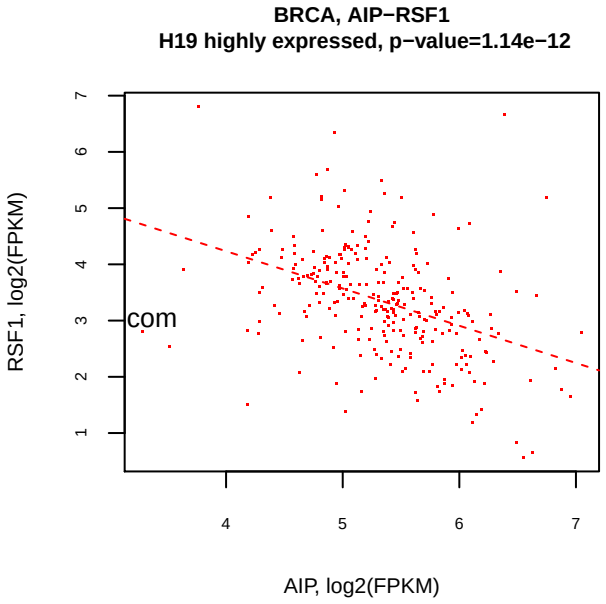
Figure S2. TF-gene regulation was affected by H19 expression level.




BRCA, AHR−SOS1
H19 lowly expressed, p−value=6.07e−13
SOS1, log2(FPKM)
AHR, log2(FPKM)


BRCA, AHR−SOS1
H19 highly expressed, p−value=6.4e−25
SOS1, log2(FPKM)
AHR, log2(FPKM)


BRCA, AIP−RSF1
H19 lowly expressed, p−value=5.21e−05
RSF1, log2(FPKM)
AIP, log2(FPKM)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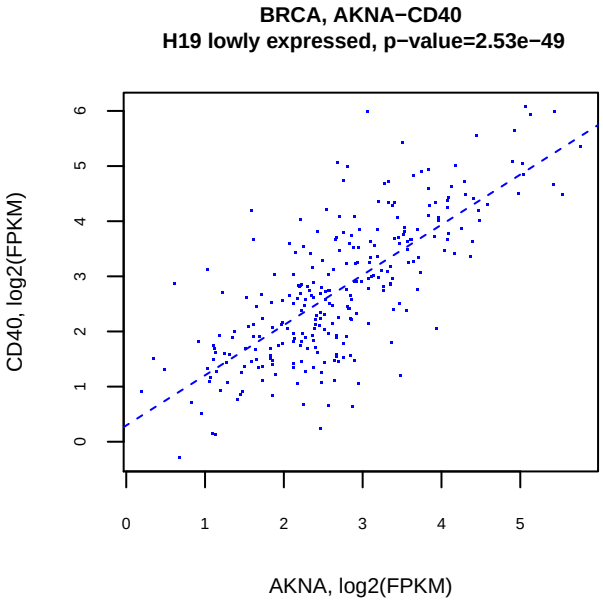
H19 highly expressed, p−value=1.14e−12
RSF1, log2(FPKM)
AIP, log2(FPKM)


BRCA, AKNA−CD40
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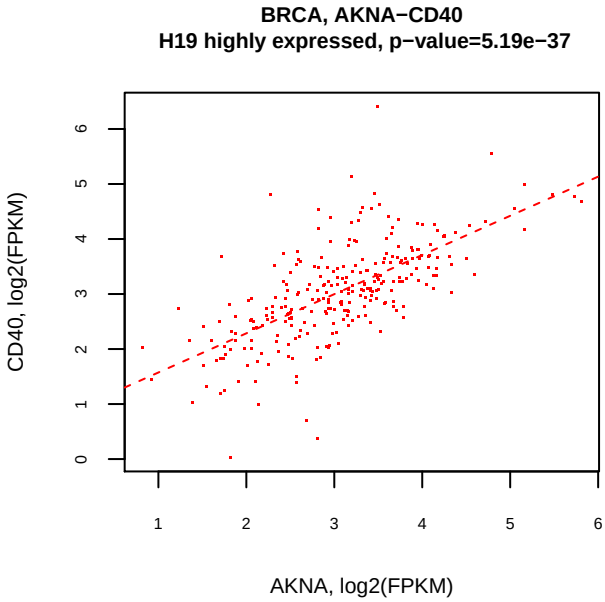
CD40, log2(FPKM)
AKNA, log2(FPKM)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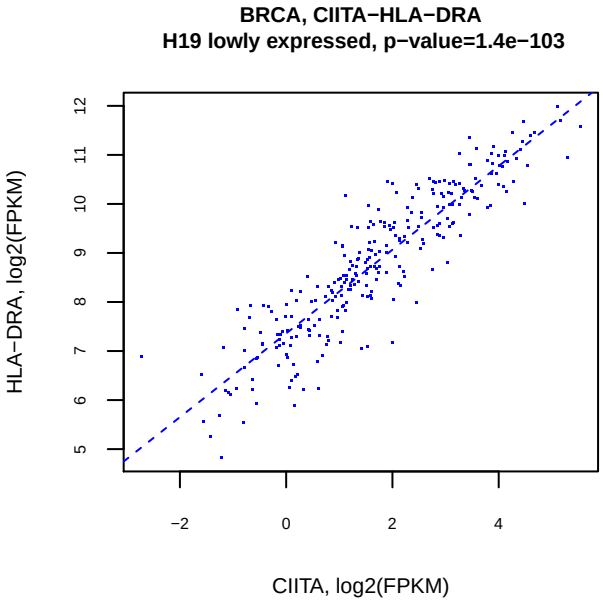
CD40, log2(FPKM)
AKNA, log2(FPKM)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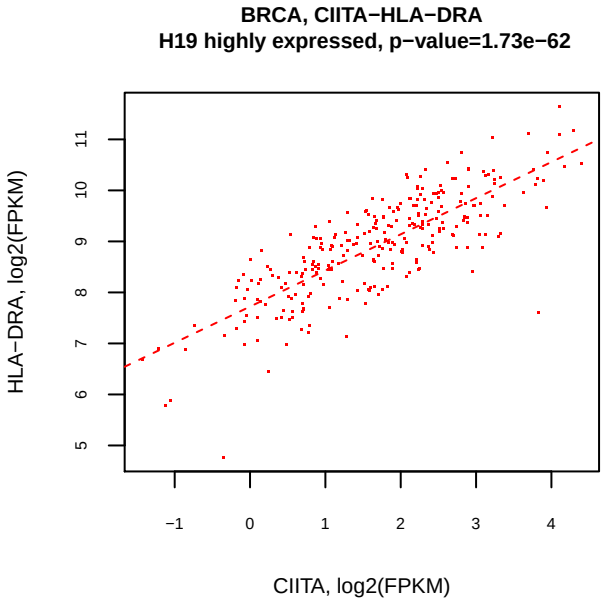
HLA−DRA, log2(FPKM)
CIITA, log2(FPKM)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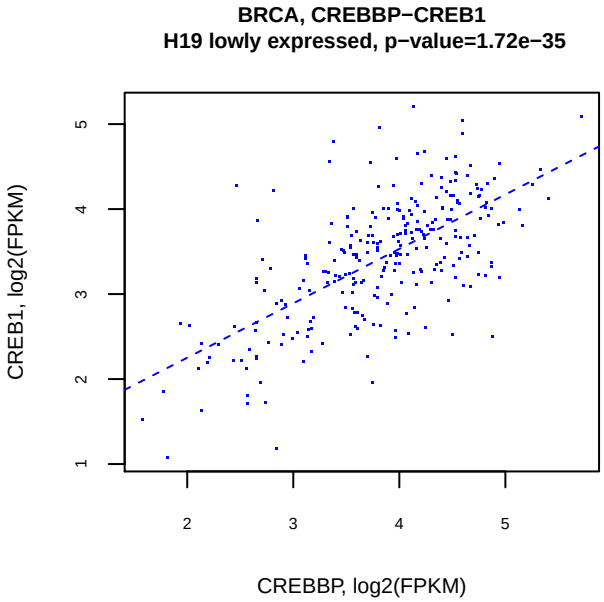
HLA−DRA, log2(FPKM)
CIITA, log2(FPKM)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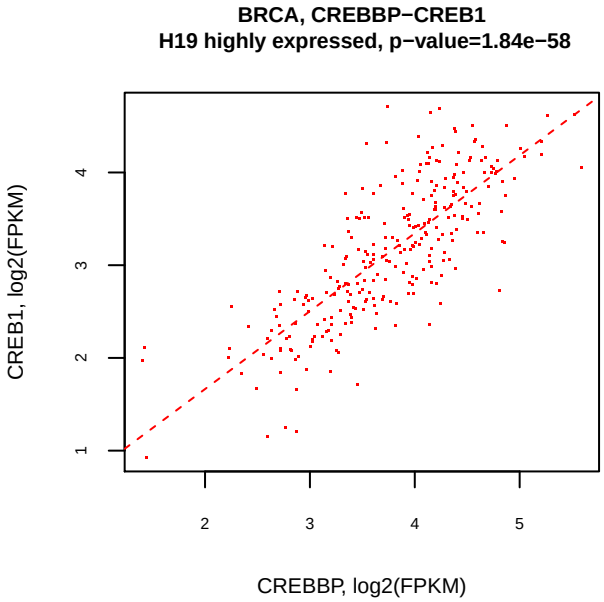
H19 lowly expressed, p−value=1.72e−35
CREB1, log2(FPKM)
CREBBP, log2(FPKM)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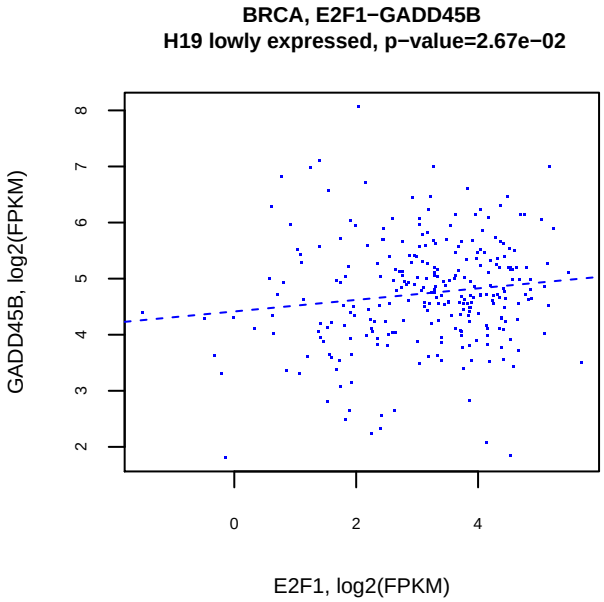
H19 highly expressed, p−value=1.84e−58
CREB1, log2(FPKM)
CREBBP, log2(FPKM)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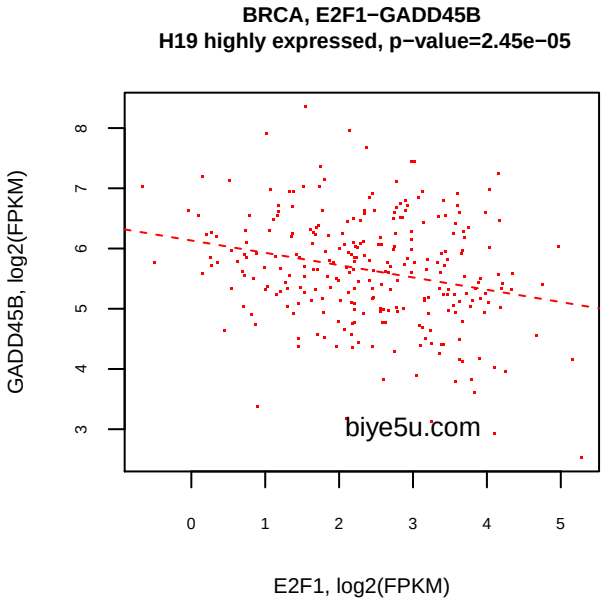
H19 lowly expressed, p−value=2.67e−02
GADD45B, log2(FPKM)
E2F1, log2(FPKM)


BRCA, E2F1−GADD45B
H19 highly expressed, p−value=2.45e−05
GADD45B, log2(FPKM)
E2F1, log2(FPKM)
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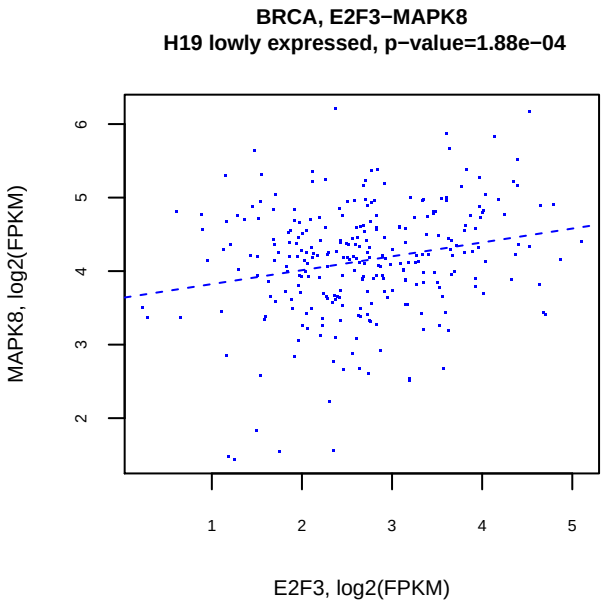
BRCA, E2F3−MAPK8
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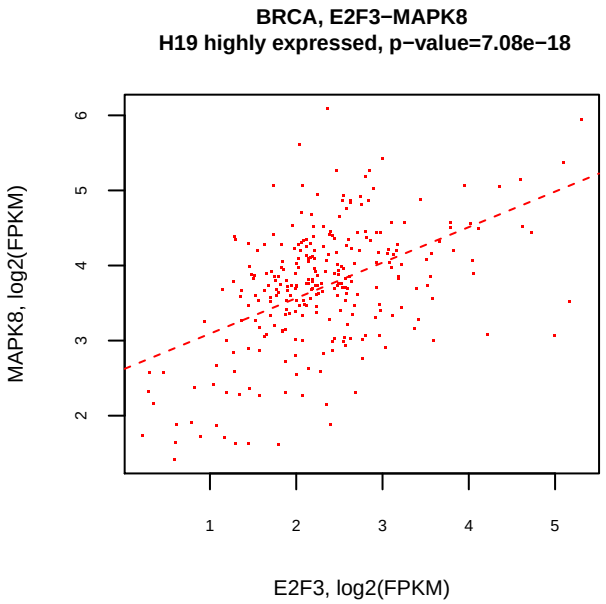
MAPK8, log2(FPKM)
E2F3, log2(FPKM)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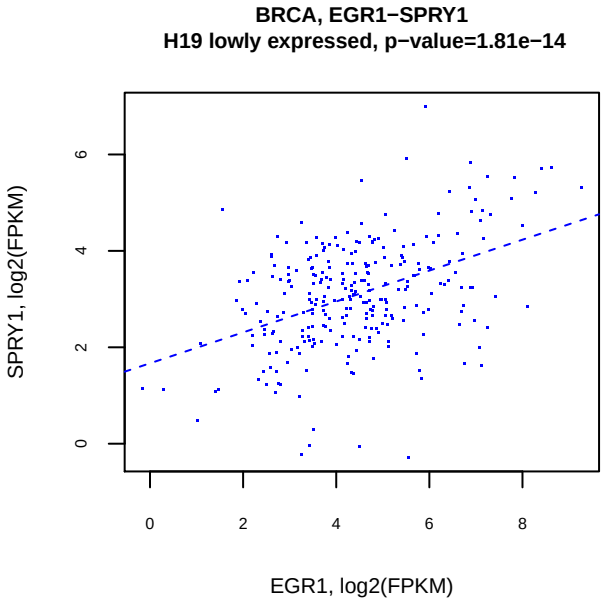
MAPK8, log2(FPKM)
E2F3, log2(FPKM)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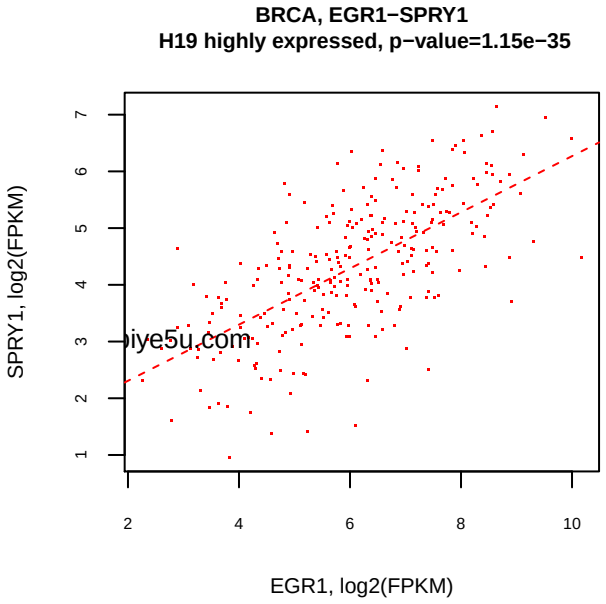
SPRY1, log2(FPKM)
EGR1, log2(FPKM)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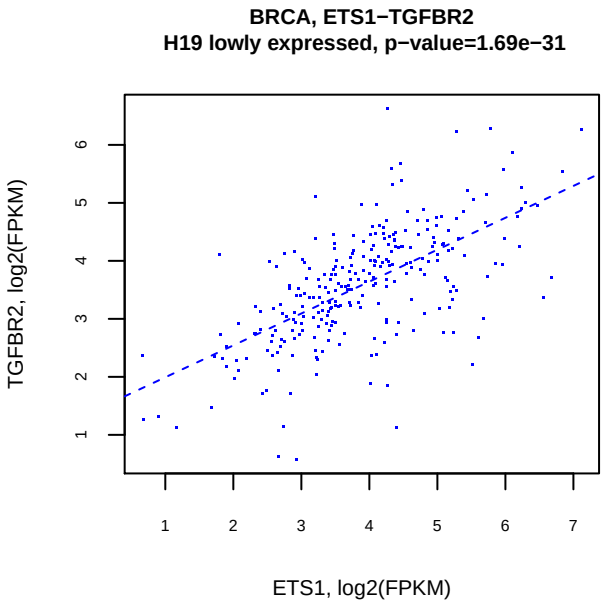
EGR1, log2(FPKM)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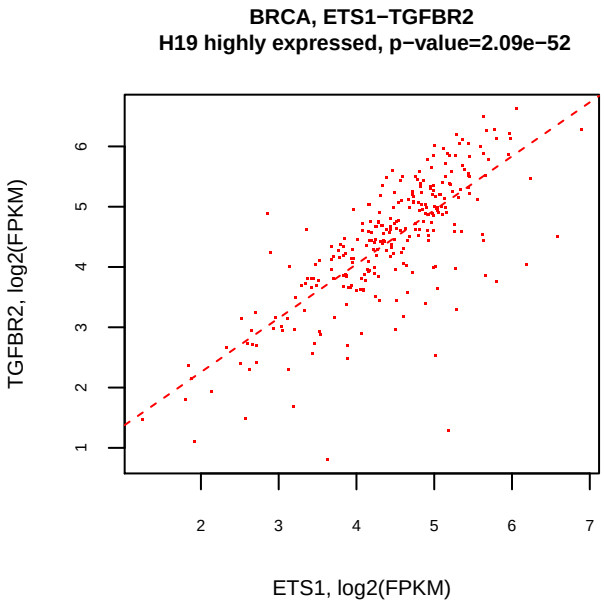
H19 lowly expressed, p−value=1.69e−31
TGFBR2, log2(FPKM)
ETS1, log2(FPKM)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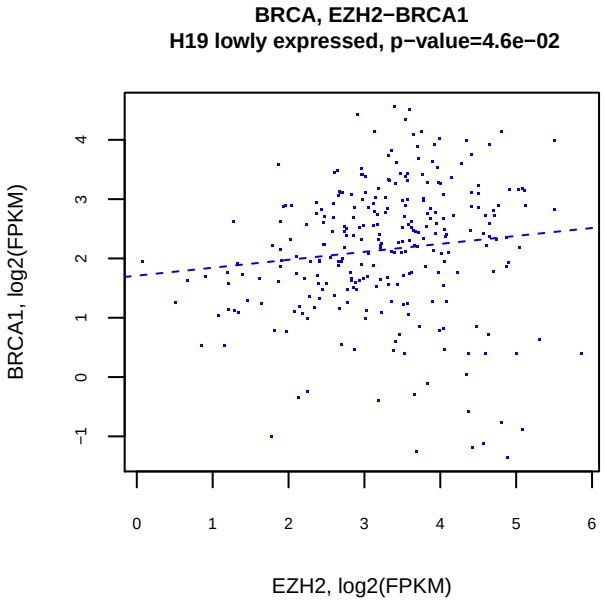
TGFBR2, log2(FPKM)
ETS1, log2(FPKM)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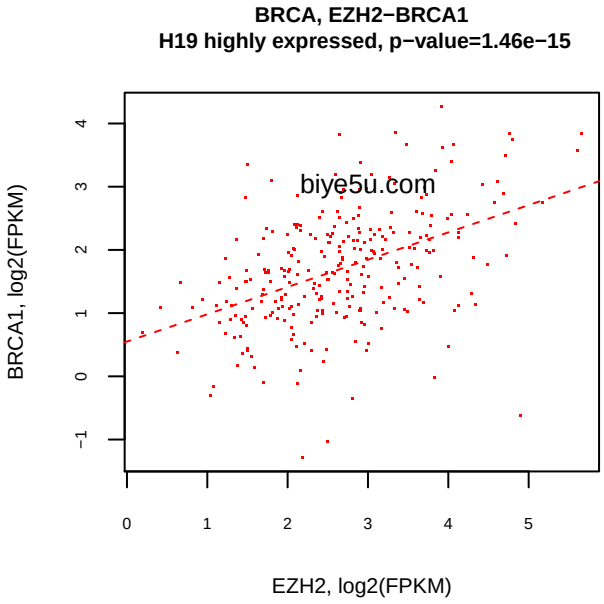
BRCA1, log2(FPKM)
EZH2, log2(FPKM)


BRCA, EZH2−BRCA1
H19 highly expressed, p−value=1.46e−15
BRCA1, log2(FPKM)
EZH2, log2(FPKM)
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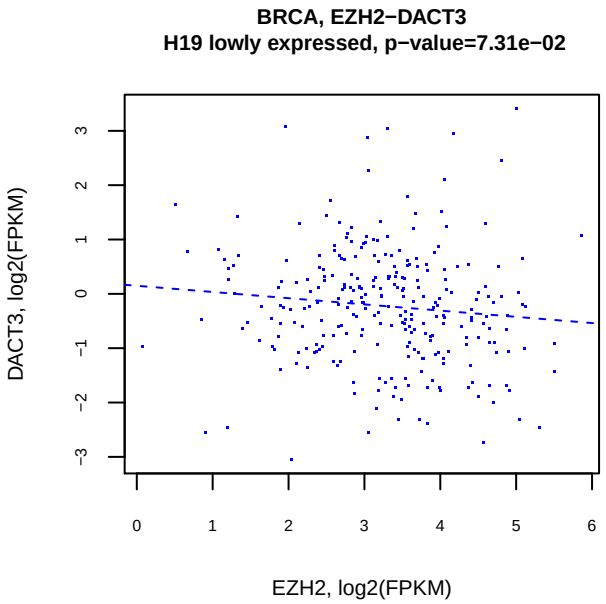
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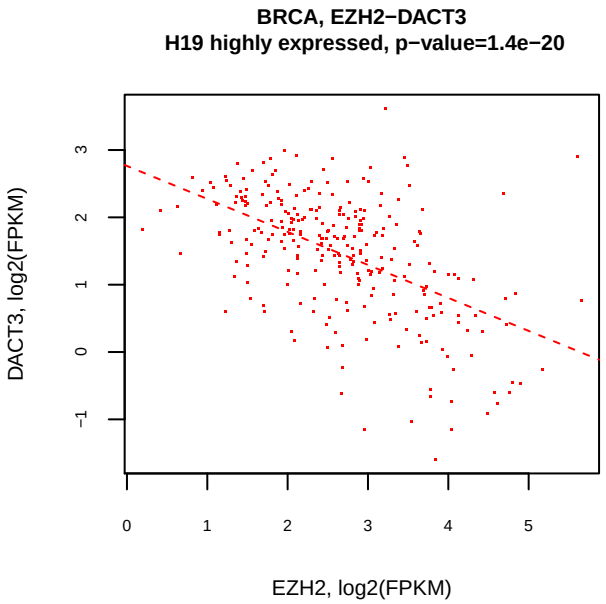
DACT3, log2(FPKM)
EZH2, log2(FPKM)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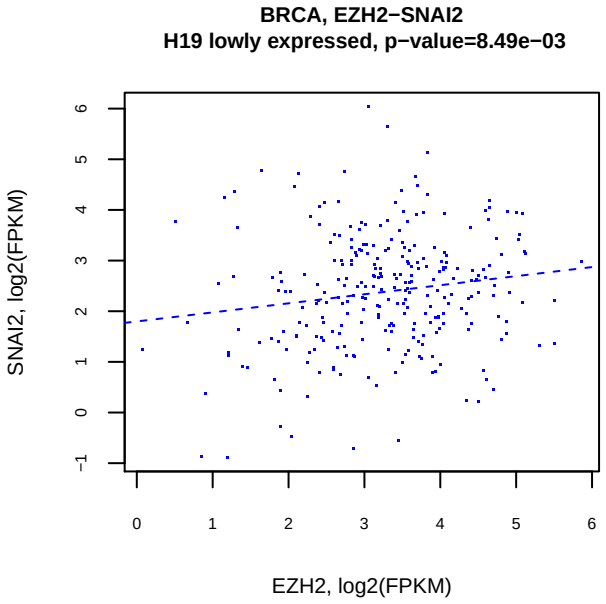
H19 highly expressed, p−value=1.4e−20
DACT3, log2(FPKM)
EZH2, log2(FPKM)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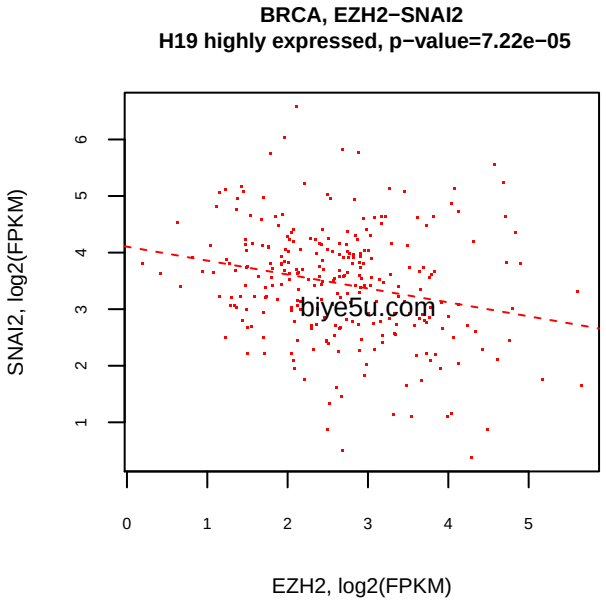
H19 lowly expressed, p−value=8.49e−03
SNAI2, log2(FPKM)
EZH2, log2(FPKM)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H19 highly expressed, p−value=7.22e−05
SNAI2, log2(FPKM)
EZH2, log2(FPKM)
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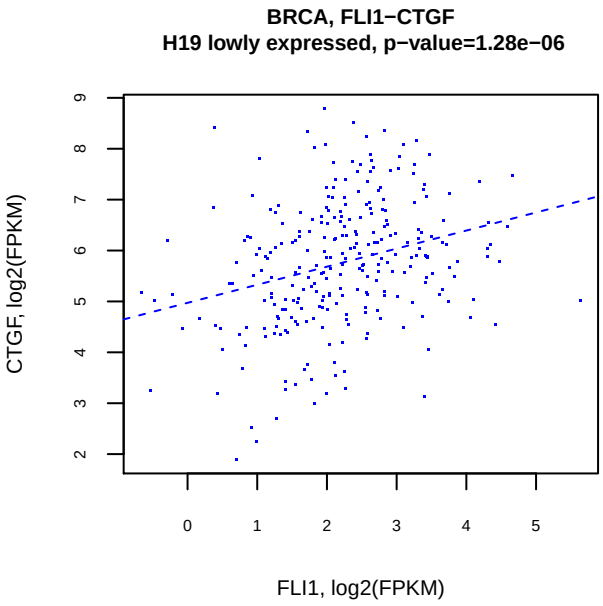
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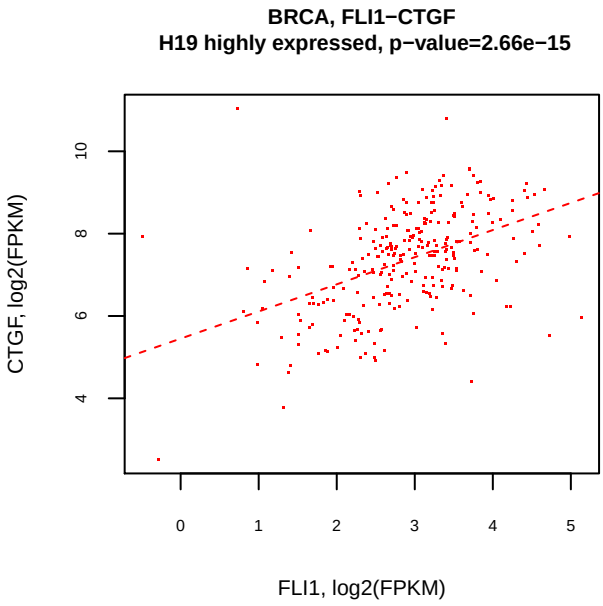
H19 lowly expressed, p−value=1.28e−06
CTGF, log2(FPKM)
FLI1, log2(FPKM)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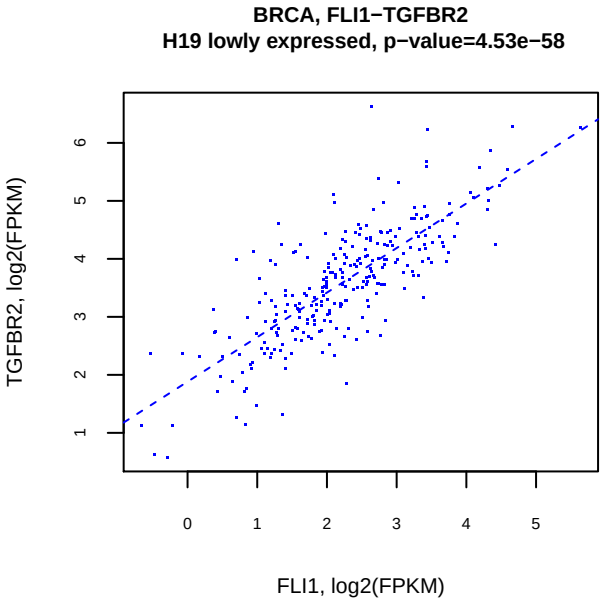
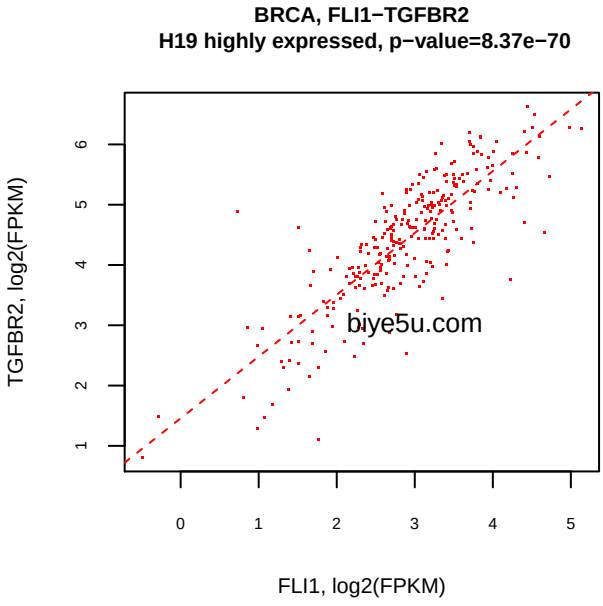
H19 highly expressed, p−value=2.66e−15
CTGF, log2(FPKM)
FLI1, log2(FPKM)


BRCA, FLI1−TGFBR2
H19 lowly expressed, p−value=4.53e−58
TGFBR2, log2(FPKM)
FLI1, log2(FPKM)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TGFBR2, log2(FPKM)
FLI1, log2(FPKM)
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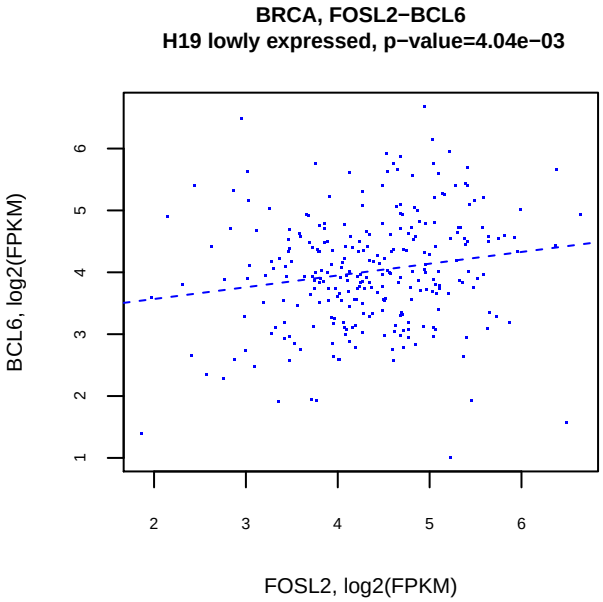
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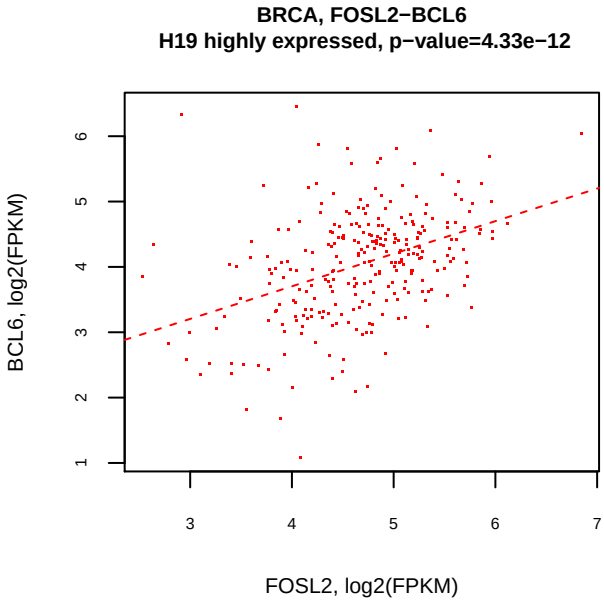
H19 lowly expressed, p−value=4.04e−03
BCL6, log2(FPKM)
FOSL2, log2(FPKM)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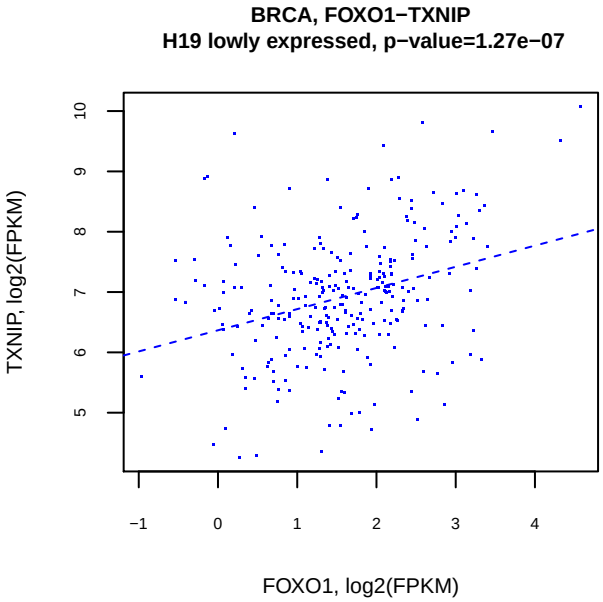
H19 highly expressed, p−value=4.33e−12
BCL6, log2(FPKM)
FOSL2, log2(FPKM)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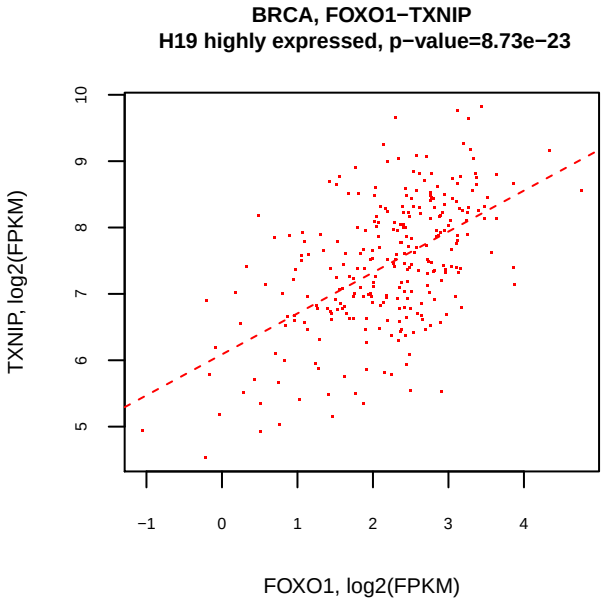
TXNIP, log2(FPKM)
FOXO1, log2(FPKM)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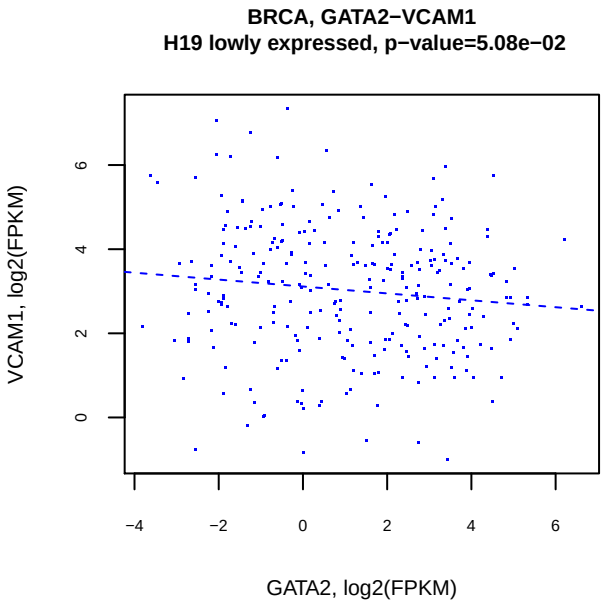
H19 highly expressed, p−value=8.73e−23
TXNIP, log2(FPKM)
FOXO1, log2(FPKM)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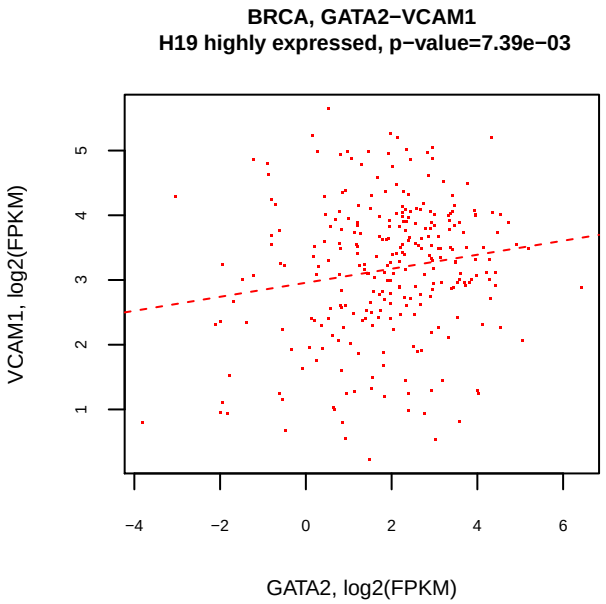
VCAM1, log2(FPKM)
GATA2, log2(FPKM)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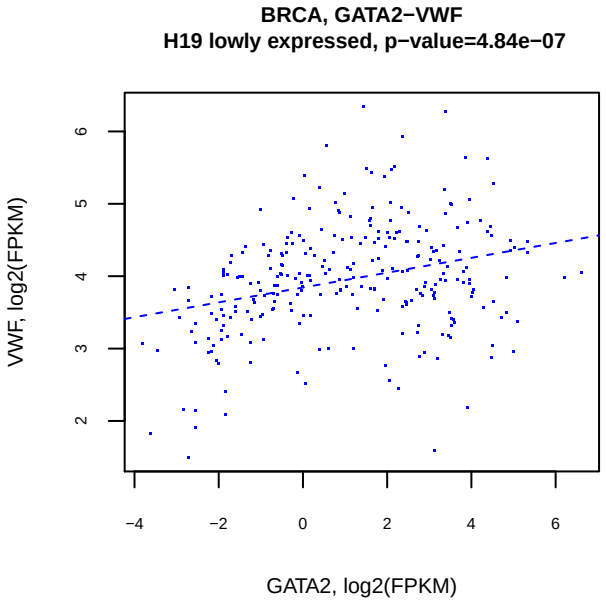
H19 highly expressed, p−value=7.39e−03
VCAM1, log2(FPKM)
GATA2, log2(FPKM)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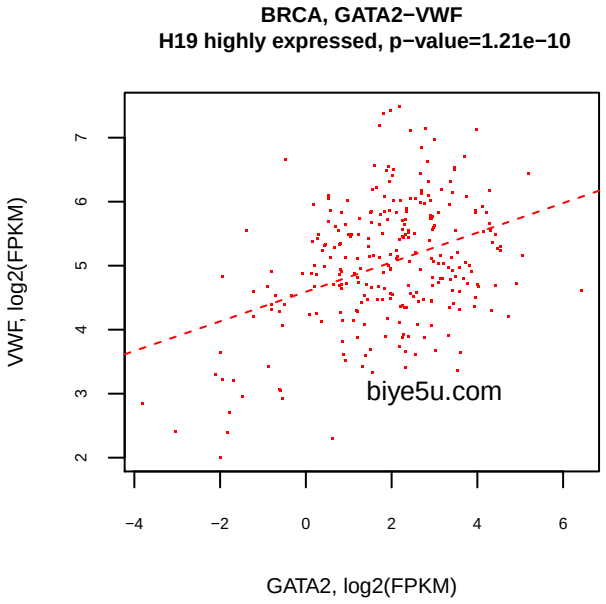
H19 lowly expressed, p−value=4.84e−07
VWF, log2(FPKM)
GATA2, log2(FPKM)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H19 highly expressed, p−value=1.21e−10
VWF, log2(FPKM)
GATA2, log2(FPKM)
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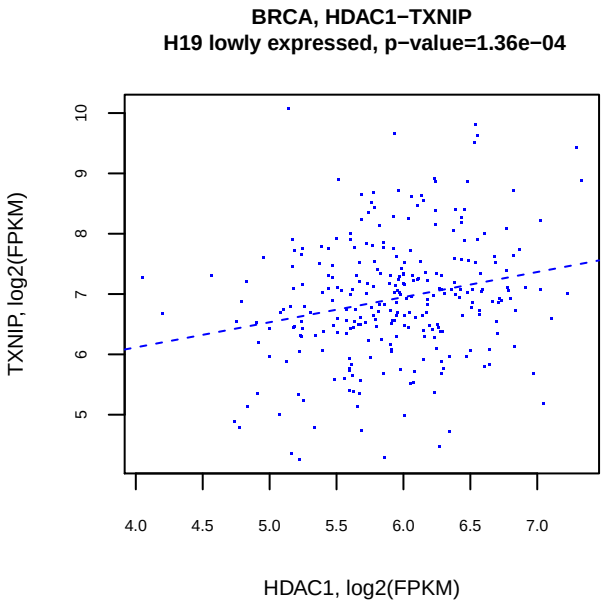
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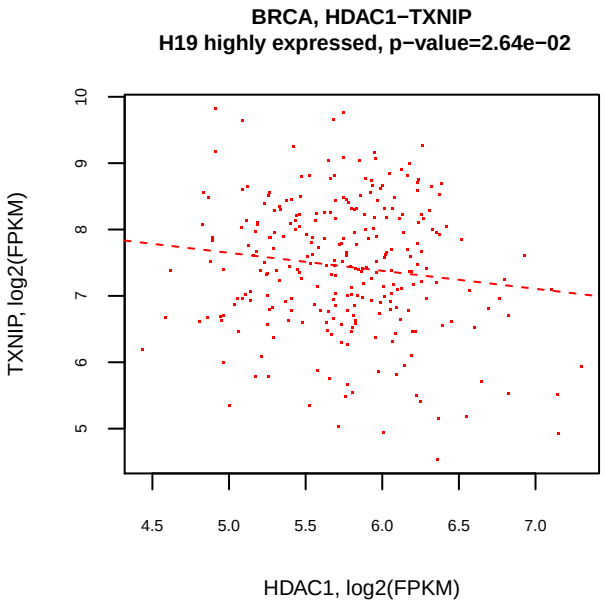
TXNIP, log2(FPKM)
HDAC1, log2(FPKM)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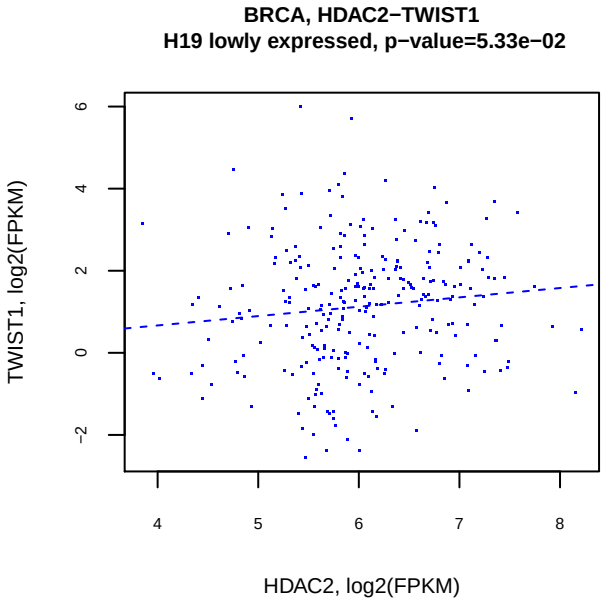
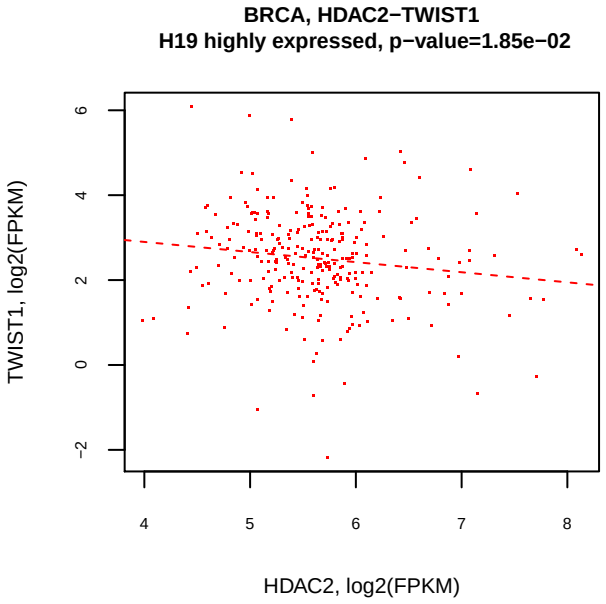
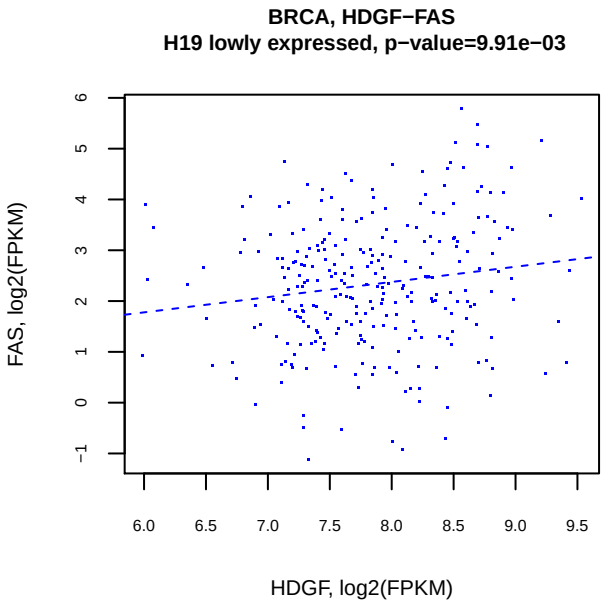
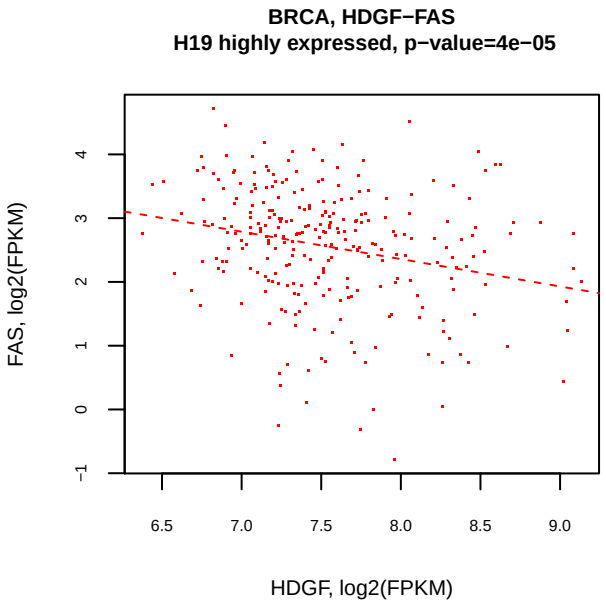
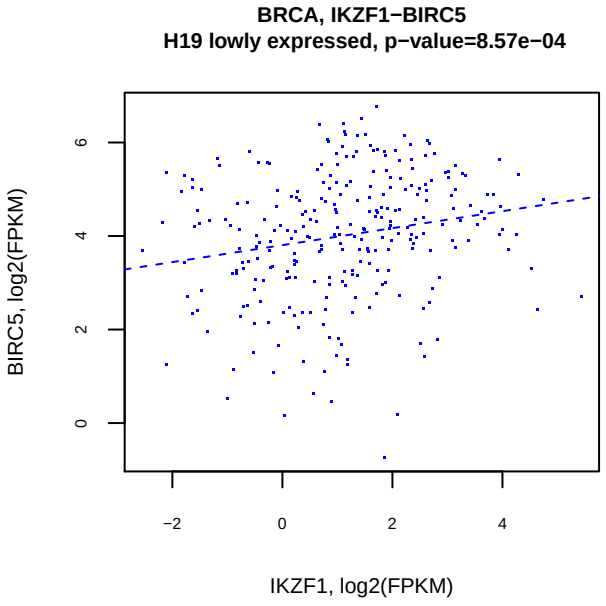
H19 highly expressed, p−value=2.64e−02
TXNIP, log2(FPKM)
HDAC1, log2(FPKM)

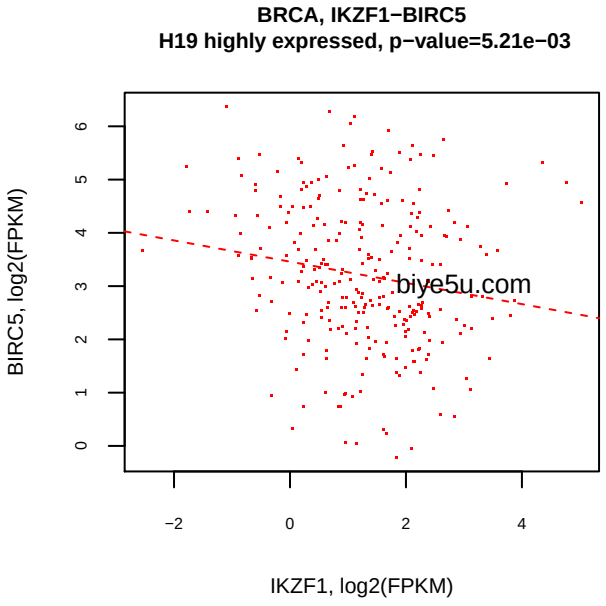

BRCA, HDAC2−TWIST1
H19 lowly expressed, p−value=5.33e−02
TWIST1, log2(FPKM)
HDAC2, log2(FPKM)


BRCA, HDAC2−TWIST1
H19 highly expressed, p−value=1.85e−02
TWIST1, log2(FPKM)
HDAC2, log2(FPKM)


BRCA, HDGF−FAS
H19 lowly expressed, p−value=9.91e−03
FAS, log2(FPKM)
HDGF, log2(FPKM)


BRCA, HDGF−FAS
H19 highly expressed, p−value=4e−05
FAS, log2(FPKM)
HDGF, log2(FPKM)


BRCA, IKZF1−BIRC5
H19 lowly expressed, p−value=8.57e−04
BIRC5, log2(FPKM)
IKZF1, log2(FPKM)


BRCA, IKZF1−BIRC5
H19 highly expressed, p−value=5.21e−03
BIRC5, log2(FPKM)
IKZF1, log2(FPKM)
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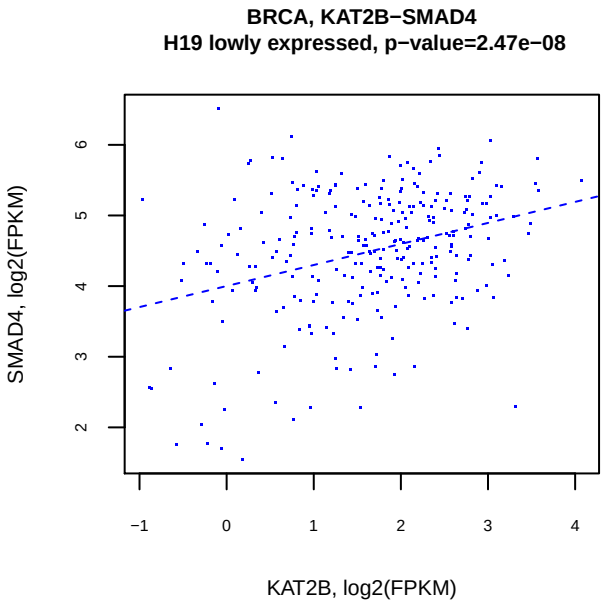
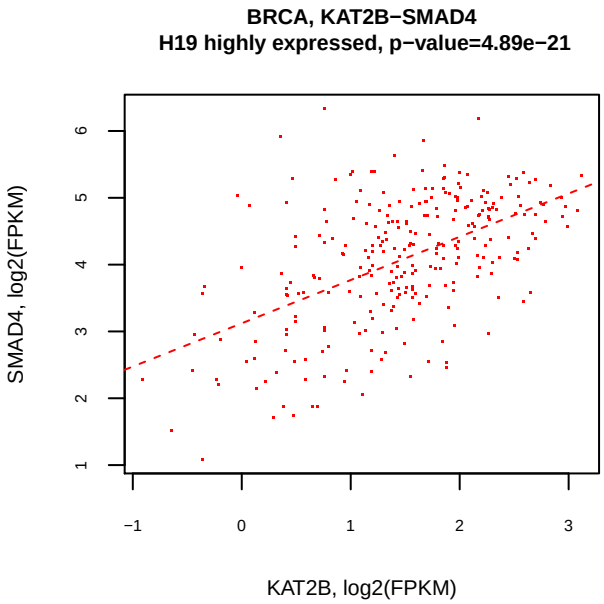
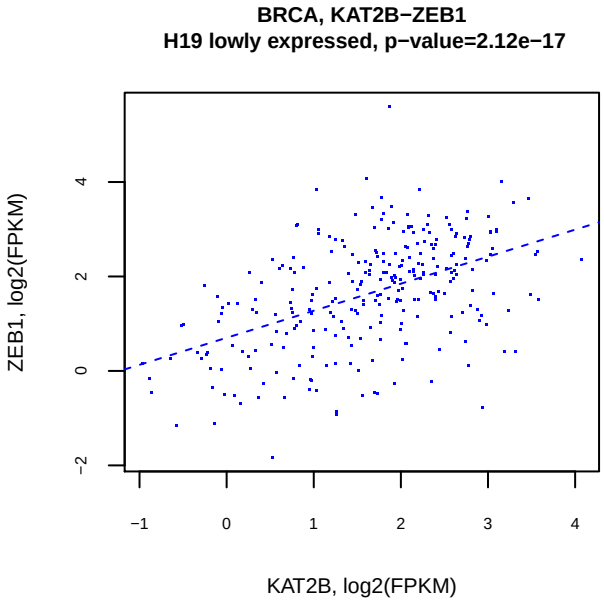
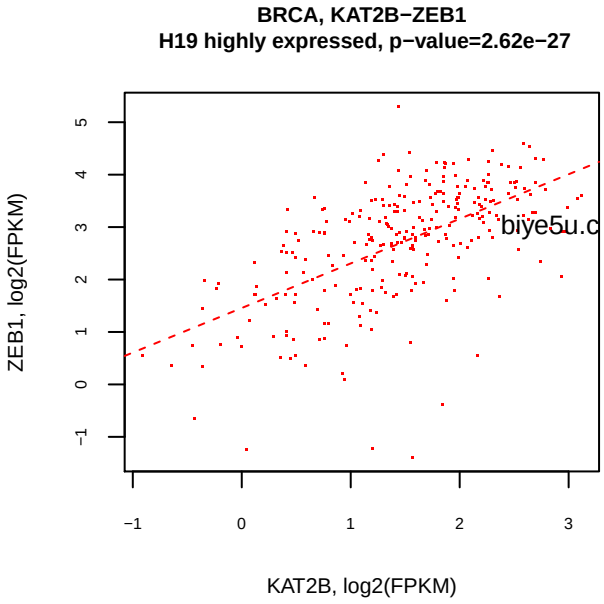

BRCA, KAT2B−SMAD4
H19 lowly expressed, p−value=2.47e−08
SMAD4, log2(FPKM)
KAT2B, log2(FPKM)


BRCA, KAT2B−SMAD4
H19 highly expressed, p−value=4.89e−21
SMAD4, log2(FPKM)
KAT2B, log2(FPKM)


BRCA, KAT2B−ZEB1
H19 lowly expressed, p−value=2.12e−17
ZEB1, log2(FPKM)
KAT2B, log2(FPKM)


BRCA, KAT2B−ZEB1
H19 highly expressed, p−value=2.62e−27
ZEB1, log2(FPKM)
KAT2B, log2(FPKM)
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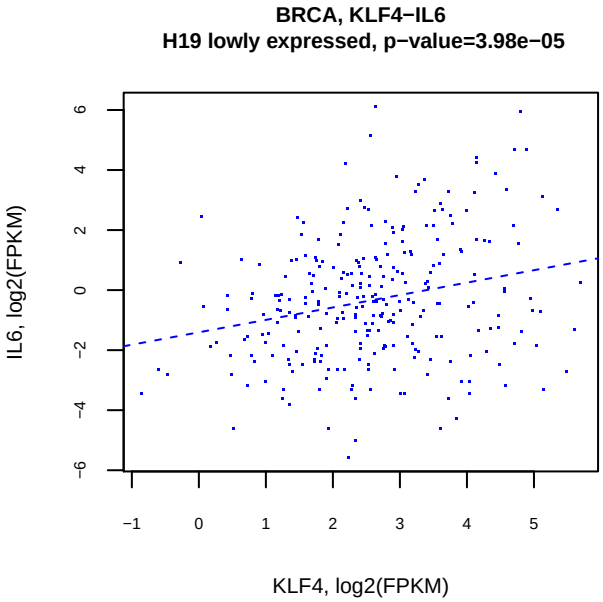
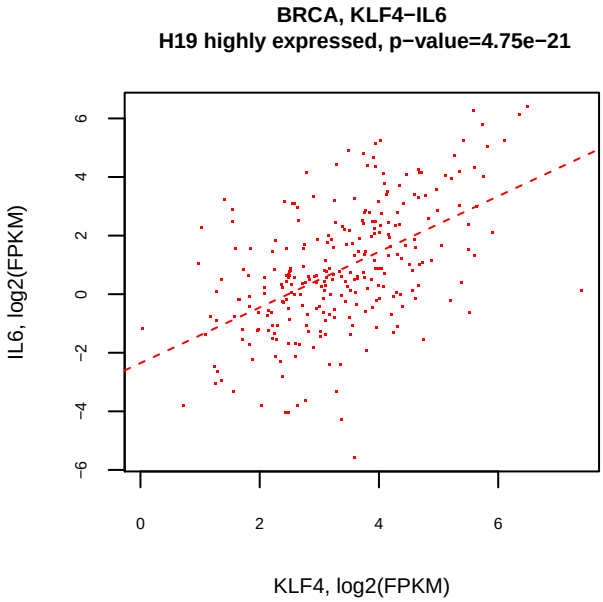
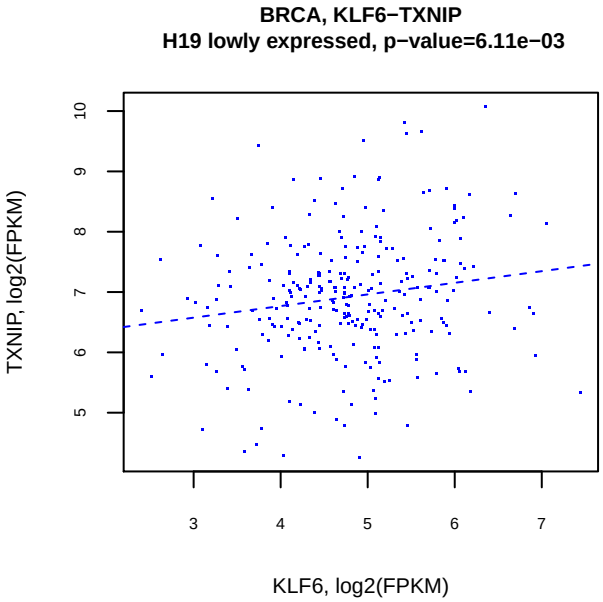
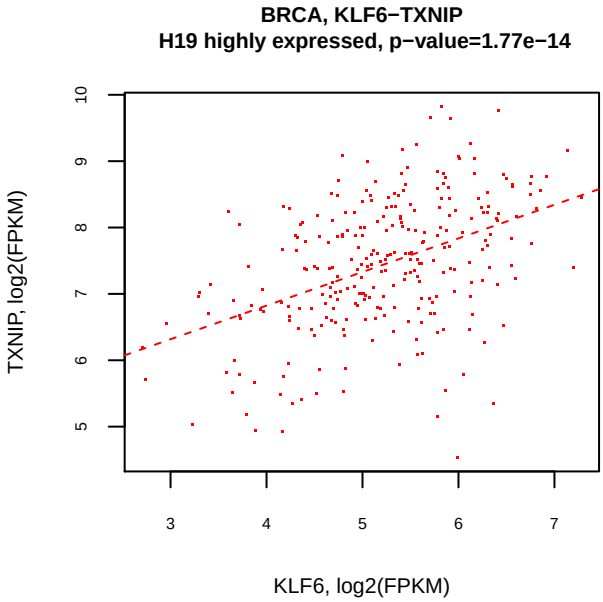
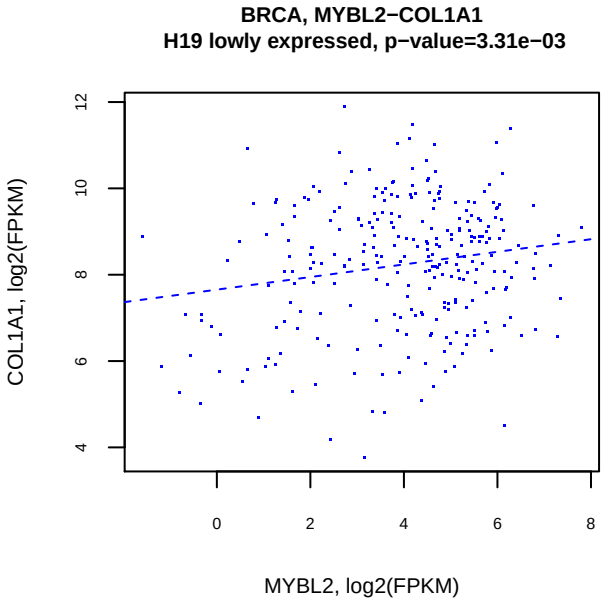
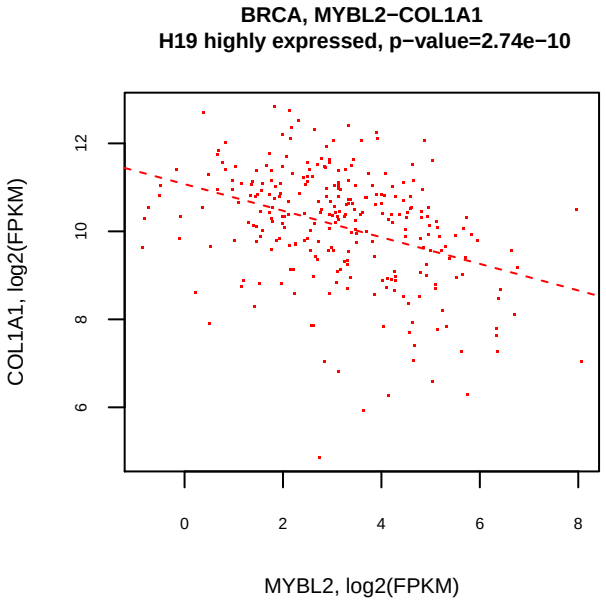

BRCA, KLF4−IL6
H19 lowly expressed, p−value=3.98e−05
IL6, log2(FPKM)
KLF4, log2(FPKM)

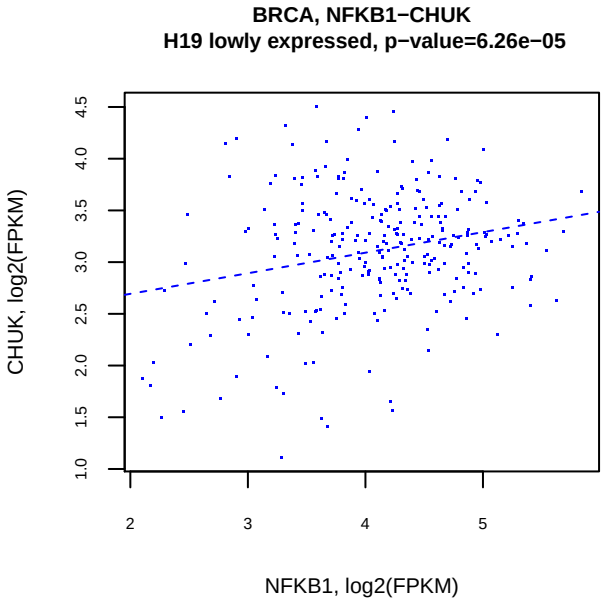

BRCA, KLF4−IL6
H19 highly expressed, p−value=4.75e−21
IL6, log2(FPKM)
KLF4, log2(FPKM)

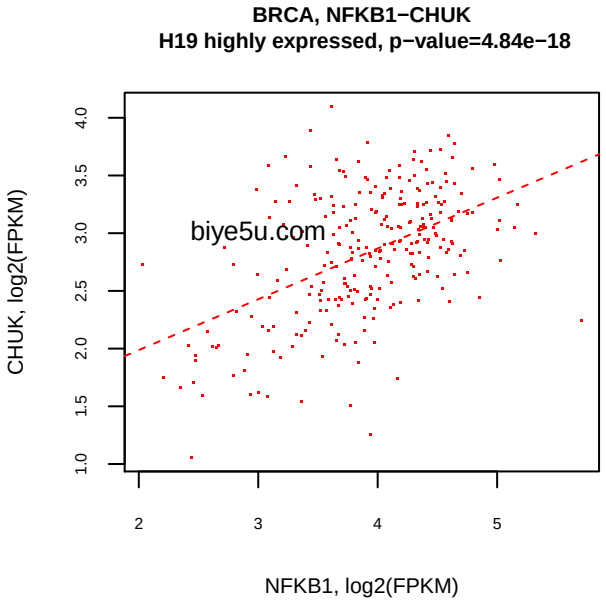

BRCA, KLF6−TXNIP
H19 lowly expressed, p−value=6.11e−03
TXNIP, log2(FPKM)
KLF6, log2(FPKM)


BRCA, KLF6−TXNIP
H19 highly expressed, p−value=1.77e−14
TXNIP, log2(FPKM)
KLF6, log2(FPKM)


BRCA, MYBL2−COL1A1
H19 lowly expressed, p−value=3.31e−03
COL1A1, log2(FPKM)
MYBL2, log2(FPKM)


BRCA, MYBL2−COL1A1
H19 highly expressed, p−value=2.74e−10
COL1A1, log2(FPKM)
MYBL2, log2(FPKM)


BRCA, NFKB1−CHUK
H19 lowly expressed, p−value=6.26e−05
CHUK, log2(FPKM)
NFKB1, log2(FPKM)


BRCA, NFKB1−CHUK
H19 highly expressed, p−value=4.84e−18
CHUK, log2(FPKM)
NFKB1, log2(FPKM)
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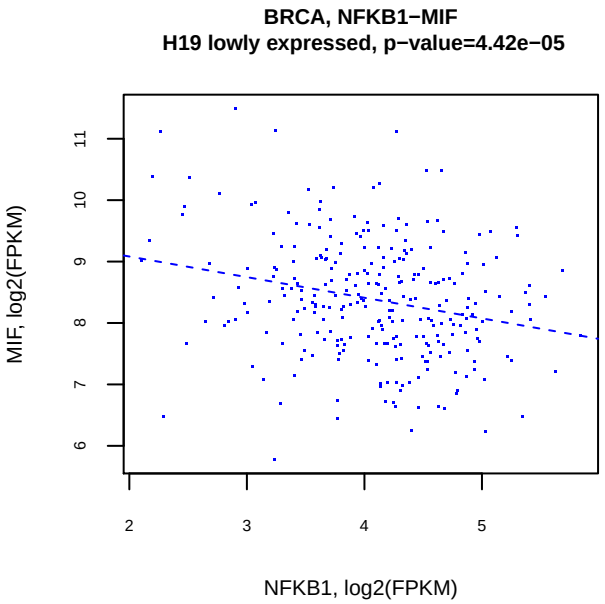
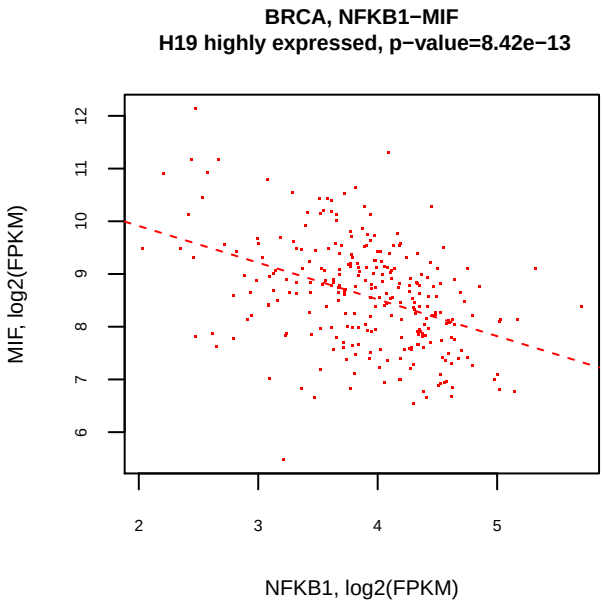
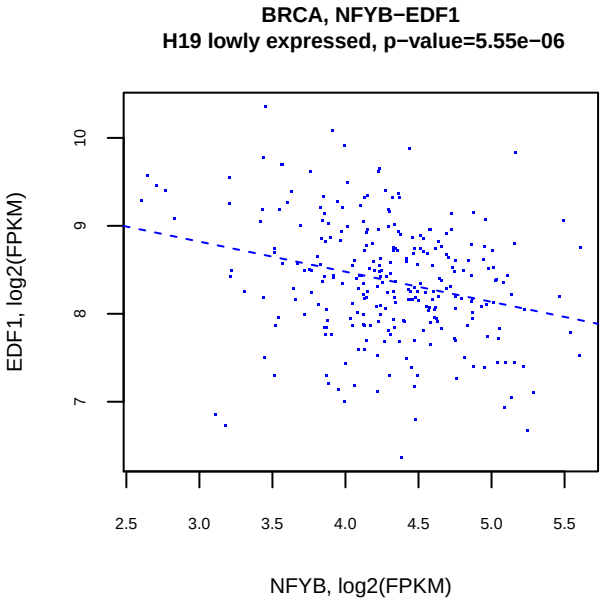
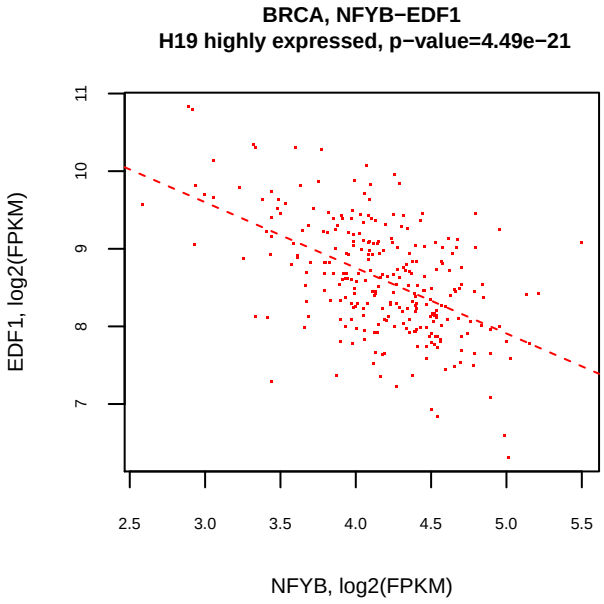
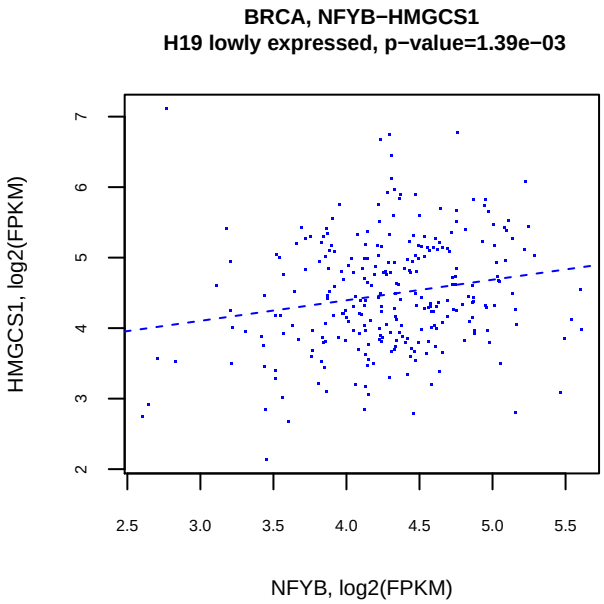
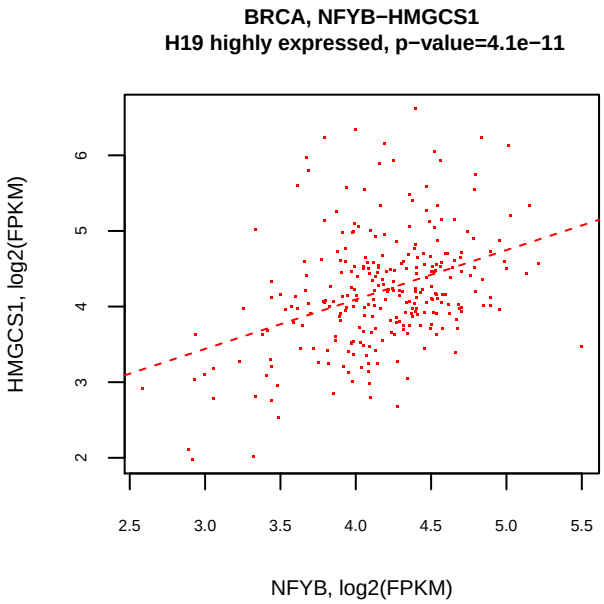

BRCA, NFKB1−MIF
H19 lowly expressed, p−value=4.42e−05
MIF, log2(FPKM)
NFKB1, log2(FPKM)

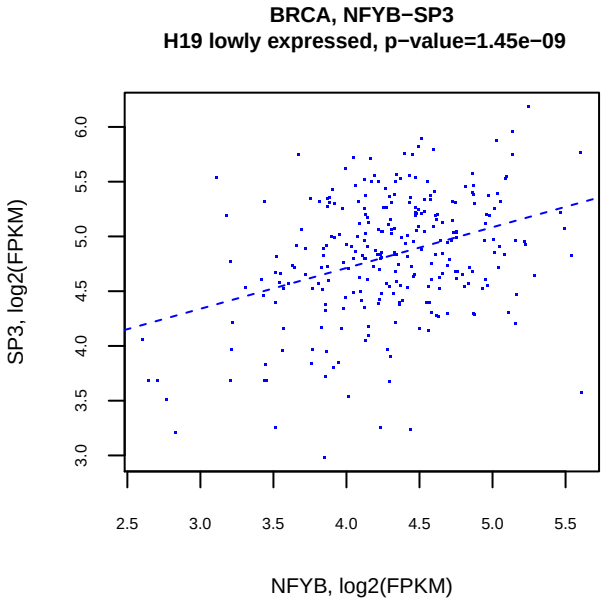

BRCA, NFKB1−MIF
H19 highly expressed, p−value=8.42e−13
MIF, log2(FPKM)
NFKB1, log2(FPKM)

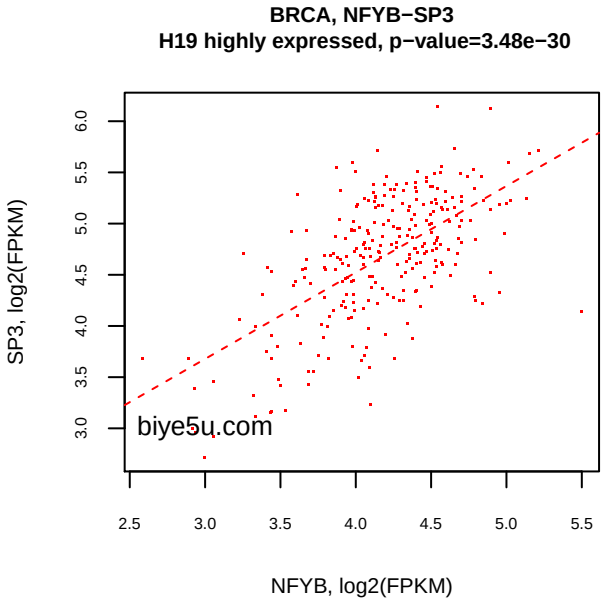

BRCA, NFYB−EDF1
H19 lowly expressed, p−value=5.55e−06
EDF1, log2(FPKM)
NFYB, log2(FPKM)


BRCA, NFYB−EDF1
H19 highly expressed, p−value=4.49e−21
EDF1, log2(FPKM)
NFYB, log2(FPKM)


BRCA, NFYB−HMGCS1
H19 lowly expressed, p−value=1.39e−03
HMGCS1, log2(FPKM)
NFYB, log2(FPKM)


BRCA, NFYB−HMGCS1
H19 highly expressed, p−value=4.1e−11
HMGCS1, log2(FPKM)
NFYB, log2(FPKM)


BRCA, NFYB−SP3
H19 lowly expressed, p−value=1.45e−09
SP3, log2(FPKM)
NFYB, log2(FPKM)


BRCA, NFYB−SP3
H19 highly expressed, p−value=3.48e−30
SP3, log2(FPKM)
NFYB, log2(FPKM)
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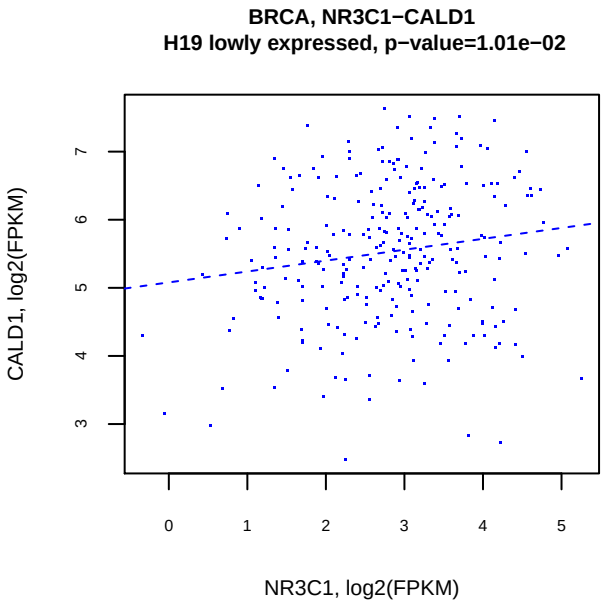
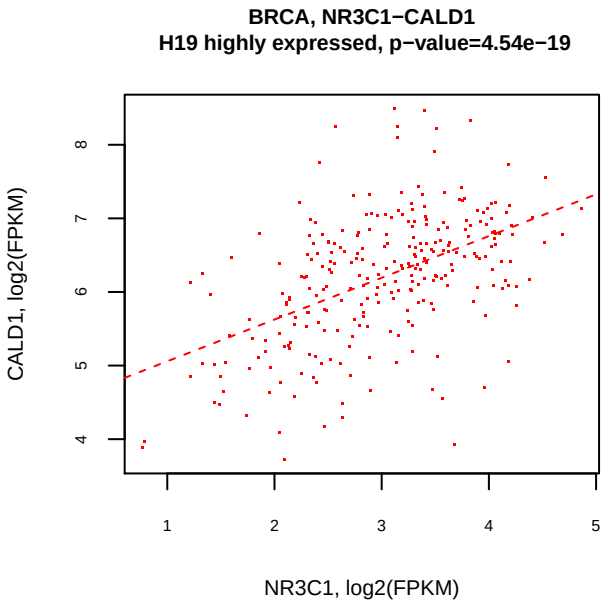
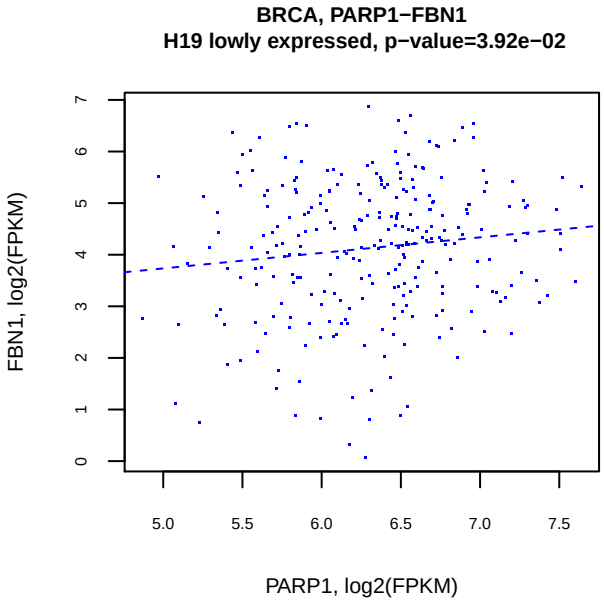
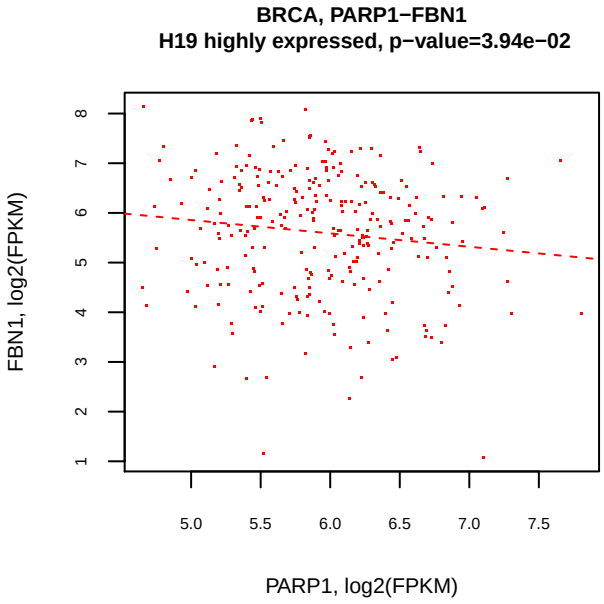
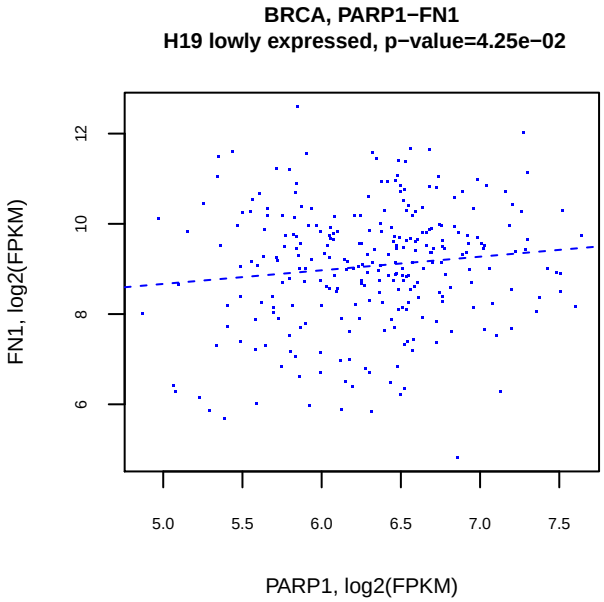
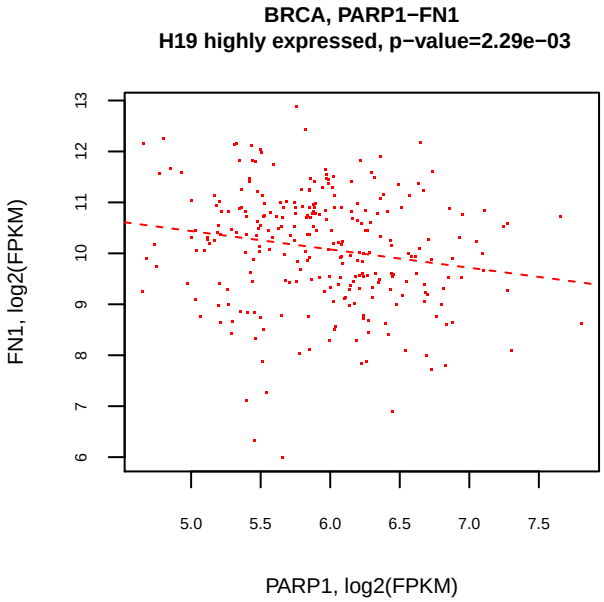

BRCA, NR3C1−CALD1
H19 lowly expressed, p−value=1.01e−02
CALD1, log2(FPKM)
NR3C1, log2(FPKM)

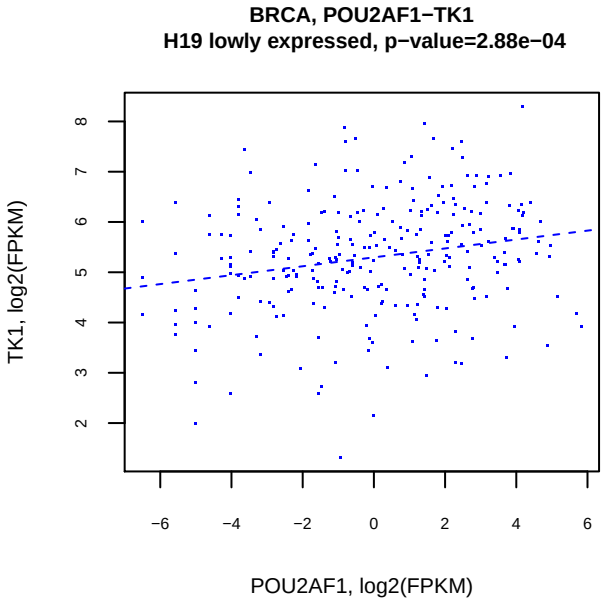

BRCA, NR3C1−CALD1
H19 highly expressed, p−value=4.54e−19
CALD1, log2(FPKM)
NR3C1, log2(FPKM)

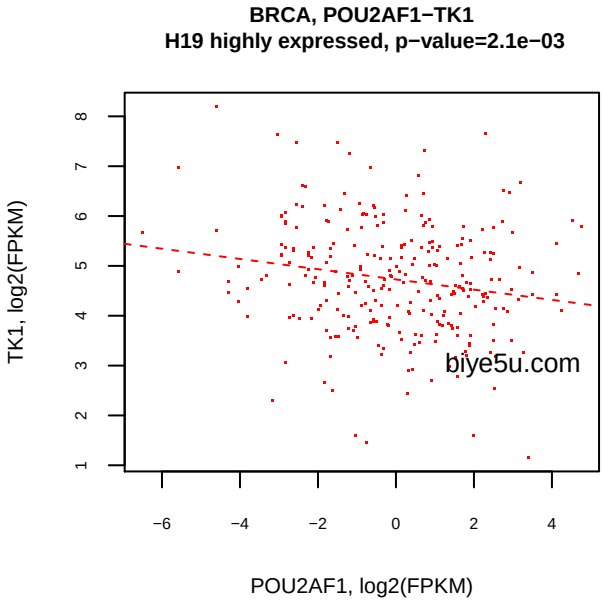

BRCA, PARP1−FBN1
H19 lowly expressed, p−value=3.92e−02
FBN1, log2(FPKM)
PARP1, log2(FPKM)


BRCA, PARP1−FBN1
H19 highly expressed, p−value=3.94e−02
FBN1, log2(FPKM)
PARP1, log2(FPKM)


BRCA, PARP1−FN1
H19 lowly expressed, p−value=4.25e−02
FN1, log2(FPKM)
PARP1, log2(FPKM)


BRCA, PARP1−FN1
H19 highly expressed, p−value=2.29e−03
FN1, log2(FPKM)
PARP1, log2(FPKM)


BRCA, POU2AF1−TK1
H19 lowly expressed, p−value=2.88e−04
TK1, log2(FPKM)
POU2AF1, log2(FPKM)


BRCA, POU2AF1−TK1
H19 highly expressed, p−value=2.1e−03
TK1, log2(FPKM)
POU2AF1, log2(FPKM)
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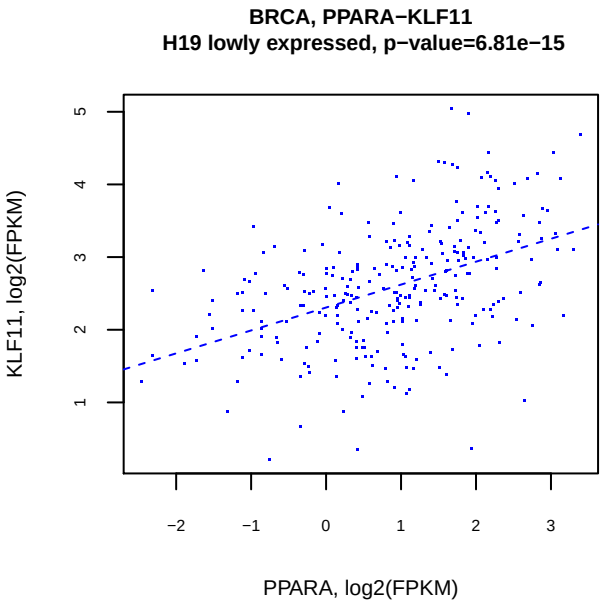
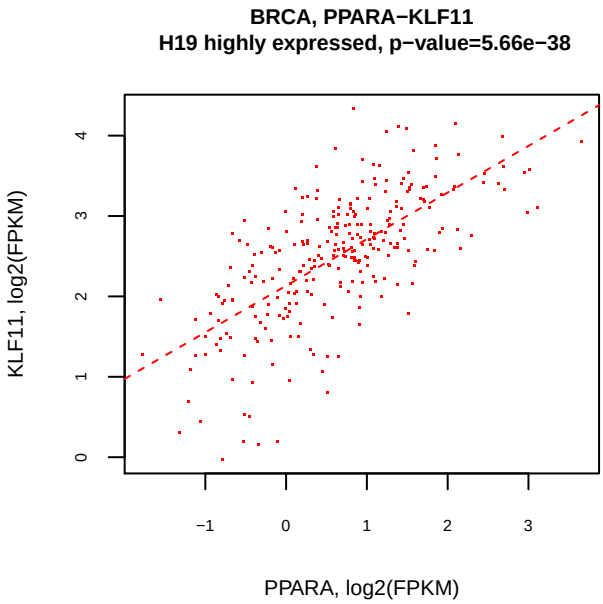
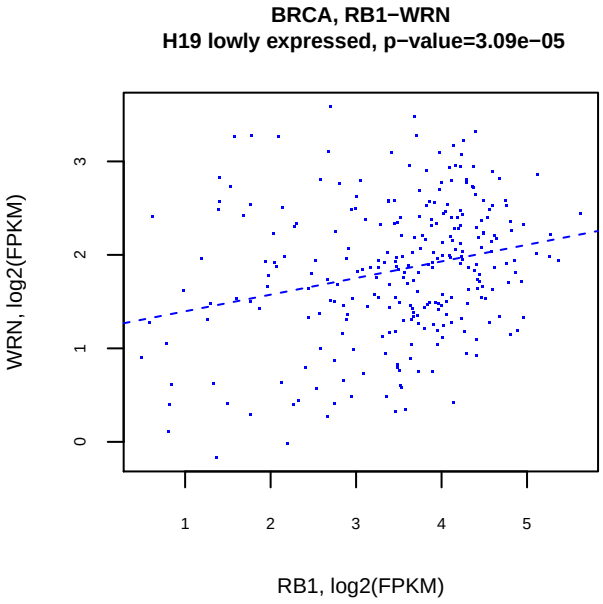
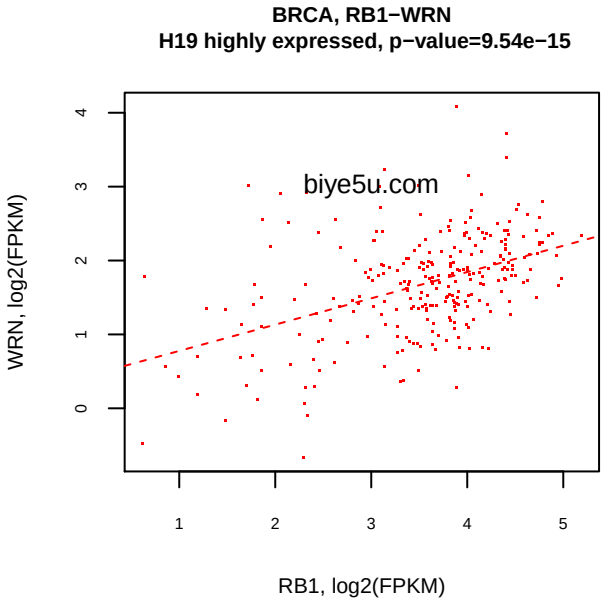

BRCA, PPARA−KLF11
H19 lowly expressed, p−value=6.81e−15
KLF11, log2(FPKM)
PPARA, log2(FPKM)


BRCA, PPARA−KLF11
H19 highly expressed, p−value=5.66e−38
KLF11, log2(FPKM)
PPARA, log2(FPKM)


BRCA, RB1−WRN
H19 lowly expressed, p−value=3.09e−05
WRN, log2(FPKM)
RB1, log2(FPKM)


BRCA, RB1−WRN
H19 highly expressed, p−value=9.54e−15
WRN, log2(FPKM)
RB1, log2(FPKM)
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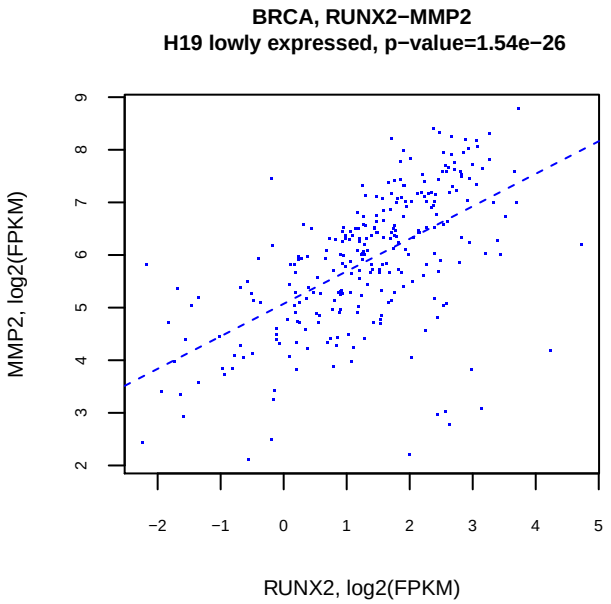
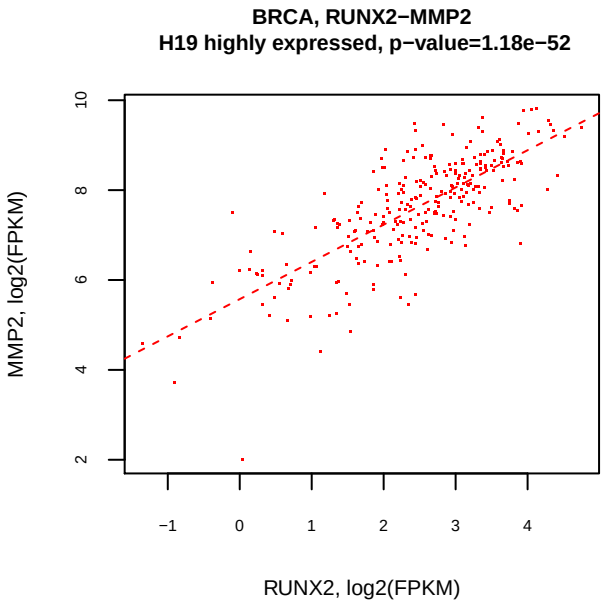
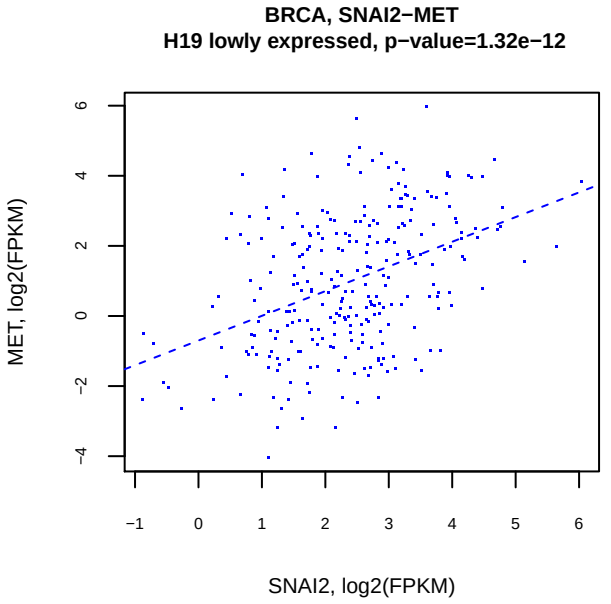
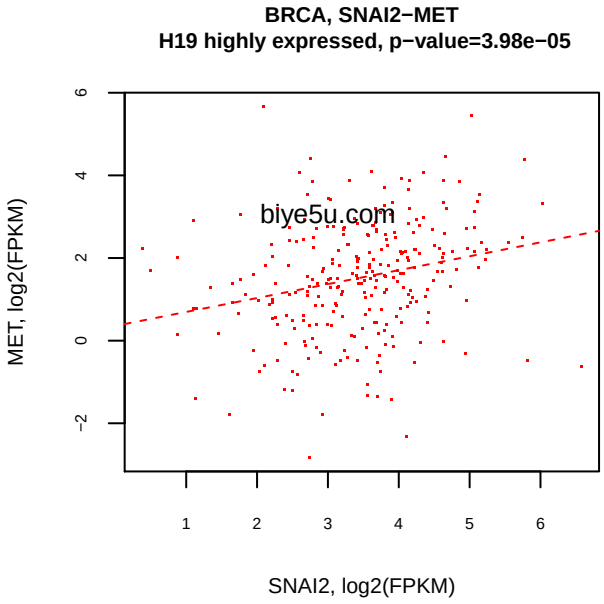

BRCA, RUNX2−MMP2
H19 lowly expressed, p−value=1.54e−26
MMP2, log2(FPKM)
RUNX2, log2(FPKM)


BRCA, RUNX2−MMP2
H19 highly expressed, p−value=1.18e−52
MMP2, log2(FPKM)
RUNX2, log2(FPKM)


BRCA, SNAI2−MET
H19 lowly expressed, p−value=1.32e−12
MET, log2(FPKM)
SNAI2, log2(FPKM)


BRCA, SNAI2−MET
H19 highly expressed, p−value=3.98e−05
MET, log2(FPKM)
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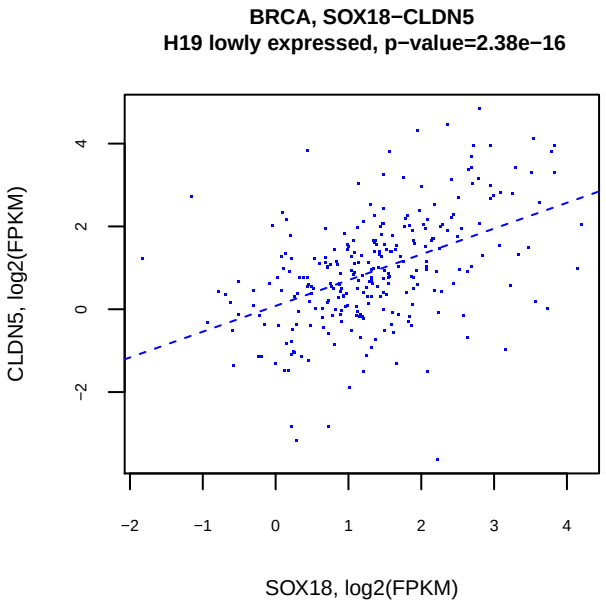
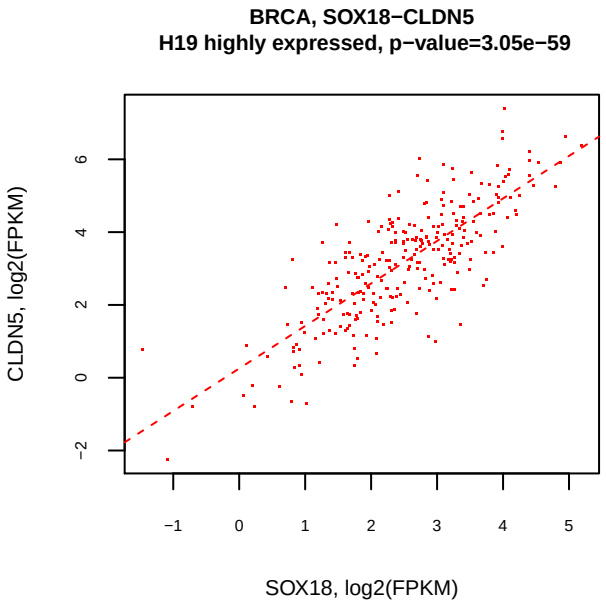
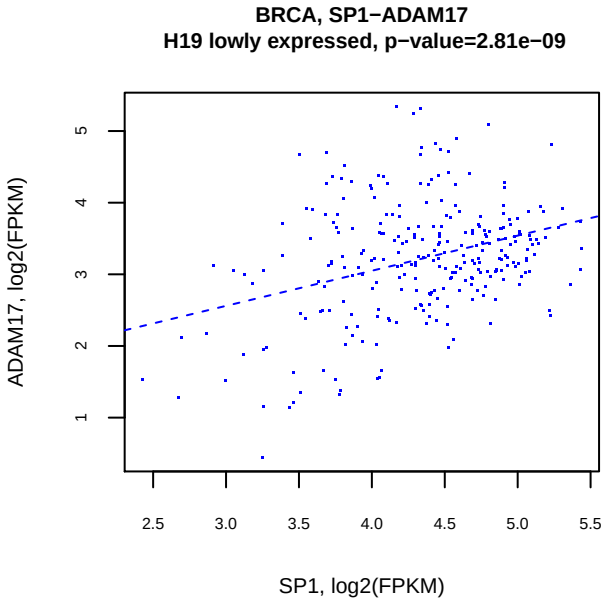
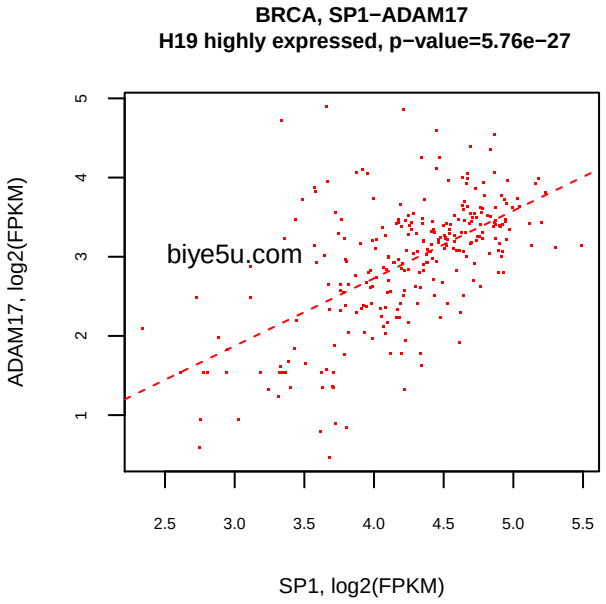
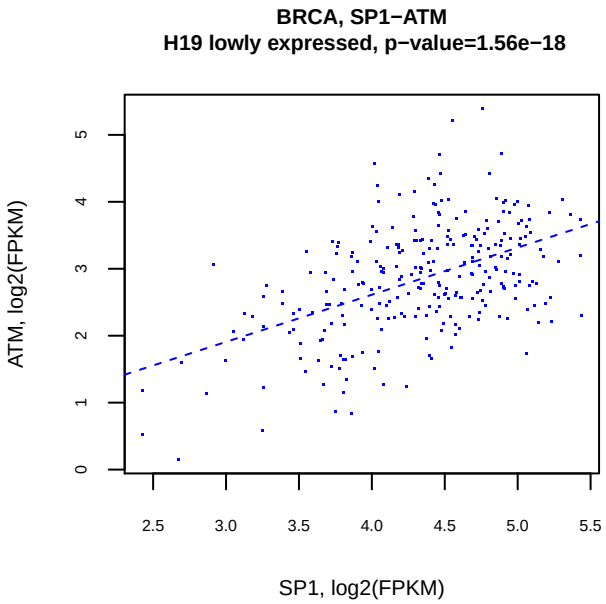
SNAI2, log2(FPKM)

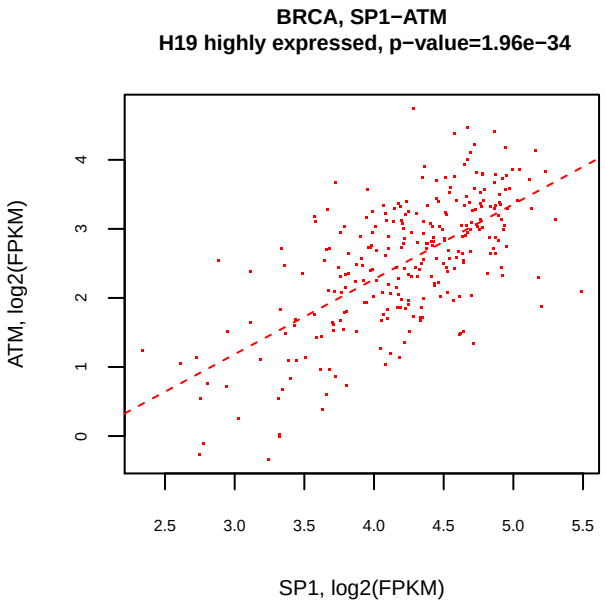

BRCA, SOX18−CLDN5
H19 lowly expressed, p−value=2.38e−16
CLDN5, log2(FPKM)
SOX18, log2(FPKM)

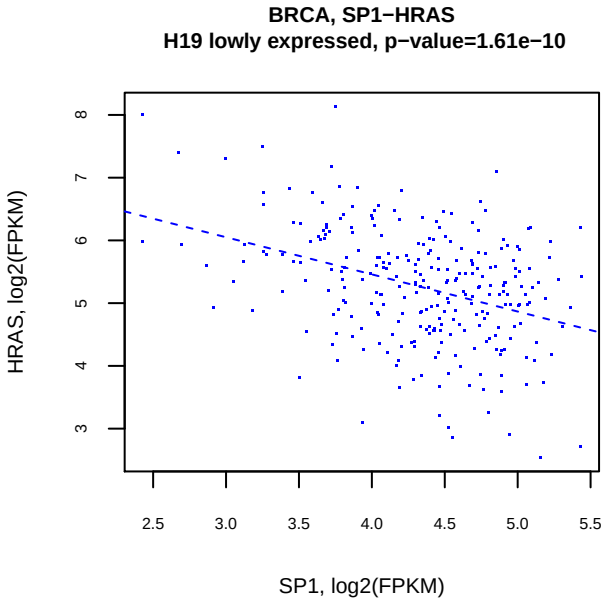

BRCA, SOX18−CLDN5
H19 highly expressed, p−value=3.05e−59
CLDN5, log2(FPKM)
SOX18, log2(FPKM)

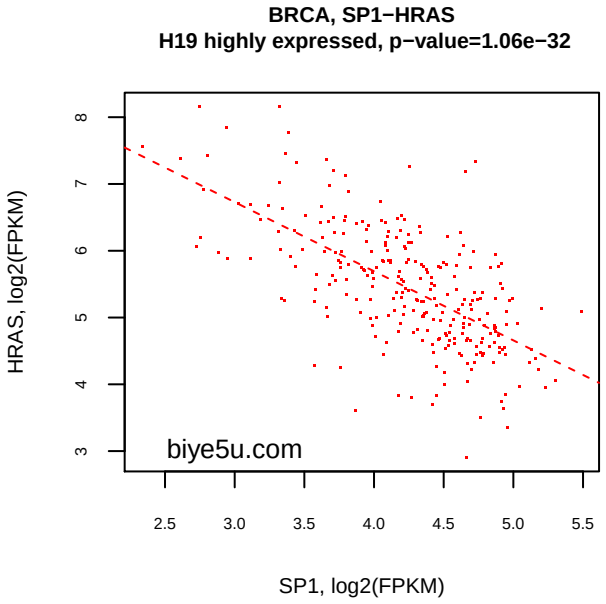

BRCA, SP1−ADAM17
H19 lowly expressed, p−value=2.81e−09
ADAM17, log2(FPKM)
SP1, log2(FPKM)


BRCA, SP1−ADAM17
H19 highly expressed, p−value=5.76e−27
ADAM17, log2(FPKM)
SP1, log2(FPKM)
biye5u.com


BRCA, SP1−ATM
H19 lowly expressed, p−value=1.56e−18
ATM, log2(FPKM)
SP1, log2(FPKM)


BRCA, SP1−ATM
H19 highly expressed, p−value=1.96e−34
ATM, log2(FPKM)
SP1, log2(FPKM)


BRCA, SP1−HRAS
H19 lowly expressed, p−value=1.61e−10
HRAS, log2(FPKM)
SP1, log2(FPKM)


BRCA, SP1−HRAS
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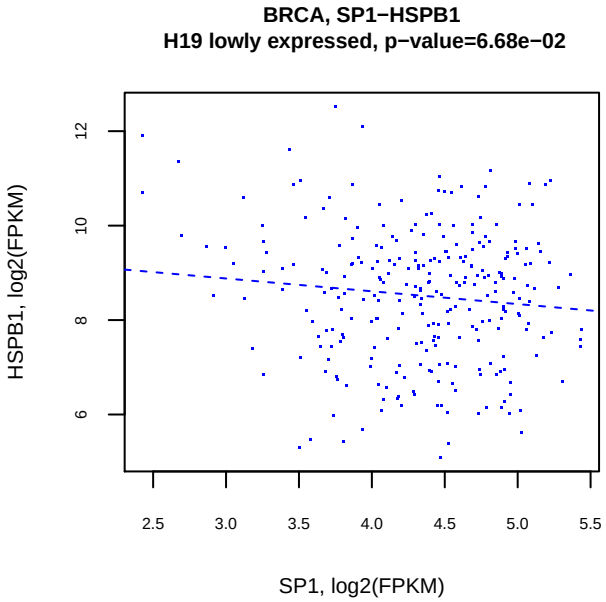
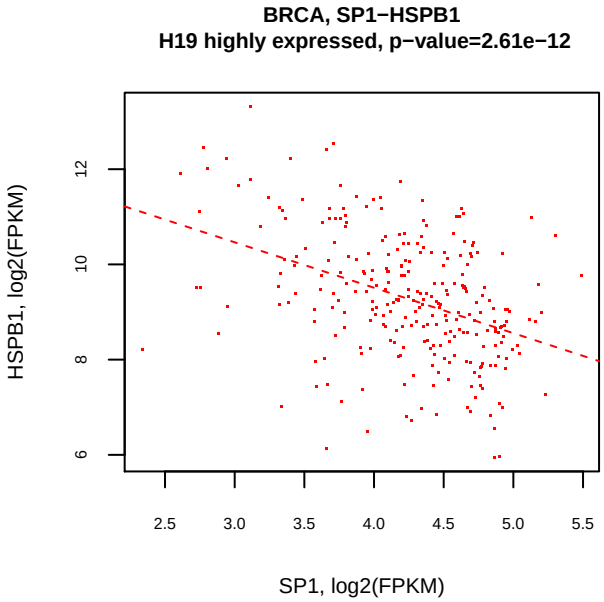
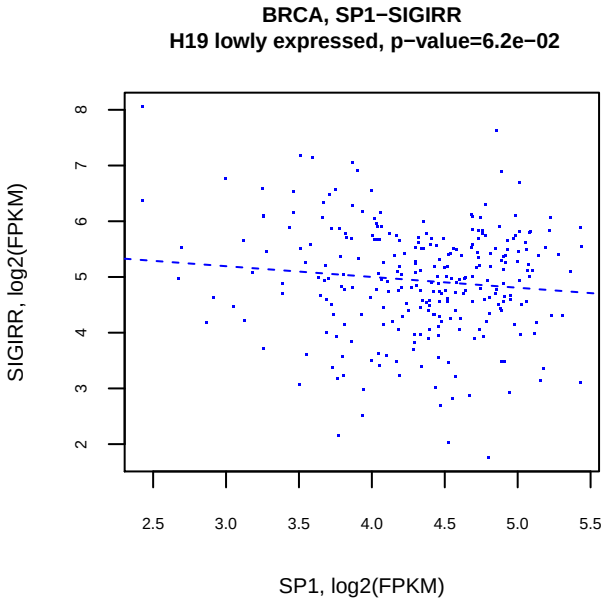
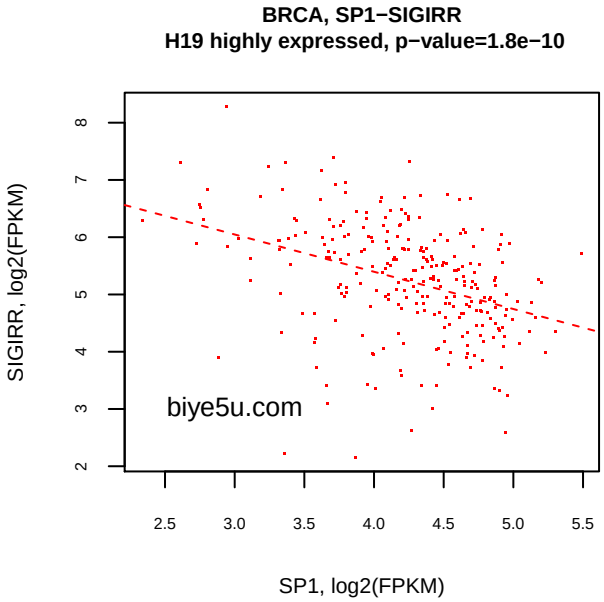
HRAS, log2(FPKM)
biye5u.com
SP1, log2(FPKM)


BRCA, SP1−HSPB1
H19 lowly expressed, p−value=6.68e−02
HSPB1, log2(FPKM)
SP1, log2(FPKM)


BRCA, SP1−HSPB1
H19 highly expressed, p−value=2.61e−12
HSPB1, log2(FPKM)
SP1, log2(FPKM)


BRCA, SP1−SIGIRR
H19 lowly expressed, p−value=6.2e−02
SIGIRR, log2(FPKM)
SP1, log2(FPKM)


BRCA, SP1−SIGIRR
H19 highly expressed, p−value=1.8e−10
SIGIRR, log2(FPKM)
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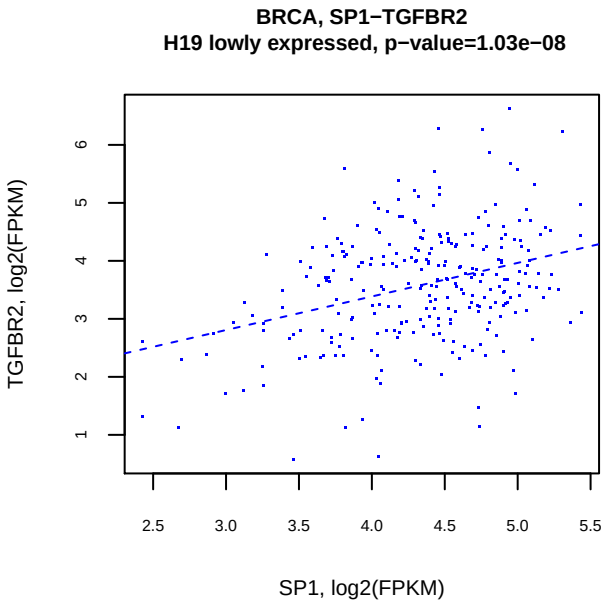
SP1, log2(FPKM)


BRCA, SP1−TGFBR2
H19 lowly expressed, p−value=1.03e−08
TGFBR2, log2(FPKM)
SP1, log2(FPKM)
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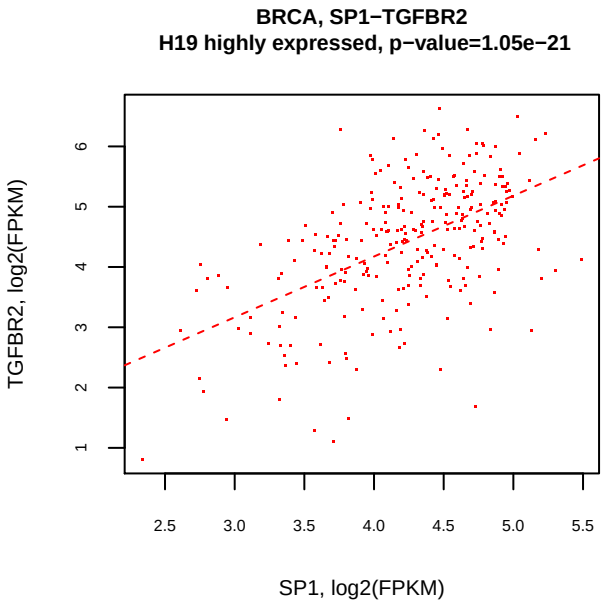
3
4
5
6
2.5
3.0
3.5
4.0
4.5
5.0
5.5


BRCA, SP1−TGFBR2
H19 highly expressed, p−value=1.05e−21
TGFBR2, log2(FPKM)
SP1, log2(FPKM)
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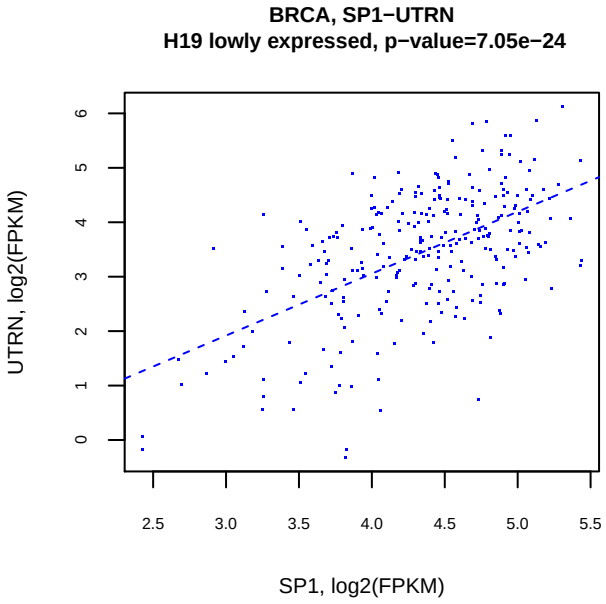
2
3
4
5
6
2.5
3.0
3.5
4.0
4.5
5.0
5.5


BRCA, SP1−UTRN
H19 lowly expressed, p−value=7.05e−24
UTRN, log2(FPKM)
SP1, log2(FPKM)
0
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2
3
4
5
6
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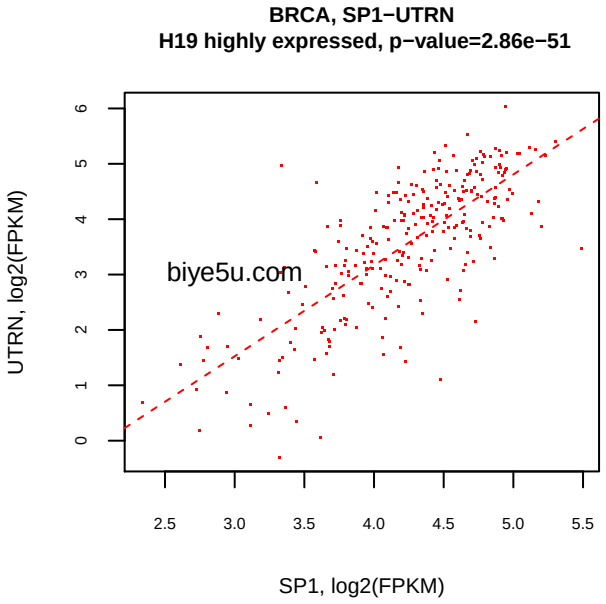
3.0
3.5
4.0
4.5
5.0
5.5


BRCA, SP1−UTRN
H19 highly expressed, p−value=2.86e−51
UTRN, log2(FPKM)
SP1, log2(FPKM)
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0
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2
3
4
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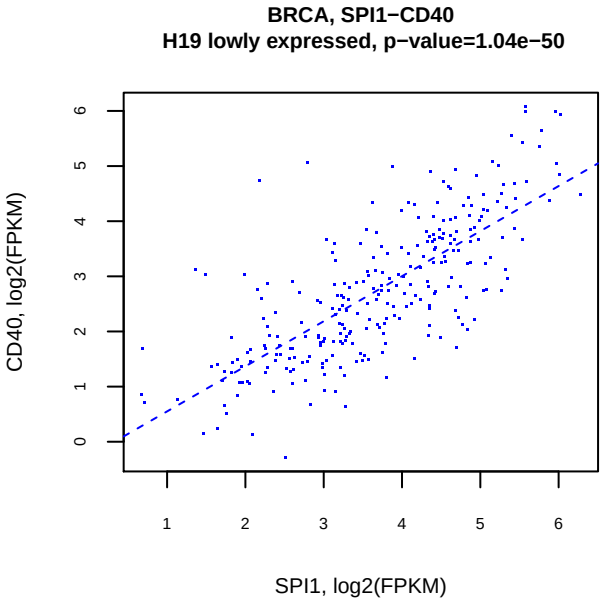
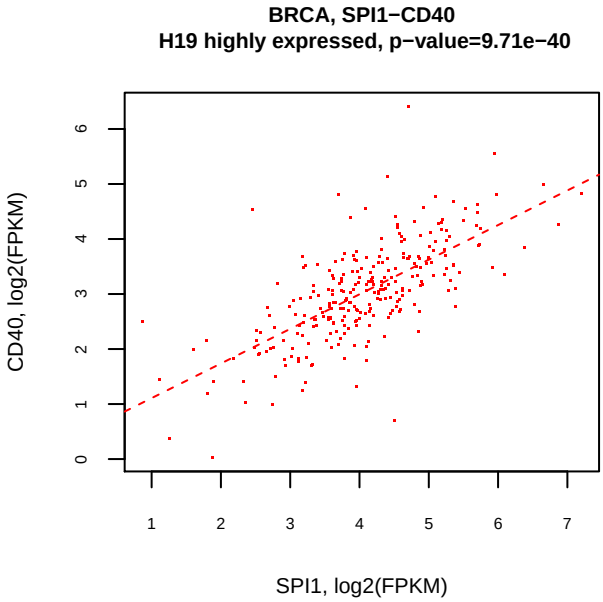
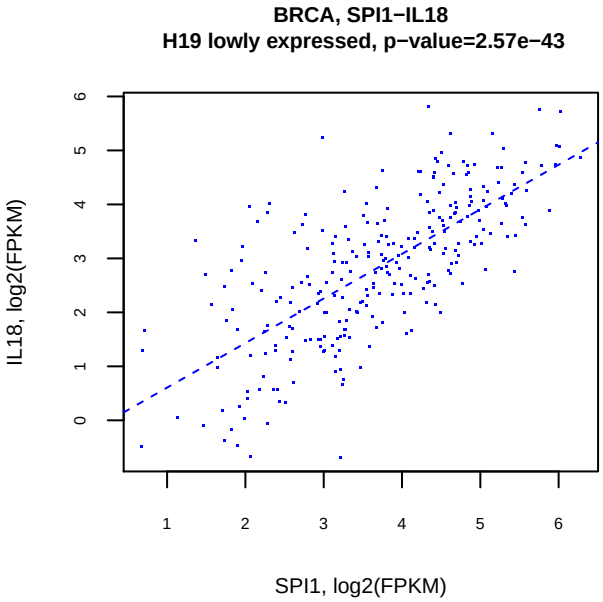
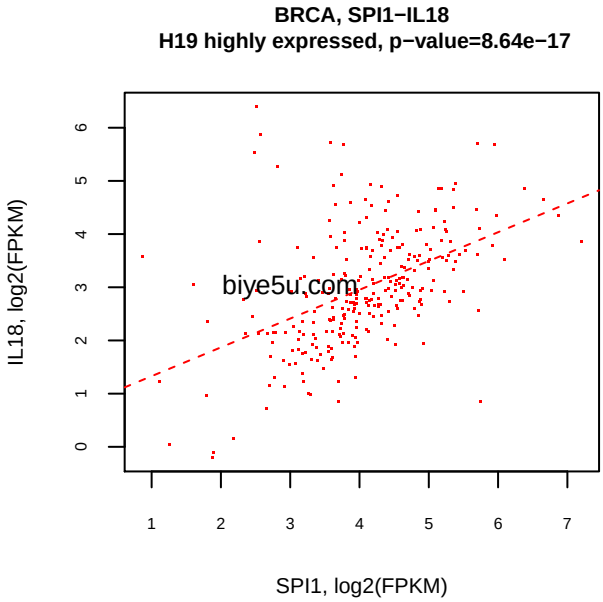
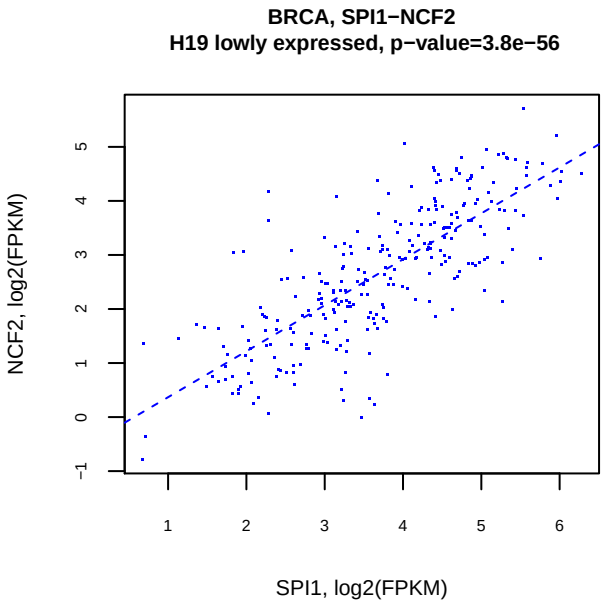
6
2.5
3.0
3.5
4.0
4.5
5.0
5.5

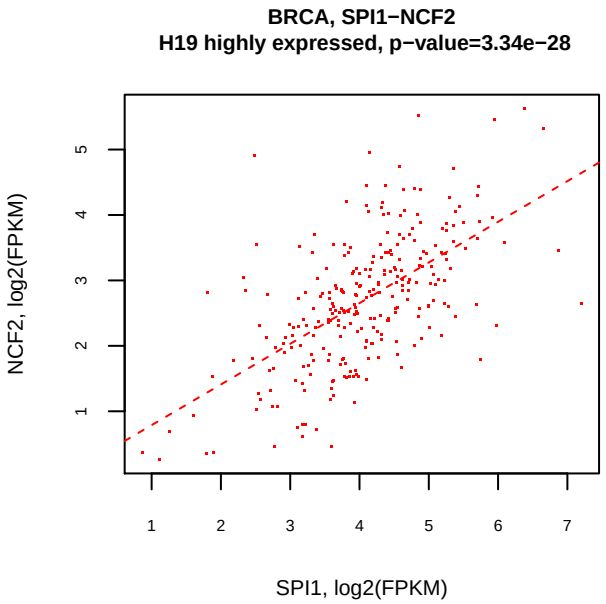

BRCA, SPI1−CD40
H19 lowly expressed, p−value=1.04e−50
CD40, log2(FPKM)
SPI1, log2(FPKM)

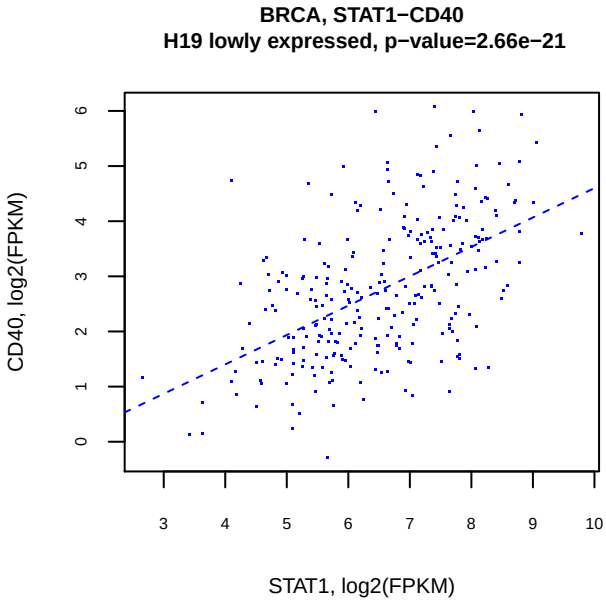

BRCA, SPI1−CD40
H19 highly expressed, p−value=9.71e−40
CD40, log2(FPKM)
SPI1, log2(FPKM)

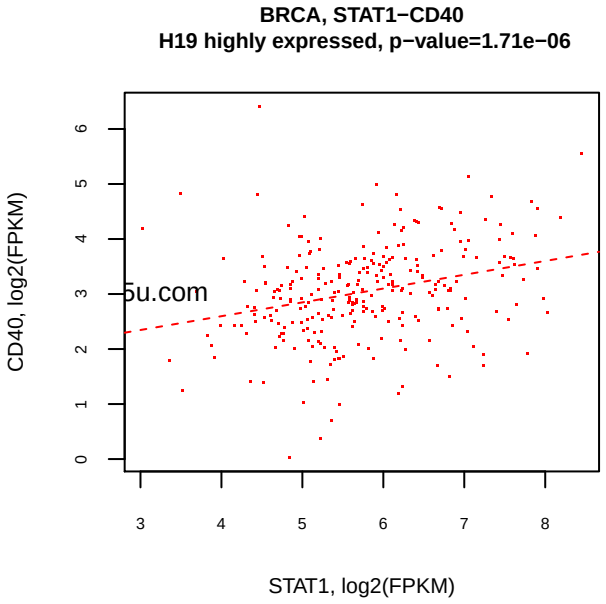

BRCA, SPI1−IL18
H19 lowly expressed, p−value=2.57e−43
IL18, log2(FPKM)
SPI1, log2(FPKM)

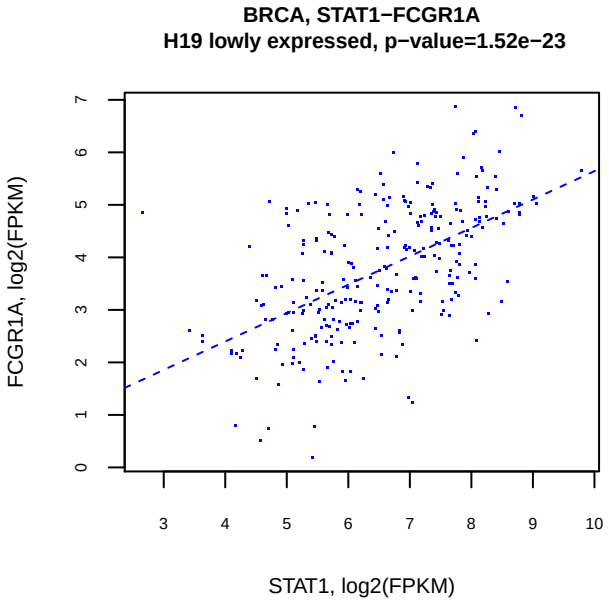

BRCA, SPI1−IL18
H19 highly expressed, p−value=8.64e−17
IL18, log2(FPKM)
biye5u.com
SPI1, log2(FPKM)

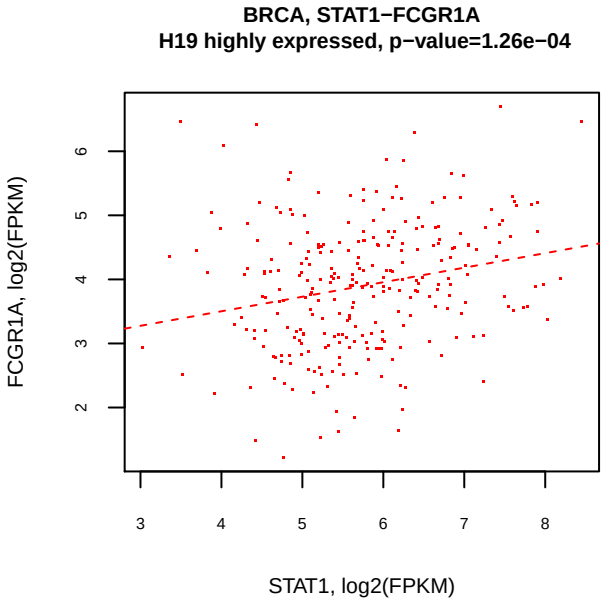

BRCA, SPI1−NCF2
H19 lowly expressed, p−value=3.8e−56
NCF2, log2(FPKM)
SPI1, log2(FPKM)

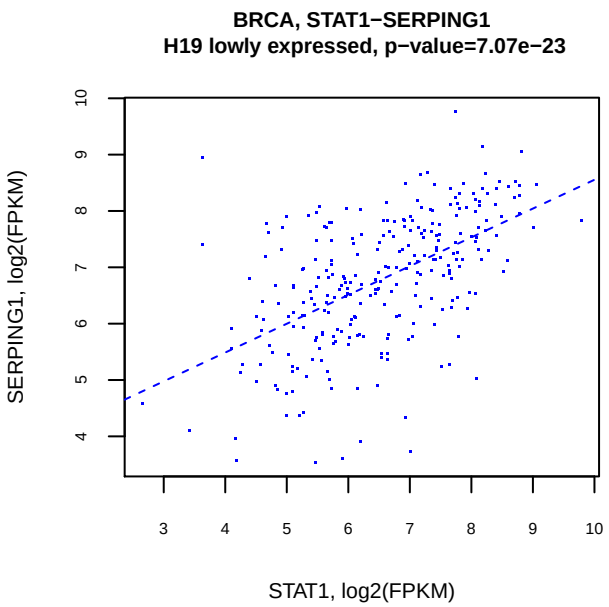

BRCA, SPI1−NCF2
H19 highly expressed, p−value=3.34e−28
NCF2, log2(FPKM)
SPI1, log2(FPKM)

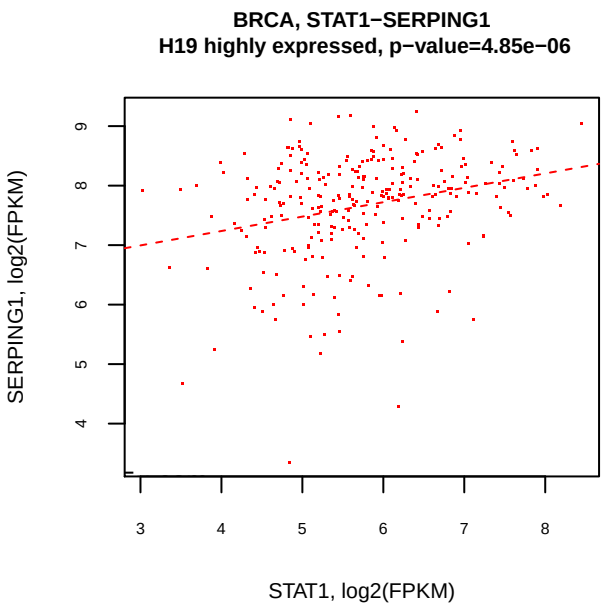

BRCA, STAT1−CD40
H19 lowly expressed, p−value=2.66e−21
CD40, log2(FPKM)
STAT1, log2(FPKM)


BRCA, STAT1−CD40
H19 highly expressed, p−value=1.71e−06
CD40, log2(FPKM)
STAT1, log2(FPKM)


BRCA, STAT1−FCGR1A
H19 lowly expressed, p−value=1.52e−23
FCGR1A, log2(FPKM)
STAT1, log2(FPKM)


BRCA, STAT1−FCGR1A
H19 highly expressed, p−value=1.26e−04
FCGR1A, log2(FPKM)
STAT1, log2(FPKM)


BRCA, STAT1−SERPING1
H19 lowly expressed, p−value=7.07e−23
SERPING1, log2(FPKM)
STAT1, log2(FPKM)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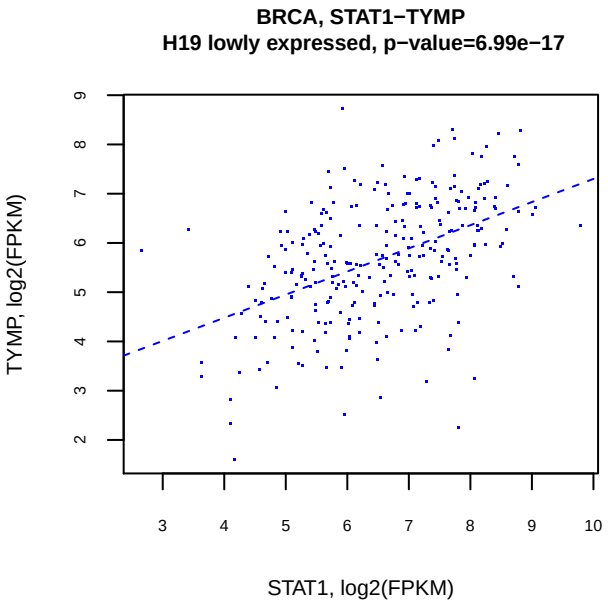
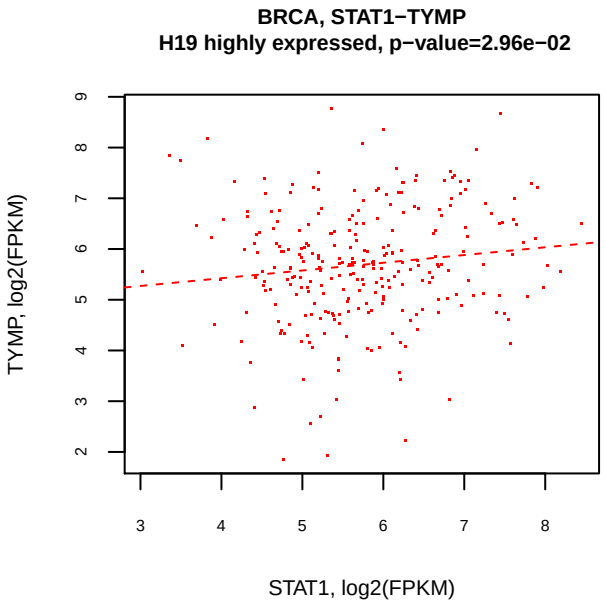
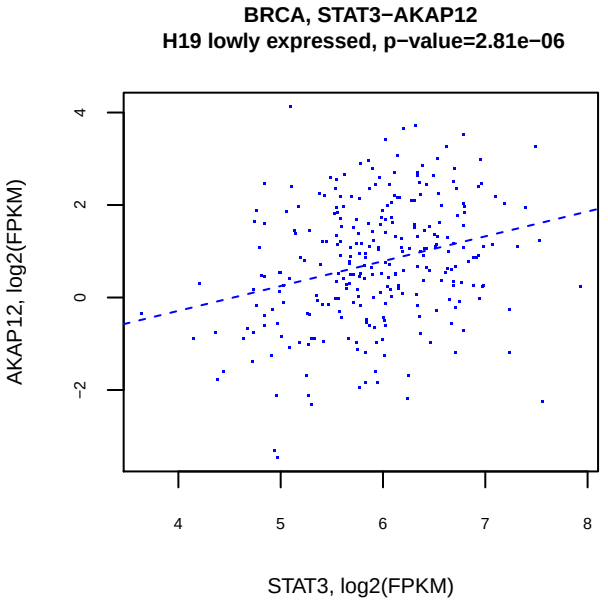
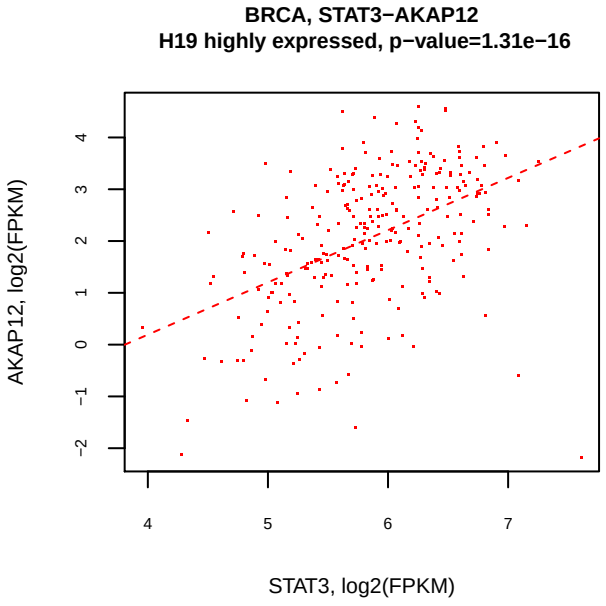
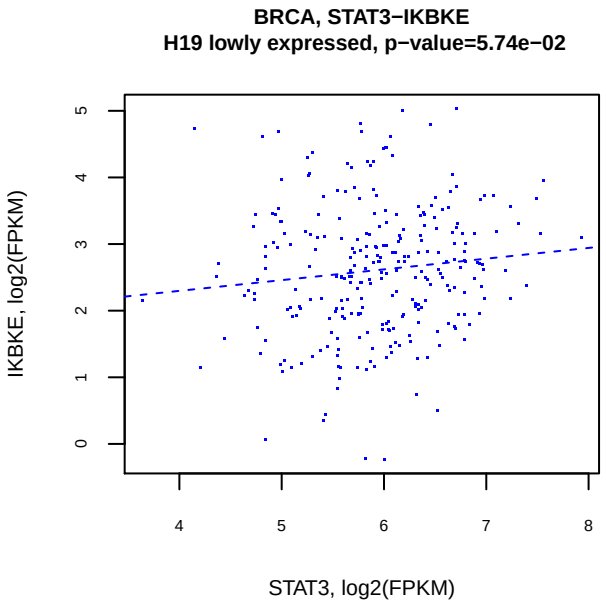
H19 highly expressed, p−value=4.85e−06
SERPING1, log2(FPKM)
STAT1, log2(FPKM)

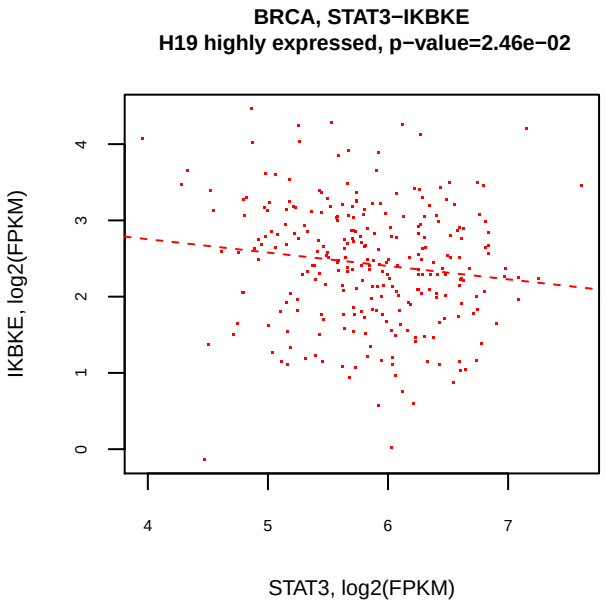

BRCA, STAT1−TYMP
H19 lowly expressed, p−value=6.99e−17
TYMP, log2(FPKM)
STAT1, log2(FPKM)

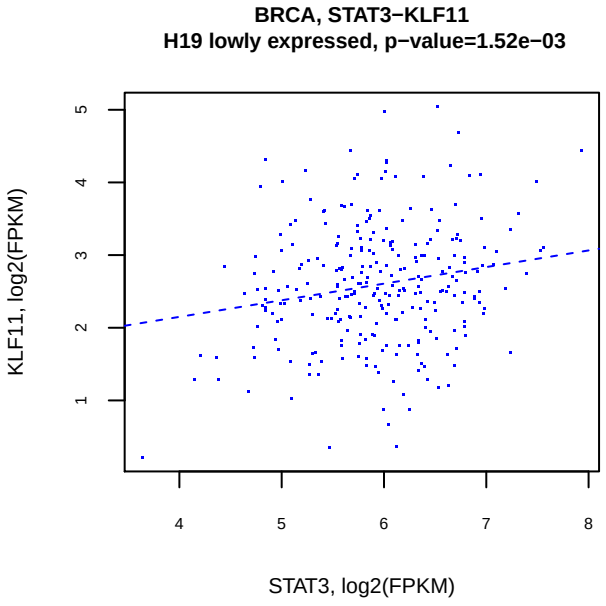

BRCA, STAT1−TYMP
H19 highly expressed, p−value=2.96e−02
TYMP, log2(FPKM)
STAT1, log2(FPKM)

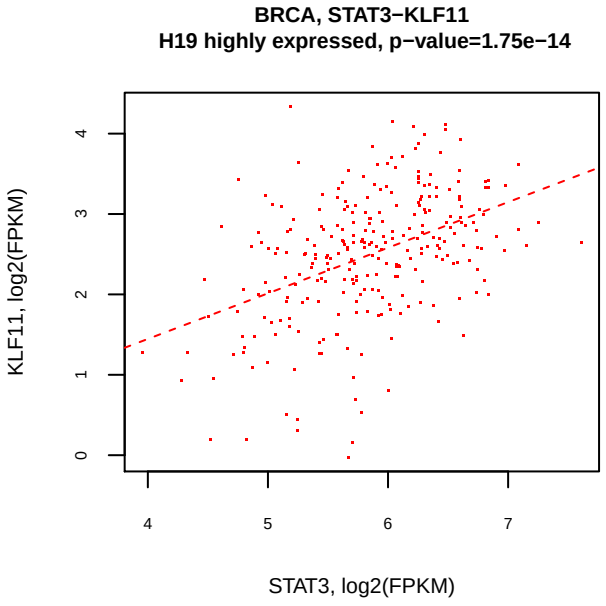

BRCA, STAT3−AKAP12
H19 lowly expressed, p−value=2.81e−06
AKAP12, log2(FPKM)
STAT3, log2(FPKM)

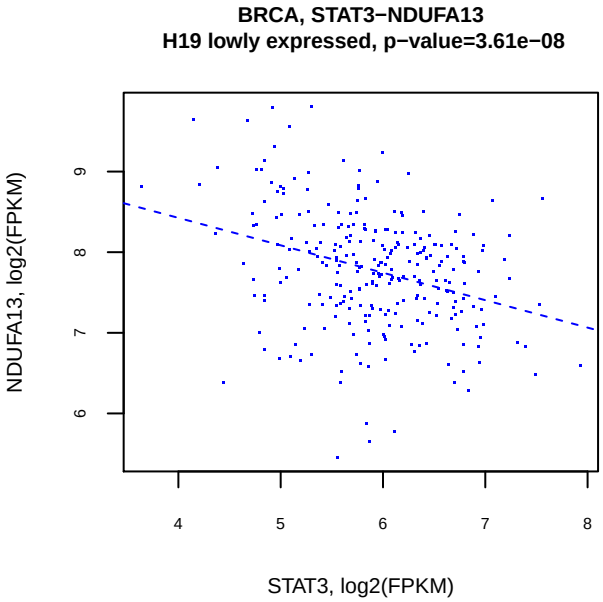

BRCA, STAT3−AKAP12
H19 highly expressed, p−value=1.31e−16
AKAP12, log2(FPKM)
STAT3, log2(FPKM)

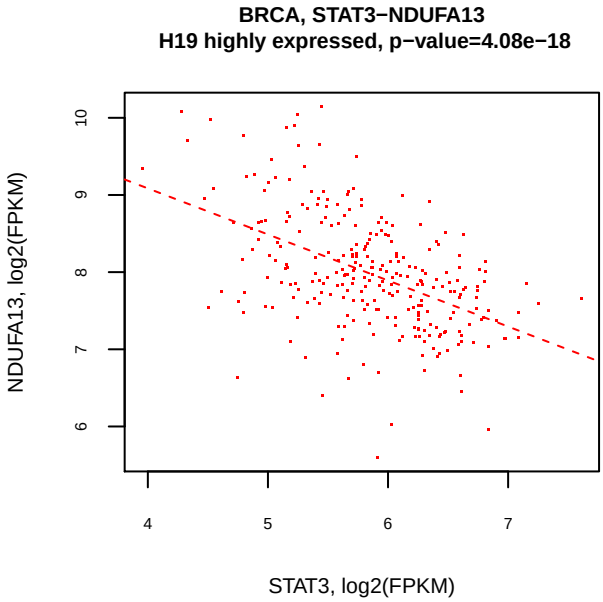

BRCA, STAT3−IKBKE
H19 lowly expressed, p−value=5.74e−02
IKBKE, log2(FPKM)
STAT3, log2(FPKM)

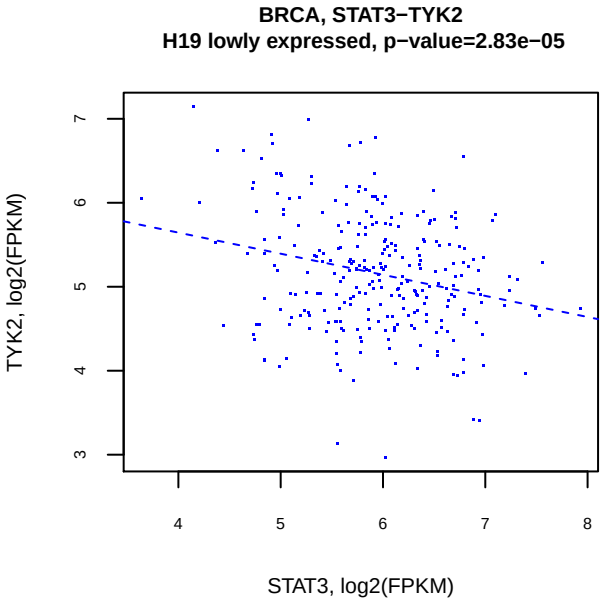

BRCA, STAT3−IKBKE
H19 highly expressed, p−value=2.46e−02
IKBKE, log2(FPKM)
STAT3, log2(FPKM)


BRCA, STAT3−KLF11
H19 lowly expressed, p−value=1.52e−03
KLF11, log2(FPKM)
STAT3, log2(FPKM)


BRCA, STAT3−KLF11
H19 highly expressed, p−value=1.75e−14
KLF11, log2(FPKM)
STAT3, log2(FPKM)


BRCA, STAT3−NDUFA13
H19 lowly expressed, p−value=3.61e−08
NDUFA13, log2(FPKM)
STAT3, log2(FPKM)


BRCA, STAT3−NDUFA13
H19 highly expressed, p−value=4.08e−18
NDUFA13, log2(FPKM)
STAT3, log2(FPKM)


BRCA, STAT3−TYK2
H19 lowly expressed, p−value=2.83e−05
TYK2, log2(FPKM)
STAT3, log2(FPKM)

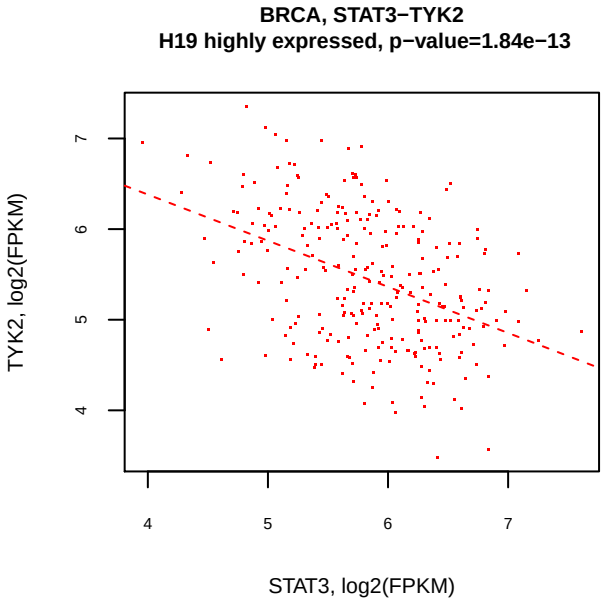

BRCA, STAT3−TYK2
H19 highly expressed, p−value=1.84e−13
TYK2, log2(FPKM)
STAT3, log2(FPKM)

Table S1. Number of Samples and Genes

Cancer			Samples				After FKPM Filtration		TF-gene Interactions		
No	**Cancer Type Abbreviation**	**Cancer Type Name**	**Total Number of Samples**	**# Primary Tumor Samples**	**# Matched Controls**	**# Other Samples**	**# Genes**	**Number of TFs**	**# Pairs (TF-gene)**	**# TFs**	**# Genes**
1	BLCA	Bladder urothelial carcinoma	426	407	19	0	11481	683	7723	607	2103
2	BRCA	Breast invasive carcinoma	1212	1092	113	7	11867	694	8181	625	2198
3	CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma	309	304	3	2	11508	709	8057	634	2161
4	COAD	Colon adenocarcinoma	331	288	41	2	11537	700	8123	631	2187
5	ESCA	Esophageal carcinoma	195	181	13	1	11727	723	8277	655	2205
6	GBM	Glioblastoma multiforme	171	153	5	13	12279	717	7755	636	2156
7	HNSC	carcinoma	564	518	44	2	11406	691	7866	621	2140
8	KIRC	Kidney renal clear cell carcinoma	91	66	25	0	11881	697	7889	628	2172
9	KIRP	Kidney renal papillary cell carcinoma	321	288	32	1	11599	667	7130	591	2030
10	LGG	Brain lower grade glioma	523	509	0	14	12104	678	6837	589	1996
11	LIHC	Liver hepatocellular carcinoma	421	369	50	2	10577	622	6988	546	1964
12	LUAD	Lung adenocarcinoma	574	513	59	2	12065	695	8223	621	2233
13	LUSC	Lung squamous cell carcinoma	548	498	50	0	12002	720	8444	653	2281
14	OV	Ovarian serous cystadenocarcinoma	427	419	0	8	11838	699	8030	622	2159
15	PAAD	Pancreatic adenocarcinoma	183	178	4	1	12346	722	8758	651	2369
16	PCPG	Paraganglioma	185	177	3	5	11520	660	6438	562	1896
17	PRAD	Prostate adenocarcinoma	548	495	52	1	11785	700	7889	624	2170
18	SARC	Sarcoma	264	258	2	4	11343	690	7353	602	2053
19	SKCM	Skin cutaneous melanoma	470	102	1	367	11028	667	7055	585	1982
20	STAD	Stomach adenocarcinoma	450	414	36	0	11792	726	8460	648	2252
21	TGCT	Testicular germ cell tumors	154	148	0	6	12184	701	8042	620	2202
22	THCA	Thyroid carcinoma	571	504	59	8	11693	666	7284	587	2020
23	THYM	Thymoma	571	504	59	8	11757	680	7270	602	2055
24	UCEC	Uterine corpus endometrial carcinoma	204	180	23	1	11718	698	8092	625	2152

Table S2. Regression of H19's regulation on TF-gene pairs

Triplet	BRCA	COAD	HNSC	KIRC	LGG	LUAD	PAAD	STAD	TGCT	THCA	# of cancer types	H19 lowley expressed	H19 highly expressed
H19_AHR_HSPB1	5.05									2.98	2	⊣	⊣⊣
H19_AIP_RSF1	2.97									2.77	2	⊣	⊣⊣
H19_EZH2_DACT3	5.87							4.90			2	⊣	⊣⊣
H19_NFKB1_MIF	2.47						3.33				2	⊣	⊣⊣
H19_NFYB_EDF1	5.59									2.28	2	⊣	⊣⊣
H19_SP1_HRAS	4.02									4.98	2	⊣	⊣⊣
H19_SP1_HSPB1	3.50									2.54	2	⊣	⊣⊣
H19_SP1_SIGIRR	3.15									2.16	2	⊣	⊣⊣
H19_SP3_EDF1				5.92						4.91	2	⊣	⊣⊣
H19_STAT3_NDUFA13	2.54									2.93	2	⊣	⊣⊣
H19_STAT3_TYK2	2.57									3.18	2	⊣	⊣⊣
H19_AHR_CCNG2	2.99						2.38				2	→	→→
H19_AHR_SOS1	3.91						2.73			2.94	3	→	→→
H19_CREBBP_CREB1	3.13					3.94					2	→	→→
H19_E2F3_MAPK8	4.49									3.59	2	→	→→
H19_EGR1_SPRY1	3.44				3.38						2	→	→→
H19_ERG_EPB41L3							2.22			2.84	2	→	→→
H19_ETS1_TGFBR2	9.19			4.21							2	→	→→
H19_EZH2_BRCA1	3.70				4.87						2	→	→→
H19_FLI1_CTGF	2.51	3.53									2	→	→→
H19_FLI1_TGFBR2	6.02		4.14								2	→	→→
H19_FOSL2_BCL6	3.02	6.40									2	→	→→
H19_FOXM1_CCNB1					3.83				3.39		2	→	→→
H19_FOXO1_TXNIP	2.93			3.12							2	→	→→
H19_GATA2_VWF	3.20			8.26							2	→	→→
H19_HNRNPK_EIF4E						2.92				5.33	2	→	→→
H19_KAT2B_SMAD4	5.05									2.19	2	→	→→
H19_KAT2B_ZEB1	2.66						2.78				2	→	→→
H19_KLF4_IL6	4.16									3.96	2	→	→→
H19_KLF6_TXNIP	3.26					2.66					2	→	→→
H19_NFKB1_CHUK	3.60									5.56	2	→	→→

Triplet	BRCA	COAD	HNSC	KIRC	LGG	LUAD	PAAD	STAD	TGCT	THCA	# of cancer types	H19 lowley expressed	H19 highly expressed
H19_NFYB_HMGCS1	2.37									3.79	2	→	→→
H19_NFYB_SP3	7.48									2.79	2	→	→→
H19_NR3C1_CALD1	5.86									2.72	2	→	→→
H19_PPARA_KLF11	6.41									3.46	2	→	→→
H19_RB1_WRN	2.40									2.86	2	→	→→
H19_RUNX2_MMP2	3.20									2.81	2	→	→→
H19_SOX18_CLDN5	9.50					3.07					2	→	→→
H19_SP1_ADAM17	3.71									5.66	2	→	→→
H19_SP1_ATM	3.51									5.70	2	→	→→
H19_SP1_TGFBR2	2.91									4.08	2	→	→→
H19_SP1_UTRN	4.22									3.01	2	→	→→
H19_STAT3_AKAP12	2.67									3.59	2	→	→→
H19_STAT3_KLF11	3.53									3.41	2	→	→→
H19_TWIST2_SRPX						3.97	3.33				2	→	→→
H19_AHR_CYP1B1									2.45	7.59	2	→→	→
H19_AKNA_CD40	2.68						3.30				2	→→	→
H19_CIITA_HLA-DRA	3.73									3.68	2	→→	→
H19_IRF8_CD68							4.43			5.10	2	→→	→
H19_SNAI2_MET	2.58		5.20								2	→→	→
H19_SPI1_ACP5							2.42			4.55	2	→→	→
H19_SPI1_CD40	3.07							3.39			2	→→	→
H19_SPI1_IL18	3.75									3.14	2	→→	→
H19_SPI1_NCF2	3.67						2.63				2	→→	→
H19_STAT1_CD40	4.37									3.12	2	→→	→
H19_STAT1_FCGR1A	4.69									2.73	2	→→	→
H19_STAT1_SERPING1	4.06									4.74	2	→→	→
H19_STAT1_TYMP	3.88					3.72					2	→→	→
H19_GATA2_VCAM1	2.95			6.16							2	⊣	→
H19_NFKB1_NCAM1							3.51			3.86	2	⊣	→
H19_SP1_ME1						4.42				5.08	2	⊣	→
H19_TP53_IGFBP3					4.07					3.41	2	⊣	→
H19_CTCF_IPO13						3.15				3.26	2	→	⊣
H19_E2F1_GADD45B	5.75	3.86									2	→	⊣

Triplet	BRCA	COAD	HNSC	KIRC	LGG	LUAD	PAAD	STAD	TGCT	THCA	# of cancer types	H19 lowley expressed	H19 highly expressed
H19_E2F1_MYC							3.64			6.27	2	→	⊣
H19_EZH2_CIITA							3.52	4.20			2	→	⊣
H19_EZH2_SNAI2	6.04	4.55									2	→	⊣
H19_FOXO1_HYOU1						2.64			9.10		2	→	⊣
H19_HDAC1_TXNIP	4.88					4.11					2	→	⊣
H19_HDAC2_TWIST1	2.77	3.76									2	→	⊣
H19_HDGF_FAS	6.14						7.27				2	→	⊣
H19_IKZF1_BIRC5	4.72						3.70				2	→	⊣
H19_MYB_COL1A1		4.33						4.66			2	→	⊣
H19_MYBL2_COL1A1	11.03	4.48						6.07			3	→	⊣
H19_MYC_E2F1							4.03			5.84	2	→	⊣
H19_NFKB2_HIF1A						3.54	3.57				2	→	⊣
H19_PARP1_FBN1	2.70								5.57		2	→	⊣
H19_PARP1_FN1	3.53	3.08									2	→	⊣
H19_POU2AF1_TK1	5.63						7.38				2	→	⊣
H19_POU2F1_VWF						7.74		5.91			2	→	⊣
H19_RELA_BGN							3.90			3.75	2	→	⊣
H19_RUNX1_SYMPK		5.54				7.74				5.65	3	→	⊣
H19_SOX9_CD3E				4.64			5.49				2	→	⊣
H19_SP1_ABCA2						8.08				4.60	2	→	⊣
H19_SP1_FLNA						5.20				5.60	2	→	⊣
H19_STAT3_DNMT1						4.92				3.38	2	→	⊣
H19_STAT3_IKBKE	2.59							6.50			2	→	⊣
H19_USF1_FMR1							3.09			2.91	2	→	⊣

Notes: The values are transformed as -log10(p-value). Pattern: → activation, ⊣ repression.

Table S3. TF-gene pairs modulated by H19 and their evidences that related to specific cancers.

No	TF/Gene	BRCA	COAD	HNSC	KIRC	LGG	LUAD	PAAD	STAD	TGCT	THCA
1	AHR	[1]						[2]			
	CCNG2	[3]						[4]			
2	AHR									[5]	[6]
	CYP1B1									[7]	[8]
3	AHR	[1]									[6]
	HSPB1	[9]									[10]
4	AHR	[1]						[2]			[6]
	SOS1	[11]						[12]			[13]
5	AIP	[14]									[15]
	RSF1	[16]									[17]
6	AKNA	[18]						[19]			
	CD40	[20]						[21]			
7	CIITA	[22]									[23]
	HLA-DRA	[24]									[25]
8	CREBBP	[26]					[27]				
	CREB1	[28]					[29]				
9	CTCF						[30]				[31]
	IPO13						?				?
10	E2F1	[32]	[33]								
	GADD45B	[34]	[35]								
11	E2F1							[36]			[37]
	MYC							[38]			[39]
12	E2F3	[40]									[41]
	MAPK8	[42]									[43]
13	EGR1	[44]				[45]					
	SPRY1	[46]				[47]					
14	ERG							[48]			[49]
	EPB41L3							[50]			[51]
15	ETS1	[52]			[53]						
	TGFBR2	[54]			[55]						
16	EZH2	[56]				[57]					
	BRCA1	[58]				[59]					
17	EZH2							[60]	[61]		
	CIITA							[62]	[63]		
18	EZH2	[56]							[61]		
	DACT3	[64]							?		
19	EZH2	[56]	[65]								
	SNAI2	[66]	[67]								
20	FLI1	[68]	[69]								
	CTGF	[70]	[71]								

No	TF/Gene	BRCA	COAD	HNSC	KIRC	LGG	LUAD	PAAD	STAD	TGCT	THCA
21	FLI1	[68]		[72]							
	TGFBR2	[52]		[73]							
22	FOSL2	[74]	[75]								
	BCL6	[76]	[77]								
23	FOXM1	[78]				[79]				[80]	
	CCNB1	[81]				[82]				[83]	
24	FOXO1	[84]					[85]			[86]	
	HYOU1	[87]					[88]			?	
25	FOXO1	[84]			[89]						
	TXNIP	[90]			[91]						
26	GATA2	[92]			[93]						
	VCAM1	[94]			[93]						
27	GATA2	[92]			[93]						
	VWF	[95]			[96]						
28	HDAC1	[97]					[98]				
	TXNIP	[90]					[99]				
29	HDAC2	[100]	[101]								
	TWIST1	[102]	[103]								
30	HDGF	[104]						[105]			
	FAS	[106]						[107]			
31	HNRNPK						[108]				[109]
	EIF4E						[110]				[111]
32	IKZF1	[112]						[113]			
	BIRC5	[114]						[115]			
33	IRF8							[116]			[117]
	CD68							[118]			[119]
34	KAT2B	[120]									[121]
	SMAD4	[122]									[123]
35	KAT2B	[120]						[124]			
	ZEB1	[125]						[126]			
36	KLF4	[127]									[128]
	IL6	[129]									[130]
37	KLF6	[131]					[132]				
	TXNIP	[90]					[99]				
38	MYB		[133]						[134]		
	COL1A1		[135]						[136]		
39	MYBL2	[137]	[35]						[138]		
	COL1A1	[139]	[135]						[136]		
40	MYC							[38]			[39]
	E2F1							[36]			[37]

No	TF/Gene	BRCA	COAD	HNSC	KIRC	LGG	LUAD	PAAD	STAD	TGCT	THCA
41	NFKB1	[140]									[141]
	CHUK	[142]									?
42	NFKB1	[143]						[144]			
	MIF							[145]			
43	NFKB1							[144]			[141]
	NCAM1							[146]			[147]
44	NFKB2						[148]	[149]			
	HIF1A						[150]	[151]			
45	NFYB	[152]									[153]
	EDF1	[154]									?
46	NFYB	[152]									[153]
	HMGCS1	[155]									[156]
47	NFYB	[152]									[153]
	SP3	[157]									[158]
48	NR3C1	[159]									[160]
	CALD1	[161]									[162]
49	PARP1	[163]								[164]	
	FBN1	[161]								[165]	
50	PARP1	[163]	[166]								
	FN1	[167]	[168]								
51	POU2AF1	[169]						[170]			
	TK1	[171]						[172]			
52	POU2F1						[173]		[174]		
	VWF						[175]		[176]		
53	PPARA	[177]									[178]
	KLF11	[179]									[180]
54	RB1	[181]									[182]
	WRN	[183]									[184]
55	RELA							[185]			[186]
	BGN							[187]			?
56	RUNX1		[188]				[189]				[190]
	SYMPK		[191]				[192]				?
57	RUNX2	[193]									[194]
	MMP2	[195]									[196]
58	SNAI2	[66]		[197]							
	MET	[198]		[199]							
59	SOX18	[200]					[201]				
	CLDN5	[202]					[203]				
60	SOX9				[204]			[205]			
	CD3E				[206]			[207]			

No	TF/Gene	BRCA	COAD	HNSC	KIRC	LGG	LUAD	PAAD	STAD	TGCT	THCA
61	SP1						[208]				[209]
	ABCA2						[210]				[211]
62	SP1	[212]									[209]
	ADAM17	[213]									[214]
63	SP1	[212]									[209]
	ATM	[215]									[216]
64	SP1	[212]					[208]				[209]
	FLNA	[217]					[218]				[219]
65	SP1	[212]									[209]
	HRAS	[220]									[221]
66	SP1	[212]									[209]
	HSPB1	[9]									[222]
67	SP1	[212]					[208]				[209]
	ME1	[223]					[224]				?
68	SP1	[212]									[209]
	SIGIRR	[225]									?
69	SP1	[212]									[209]
	TGFBR2	[52]									[226]
70	SP1	[212]									[209]
	UTRN	[227]									[228]
71	SP3				[229]						[158]
	EDF1				?						?
72	SPI1							[187]			[230]
	ACP5							[231]			[232]
73	SPI1	[233]							[234]		
	CD40	[20]							[235]		
74	SPI1	[233]									[230]
	IL18	[236]									[237]
75	SPI1	[233]						[187]			
	NCF2	[238]						[239]			
76	STAT1	[240]									[241]
	CD40	[20]									[242]
77	STAT1	[240]									[241]
	FCGR1A	[243]									[244]
78	STAT1	[240]									[241]
	SERPING1	[245]									[246]
79	STAT1	[240]					[247]				
	TYMP	[248]					[249]				
80	STAT3	[250]									[251]
	AKAP12	[252]									[253]

No	TF/Gene	BRCA	COAD	HNSC	KIRC	LGG	LUAD	PAAD	STAD	TGCT	THCA
81	STAT3						[254]				[251]
	DNMT1						[255]				[256]
82	STAT3	[250]							[257]		
	IKBKE	[258]							[259]		
83	STAT3	[250]									[251]
	KLF11	[179]									[180]
84	STAT3	[250]									[251]
	NDUFA13	[260]									[261]
85	STAT3	[250]									[251]
	TYK2	[262]									[263]
86	TP53					[264]					[265]
	IGFBP3					[266]					[267]
87	TWIST2						[268]	[269]			
	SRPX						[270]	[271]			
88	USF1							?			[272]
	FMR1							[273]			[274]

Notes: '?' means having not found related evidences. There are 13 TFs/genes which have not evidences to support their relation to specific cancers. TF: Transcription Factor, BRCA: Breast invasive carcinoma, COAD: Colon adenocarcinoma, HNSC: Head and Neck squamous cell carcinoma, KIRC: Kidney renal clear cell carcinoma, LGG: Brain Lower Grade Glioma, LUAD: Lung adenocarcinoma, PAAD: Pancreatic adenocarcinoma, STAD: Stomach adenocarcinoma, TGCT: Testicular Germ Cell Tumors, THCA: Thyroid carcinoma.

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Table S4. miRNAs targeted by H19

miRNA	Description	Reference
let-7a	➢ The H19/let-7 double-negative feedback loop contributes to glucose metabolism in muscle cells. ➢ The imprinted H19 lncRNA antagonizes let-7 microRNAs. ➢ H19 lncRNA alters stromal cell growth via IGF signaling in the endometrium of women with endometriosis. ➢ Glycolysis gatekeeper PDK1 reprograms breast cancer stem cells under hypoxia.	[1] [2] [3] [4]
let-7b	➢ The imprinted H19 lncRNA antagonizes let-7 microRNAs. ➢ Glycolysis gatekeeper PDK1 reprograms breast cancer stem cells under hypoxia. ➢ The lncRNA H19 mediates breast cancer cell plasticity during EMT and MET plasticity by differentially sponging miR-200b/c and let-7b.	[2] [4] [5]
let-7g	➢ The imprinted H19 lncRNA antagonizes let-7 microRNAs. ➢ H19 lncRNA alters stromal cell growth via IGF signaling in the endometrium of women with endometriosis.	[2] [3]
let-7i	➢ H19/let-7/LIN28 reciprocal negative regulatory circuit promotes breast cancer stem cell maintenance.	[6]
miR-106a	➢ miR-CLIP capture of a miRNA targetome uncovers a lincRNA H19-miR-106a interaction.	[7]
miR-130b-3p	➢ H19 lncRNA regulates keratinocyte differentiation by targeting miR-130b-3p.	[8]
miR-138-5p	➢ Decreased Expression of MiR-138-5p by LncRNA H19 in Cervical Cancer Promotes Tumor Proliferation.	[9]
miR-139	➢ H19 lncRNA alters stromal cell growth via IGF signaling in the endometrium of women with endometriosis. ➢ Long Non-Coding RNA H19 Protects H9c2 Cells against Hypoxia-Induced Injury by Targeting MicroRNA-139.	[3] [10]
miR-141	➢ H19 activates Wnt signaling and promotes osteoblast differentiation by functioning as a competing endogenous RNA.	[11]
miR-152-3p	➢ Long non-coding RNA H19 promotes the proliferation and invasion of breast cancer through upregulating DNMT1 expression by sponging miR-152.	[12]
miR-152-5p	➢ Long non-coding RNA H19 promotes the proliferation and invasion of breast cancer through upregulating DNMT1 expression by sponging miR-152.	[12]
miR-17-5p	➢ Long noncoding RNA H19 competitively binds miR-17-5p to regulate YES1 expression in thyroid cancer. ➢ Long non-coding RNA H19 suppresses retinoblastoma progression	[13] [14]

		via counteracting miR-17-92 cluster.	
miR-181d-3p	➢	Hypoxia induces H19 expression through direct and indirect Hif-1α activity, promoting oncogenic effects in glioblastoma.	[15]
miR-181d-5p	➢	Hypoxia induces H19 expression through direct and indirect Hif-1α activity, promoting oncogenic effects in glioblastoma.	[15]
miR-18a	➢	Long non-coding RNA H19 suppresses retinoblastoma progression via counteracting miR-17-92 cluster.	[14]
miR-194-5p	➢	Long noncoding RNA H19 contributes to gallbladder cancer cell proliferation by modulated miR-194-5p targeting AKT2.	[16]
miR-196a	➢	The lncRNA H19 Mediates Pulmonary Fibrosis by Regulating the miR-196a/COL1A1 Axis.	[17]
miR-19a	➢	Long non-coding RNA H19 suppresses retinoblastoma progression via counteracting miR-17-92 cluster.	[14]
miR-19b-1	➢	Long non-coding RNA H19 suppresses retinoblastoma progression via counteracting miR-17-92 cluster.	[14]
miR-200b	➢	The lncRNA H19 mediates breast cancer cell plasticity during EMT and MET plasticity by differentially sponging miR-200b/c and let-7b.	[5]
miR-200c	➢	The lncRNA H19 mediates breast cancer cell plasticity during EMT and MET plasticity by differentially sponging miR-200b/c and let-7b.	[5]
miR-20a	➢	Long non-coding RNA H19 suppresses retinoblastoma progression via counteracting miR-17-92 cluster.	[14]
miR-22	➢	H19 activates Wnt signaling and promotes osteoblast differentiation by functioning as a competing endogenous RNA.	[11]
miR-29a	➢	Long non-coding RNA H19 regulates glioma angiogenesis and the biological behavior of glioma-associated endothelial cells by inhibiting microRNA-29a.	[18]
miR-29b	➢	Long noncoding RNA H19 accelerates tenogenic differentiation and promotes tendon healing through targeting miR-29b-3p and activating TGF-β1 signaling.	[19]
miR-342-3p	➢	Long non-coding RNA H19 regulates FOXM1 expression by competitively binding endogenous miR-342-3p in gallbladder cancer.	[20]
miR-630	➢	Long noncoding RNA H19 regulates EZH2 expression by interacting with miR-630 and promotes cell invasion in nasopharyngeal carcinoma.	[21]
miR-874	➢	LncRNA H19 functions as a competing endogenous RNA to regulate AQP3 expression by sponging miR-874 in the intestinal barrier.	[22]
miR-92a-1	➢	Long non-coding RNA H19 suppresses retinoblastoma progression via counteracting miR-17-92 cluster.	[14]

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Table S5. Regulation of 29 miRNAs in eight triplets.

H19-ETS1-TGFBR2

miRNAs	miR-106a	miR-130b-3p	miR-138-5p	miR-139	miR-141	miR-152-3p	miR-152-5p
Predicted targets of miRNAs							
TFs	RUNX1	FOSL2	EZH2	ETS1	CREBBP	KLF6	KLF6
	E2F1	MYB	POU2F1		POU2F1	KLF4	E2F3
	PPARA	STAT3	RELA				KLF4
	RB1		SP1				
	SP1						
	STAT3						
	KAT2B						
Genes	CALD1	FMR1	HIF1A	FMR1	FMR1	CHUK	DNMT1
	CCNG2	MET	KLF11	MAPK8		DNMT1	FBN1
	E2F1	TGFBR2		ZEB1		FBN1	FMR1
	HIF1A					FMR1	SOS1
	SMAD4					SOS1	
	MMP2						
	MAPK8						
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						
Validated targets of miRNAs							
TFs	E2F1	AHR	EZH2	NFKB1	E2F3	KLF4	
	MYB	E2F1	NFKB1		PPARA		
	RB1	NR3C1	SNAI2		HDGF		
	RUNX1	PPARA	SOX9				
	STAT3	RB1	TWIST2				
		STAT3					
Genes	E2F1	E2F1	HIF1A	HRAS	ZEB1	DNMT1	
	FAS	KLF11	SNAI2	MET	EIF4E	ADAM17	
	TGFBR2	SMAD4			KLF11		
	ATM	TGFBR2			ZEB1		
	HIF1A	ZEB1					
		FMR1					
		MMP2					

Notes: In the H19-ETS1-TGFBR2 sheet, we list all the 29 miRNAs and their targets (TFs and genes). Some of the targets were predicted and then verified. In the H19-ETS1-TGFBR2 table, TFs are marked in yellow if miRNAs target them, and genes are marked in red if miRNAs target them.

miRNAs	miR-17	miR-181d-3p	miR-181d-5p	miR-18a	miR-194-5p	miR-196a	miR-19a
Predicted targets of miRNAs							
TFs	RUNX1		RUNX1	RUNX1	E2F3	ERG	
	E2F1		KLF6	KLF6	FLI1	FLI1	
	RB1		ETS1	NR3C1	SP3		
	STAT3		NR3C1	POU2F1			
	KAT2B		KAT2B				
Genes	CALD1		ATM	ATM	ACP5	FAS	FMR1
	CCNG2		SOS1	CTGF	FMR1	COL1A1	IL18
	E2F1		VCAM1	HIF1A	SP3	MAPK8	
	HIF1A		EPB41L3	HMGCS1	RSF1	ZEB1	
	MMP2			MAPK8			
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						

Validated targets of miRNAs							
TFs	E2F1			NR3C1	FOXM1	FOXO1	KAT2B
	E2F3			RUNX1			
	KAT2B						
	MYC						
	RB1						
	RUNX1						
	STAT3						
Genes	E2F1		HRAS	CTGF		FLNA	CTGF
	MMP2			EDF1		TGFBR2	SMAD4
	MYC			ATM			TGFBR2
	SMAD4			HIF1A			DNMT1
	TGFBR2			HMGCS1			
	HIF1A			SMAD4			
	DNMT1			TGFBR2			
	IGFBP3			DNMT1			

miRNAs	miR-19b-1	miR-200b	miR-200c	miR-20a	miR-22	miR-29a	miR-29b
Predicted targets of miRNAs							
TFs		KLF6		E2F1	FOXO1	ETS1	MYBL2
		SP3		E2F3	HNRNPK	KAT2B	
				EZH2			
				PPARA			
				RB1			
				STAT3			
				KAT2B			
Genes		NCF2		CALD1	CD68		DNMT1
		MAPK8		CCNG2	SOS1		FBN1
		SP3		E2F1	UTRN		EDF1
				HIF1A	VCAM1		
				SMAD4	WRN		
				MMP2			
				MAPK8			
				SOS1			
				TGFBR2			
				KLF11			
				TXNIP			

Validated targets of miRNAs							
TFs	KAT2B	E2F3	MYB	E2F1	PPARA	KLF4	SP1
	NR3C1	ETS1	ETS1	E2F3		AHR	STAT3
		MYB	SP1	MYC		MYC	SP1
		SP1	E2F3	RB1			STAT3
		EZH2	FOXO1	RUNX1			MYC
			E2F3	STAT3			
Genes	CTGF	CREB1	FLNA	CCNB1	HIF1A	MMP2	COL1A1
	FMR1	FN1	FN1	E2F1		DNMT1	DNMT1
	ATM	KLF11	KLF11	FLNA		FBN1	MMP2
	HMGCS1	ZEB1	ZEB1	HIF1A		MYC	FBN1
	SMAD4	DNMT1	NCAM1	MYC			MYC
	TGFBR2		CYP1B1	SMAD4			
	DNMT1			TGFBR2			
				DNMT1			

miRNAs	miR-342-3p	miR-630	miR-874	miR-92a-1	let-7a	let-7b	let-7g
Predicted targets of miRNAs							
TFs	E2F3	KLF6	POU2F1		EZH2	EZH2	EZH2
		EZH2	STAT3		POU2F1	POU2F1	POU2F1
					RB1	RB1	RB1
					TP53	TP53	TP53
Genes	DNMT1		FBN1	COL1A1	FAS	FAS	FAS
	ZEB1		FMR1	DACT3	COL1A1	COL1A1	COL1A1
			SIGIRR		IL6	IL6	IL6
					MAPK8	MAPK8	MAPK8
					UTRN	UTRN	UTRN

Validated targets of miRNAs							
TFs	FOSL2	SNAI2	PARP1	HDAC1	E2F1	CTCF	MYC
	E2F1	FOXM1	HDAC1	HDGF	EZH2	E2F3	
			STAT3	KAT2B	MYC	EZH2	
			E2F3	MYBL2	NFKB1	MYC	
				NFKB1	PARP1	SOX9	
				STAT3	SP1	SP1	
				HDAC2	STAT3		
				KLF4			
				IKZF1			
Genes	DNMT1	SNAI2		ATM	MYC	BIRC5	MYC
	E2F1			CCNB1	HRAS	CCNB1	FN1
				EPB41L3	E2F1	EPB41L3	
				FLNA	IL6	FLNA	
				HMGCS1		HIF1A	
				SMAD4		HMGCS1	
				TGFBR2		MYC	
				TYMP		UTRN	
				MAPK8		HRAS	
				DNMT1			

miRNAs	let-7i

Predicted targets of miRNAs

TFs	EZH2
	POU2F1
	RB1
	TP53
Genes	FAS
	CHUK
	COL1A1
	IL6
	MAPK8
	UTRN

Validated targets of miRNAs

TFs	
Genes	

H19-FLI1-TGFBR2

miRNAs	miR-106a	miR-130b-3p	miR-138-5p	miR-139	miR-141	miR-152-3p	miR-152-5p	miR-17

Predicted targets of miRNAs

TFs	RUNX1	FOSL2	EZH2	ETS1	CREBBP	KLF6	KLF6	RUNX1
	E2F1	MYB	POU2F1		POU2F1	KLF4	E2F3	E2F1
	PPARA	STAT3	RELA				KLF4	RB1
	RB1		SP1					STAT3
	SP1							KAT2B
	STAT3							
	KAT2B							
Genes	CALD1	FMR1	HIF1A	FMR1	FMR1	CHUK	DNMT1	CALD1
	CCNG2	MET	KLF11	MAPK8		DNMT1	FBN1	CCNG2
	E2F1	TGFBR2		ZEB1		FBN1	FMR1	E2F1
	HIF1A					FMR1	SOS1	HIF1A
	SMAD4					SOS1		MMP2
	MMP2							SOS1
	MAPK8							TGFBR2
	SOS1							KLF11
	TGFBR2							TXNIP
	KLF11							
	TXNIP							

Validated targets of miRNAs

TFs	E2F1	AHR	EZH2	NFKB1	E2F3	KLF4		E2F1
	MYB	E2F1	NFKB1		PPARA			E2F3
	RB1	NR3C1	SNAI2		HDGF			KAT2B
	RUNX1	PPARA	SOX9					MYC
	STAT3	RB1	TWIST2					RB1
		STAT3						RUNX1
								STAT3
Genes	E2F1	E2F1	HIF1A	HRAS	ZEB1	DNMT1		E2F1
	FAS	KLF11	SNAI2	MET	EIF4E	ADAM17		MMP2
	TGFBR2	SMAD4			KLF11			MYC
	ATM	TGFBR2			ZEB1			SMAD4
	HIF1A	ZEB1						TGFBR2
		FMR1						HIF1A
		MMP2						DNMT1
								IGFBP3

miRNAs	miR-181d-3p	miR-181d-5p	miR-18a	miR-194-5p	miR-196a	miR-19a	miR-19b-1	miR-200b
Predicted targets of miRNAs								
TFs		RUNX1	RUNX1	E2F3	ERG			KLF6
		KLF6	KLF6	FLI1	FLI1			SP3
		ETS1	NR3C1	SP3				
		NR3C1	POU2F1					
		KAT2B						
Genes		ATM	ATM	ACP5	FAS	FMR1		NCF2
		SOS1	CTGF	FMR1	COL1A1	IL18		MAPK8
		VCAM1	HIF1A	SP3	MAPK8			SP3
		EPB41L3	HMGCS1	RSF1	ZEB1			
			MAPK8					

Validated targets of miRNAs								
TFs			NR3C1	FOXM1	FOXO1	KAT2B	KAT2B	E2F3
			RUNX1				NR3C1	ETS1
								MYB
								SP1
								EZH2
Genes		HRAS	CTGF		FLNA	CTGF	CTGF	CREB1
			EDF1		TGFBR2	SMAD4	FMR1	FN1
			ATM			TGFBR2	ATM	KLF11
			HIF1A			DNMT1	HMGCS1	ZEB1
			HMGCS1				SMAD4	DNMT1
			SMAD4				TGFBR2	
			TGFBR2				DNMT1	
			DNMT1					

miRNAs	miR-200c	miR-20a	miR-22	miR-29a	miR-29b	miR-342-3p	miR-630	miR-874
Predicted targets of miRNAs								
TFs		E2F1	FOXO1	ETS1	MYBL2	E2F3	KLF6	POU2F1
		E2F3	HNRNPK	KAT2B			EZH2	STAT3
		EZH2						
		PPARA						
		RB1						
		STAT3						
		KAT2B						
Genes		CALD1	CD68		DNMT1	DNMT1		FBN1
		CCNG2	SOS1		FBN1	ZEB1		FMR1
		E2F1	UTRN		EDF1			SIGIRR
		HIF1A	VCAM1					
		SMAD4	WRN					
		MMP2						
		MAPK8						
		SOS1						
		TGFBR2						
		KLF11						
		TXNIP						

Validated targets of miRNAs								
TFs	MYB	E2F1	PPARA	KLF4	SP1	FOSL2	SNAI2	PARP1
	ETS1	E2F3		AHR	STAT3	E2F1	FOXM1	HDAC1
	SP1	MYC		MYC	SP1			STAT3
	E2F3	RB1			STAT3			E2F3
	FOXO1	RUNX1			MYC			
	E2F3	STAT3						
Genes	FLNA	CCNB1	HIF1A	MMP2	COL1A1	DNMT1	SNAI2	
	FN1	E2F1		DNMT1	DNMT1	E2F1		
	KLF11	FLNA		FBN1	MMP2			
	ZEB1	HIF1A		MYC	FBN1			
	NCAM1	MYC			MYC			
	CYP1B1	SMAD4						
		TGFBR2						
		DNMT1						

miRNAs	miR-92a-1	let-7a	let-7b	let-7g	let-7i
Predicted targets of miRNAs					
TFs		EZH2	EZH2	EZH2	EZH2
		POU2F1	POU2F1	POU2F1	POU2F1
		RB1	RB1	RB1	RB1
		TP53	TP53	TP53	TP53
Genes	COL1A1	FAS	FAS	FAS	FAS
	DACT3	COL1A1	COL1A1	COL1A1	CHUK
		IL6	IL6	IL6	COL1A1
		MAPK8	MAPK8	MAPK8	IL6
		UTRN	UTRN	UTRN	MAPK8
					UTRN
Validated targets of miRNAs					
TFs	HDAC1	E2F1	CTCF	MYC	
	HDGF	EZH2	E2F3		
	KAT2B	MYC	EZH2		
	MYBL2	NFKB1	MYC		
	NFKB1	PARP1	SOX9		
	STAT3	SP1	SP1		
	HDAC2	STAT3			
	KLF4				
	IKZF1				
Genes	ATM	MYC	BIRC5	MYC	
	CCNB1	HRAS	CCNB1	FN1	
	EPB41L3	E2F1	EPB41L3		
	FLNA	IL6	FLNA		
	HMGCS1		HIF1A		
	SMAD4		HMGCS1		
	TGFBR2		MYC		
	TYMP		UTRN		
	MAPK8		HRAS		
	DNMT1				

H19-FOXO1-TXNIP

miRNAs	miR-106a	miR-130b-3p	miR-138-5p	miR-139	miR-141	miR-152-3p	miR-152-5p
Predicted targets of miRNAs							
TFs	RUNX1	FOSL2	EZH2	ETS1	CREBBP	KLF6	KLF6
	E2F1	MYB	POU2F1		POU2F1	KLF4	E2F3
	PPARA	STAT3	RELA				KLF4
	RB1		SP1				
	SP1						
	STAT3						
	KAT2B						
Genes	CALD1	FMR1	HIF1A	FMR1	FMR1	CHUK	DNMT1
	CCNG2	MET	KLF11	MAPK8		DNMT1	FBN1
	E2F1	TGFBR2		ZEB1		FBN1	FMR1
	HIF1A					FMR1	SOS1
	SMAD4					SOS1	
	MMP2						
	MAPK8						
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						

Validated targets of miRNAs							
TFs	E2F1	AHR	EZH2	NFKB1	E2F3	KLF4	
	MYB	E2F1	NFKB1		PPARA		
	RB1	NR3C1	SNAI2		HDGF		
	RUNX1	PPARA	SOX9				
	STAT3	RB1	TWIST2				
		STAT3					
Genes	E2F1	E2F1	HIF1A	HRAS	ZEB1	DNMT1	
	FAS	KLF11	SNAI2	MET	EIF4E	ADAM17	
	TGFBR2	SMAD4			KLF11		
	ATM	TGFBR2			ZEB1		
	HIF1A	ZEB1					
		FMR1					
		MMP2					

miRNAs	miR-17	miR-181d-3p	miR-181d-5p	miR-18a	miR-194-5p	miR-196a	miR-19a
Predicted targets of miRNAs							
TFs	RUNX1		RUNX1	RUNX1	E2F3	ERG	
	E2F1		KLF6	KLF6	FLI1	FLI1	
	RB1		ETS1	NR3C1	SP3		
	STAT3		NR3C1	POU2F1			
	KAT2B		KAT2B				
Genes	CALD1		ATM	ATM	ACP5	FAS	FMR1
	CCNG2		SOS1	CTGF	FMR1	COL1A1	IL18
	E2F1		VCAM1	HIF1A	SP3	MAPK8	
	HIF1A		EPB41L3	HMGCS1	RSF1	ZEB1	
	MMP2			MAPK8			
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						

Validated targets of miRNAs							
TFs	E2F1			NR3C1	FOXM1	FOXO1	KAT2B
	E2F3			RUNX1			
	KAT2B						
	MYC						
	RB1						
	RUNX1						
	STAT3						
Genes	E2F1		HRAS	CTGF		FLNA	CTGF
	MMP2			EDF1		TGFBR2	SMAD4
	MYC			ATM			TGFBR2
	SMAD4			HIF1A			DNMT1
	TGFBR2			HMGCS1			
	HIF1A			SMAD4			
	DNMT1			TGFBR2			
	IGFBP3			DNMT1			

miRNAs	miR-19b-1	miR-200b	miR-200c	miR-20a	miR-22	miR-29a	miR-29b
Predicted targets of miRNAs							
TFs		KLF6		E2F1	FOXO1	ETS1	MYBL2
		SP3		E2F3	HNRNPK	KAT2B	
				EZH2			
				PPARA			
				RB1			
				STAT3			
				KAT2B			
Genes		NCF2		CALD1	CD68		DNMT1
		MAPK8		CCNG2	SOS1		FBN1
		SP3		E2F1	UTRN		EDF1
				HIF1A	VCAM1		
				SMAD4	WRN		
				MMP2			
				MAPK8			
				SOS1			
				TGFBR2			
				KLF11			
				TXNIP			

Validated targets of miRNAs							
TFs	KAT2B	E2F3	MYB	E2F1	PPARA	KLF4	SP1
	NR3C1	ETS1	ETS1	E2F3		AHR	STAT3
		MYB	SP1	MYC		MYC	SP1
		SP1	E2F3	RB1			STAT3
		EZH2	FOXO1	RUNX1			MYC
			E2F3	STAT3			
Genes	CTGF	CREB1	FLNA	CCNB1	HIF1A	MMP2	COL1A1
	FMR1	FN1	FN1	E2F1		DNMT1	DNMT1
	ATM	KLF11	KLF11	FLNA		FBN1	MMP2
	HMGCS1	ZEB1	ZEB1	HIF1A		MYC	FBN1
	SMAD4	DNMT1	NCAM1	MYC			MYC
	TGFBR2		CYP1B1	SMAD4			
	DNMT1			TGFBR2			
				DNMT1			

miRNAs	miR-342-3p	miR-630	miR-874	miR-92a-1	let-7a	let-7b	let-7g
Predicted targets of miRNAs							
TFs	E2F3	KLF6	POU2F1		EZH2	EZH2	EZH2
		EZH2	STAT3		POU2F1	POU2F1	POU2F1
					RB1	RB1	RB1
					TP53	TP53	TP53
Genes	DNMT1		FBN1	COL1A1	FAS	FAS	FAS
	ZEB1		FMR1	DACT3	COL1A1	COL1A1	COL1A1
			SIGIRR		IL6	IL6	IL6
					MAPK8	MAPK8	MAPK8
					UTRN	UTRN	UTRN
Validated targets of miRNAs							
TFs	FOSL2	SNAI2	PARP1	HDAC1	E2F1	CTCF	MYC
	E2F1	FOXM1	HDAC1	HDGF	EZH2	E2F3	
			STAT3	KAT2B	MYC	EZH2	
			E2F3	MYBL2	NFKB1	MYC	
				NFKB1	PARP1	SOX9	
				STAT3	SP1	SP1	
				HDAC2	STAT3		
				KLF4			
				IKZF1			
Genes	DNMT1	SNAI2		ATM	MYC	BIRC5	MYC
	E2F1			CCNB1	HRAS	CCNB1	FN1
				EPB41L3	E2F1	EPB41L3	
				FLNA	IL6	FLNA	
				HMGCS1		HIF1A	
				SMAD4		HMGCS1	
				TGFBR2		MYC	
				TYMP		UTRN	
				MAPK8		HRAS	
				DNMT1			

miRNAs	let-7i

Predicted targets of miRNAs

TFs	EZH2
	POU2F1
	RB1
	TP53
Genes	FAS
	CHUK
	COL1A1
	IL6
	MAPK8
	UTRN

Validated targets of miRNAs

TFs	
Genes	

H19-KLF6-TXNIP

miRNAs	miR-106a	miR-130b-3p	miR-138-5p	miR-139	miR-141	miR-152-3p	miR-152-5p
Predicted targets of miRNAs							
TFs	RUNX1	FOSL2	EZH2	ETS1	CREBBP	KLF6	KLF6
	E2F1	MYB	POU2F1		POU2F1	KLF4	E2F3
	PPARA	STAT3	RELA				KLF4
	RB1		SP1				
	SP1						
	STAT3						
	KAT2B						
Genes	CALD1	FMR1	HIF1A	FMR1	FMR1	CHUK	DNMT1
	CCNG2	MET	KLF11	MAPK8		DNMT1	FBN1
	E2F1	TGFBR2		ZEB1		FBN1	FMR1
	HIF1A					FMR1	SOS1
	SMAD4					SOS1	
	MMP2						
	MAPK8						
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						

Validated targets of miRNAs							
TFs	E2F1	AHR	EZH2	NFKB1	E2F3	KLF4	
	MYB	E2F1	NFKB1		PPARA		
	RB1	NR3C1	SNAI2		HDGF		
	RUNX1	PPARA	SOX9		KLF6????		
	STAT3	RB1	TWIST2				
		STAT3					
Genes	E2F1	E2F1	HIF1A	HRAS	ZEB1	DNMT1	
	FAS	KLF11	SNAI2	MET	EIF4E	ADAM17	
	TGFBR2	SMAD4			KLF11		
	ATM	TGFBR2			ZEB1		
	HIF1A	ZEB1					
		FMR1					
		MMP2					

miRNAs	miR-17	miR-181d-3p	miR-181d-5p	miR-18a	miR-194-5p	miR-196a	miR-19a
Predicted targets of miRNAs							
TFs	RUNX1		RUNX1	RUNX1	E2F3	ERG	
	E2F1		KLF6	KLF6	FLI1	FLI1	
	RB1		ETS1	NR3C1	SP3		
	STAT3		NR3C1	POU2F1			
	KAT2B		KAT2B				
Genes	CALD1		ATM	ATM	ACP5	FAS	FMR1
	CCNG2		SOS1	CTGF	FMR1	COL1A1	IL18
	E2F1		VCAM1	HIF1A	SP3	MAPK8	
	HIF1A		EPB41L3	HMGCS1	RSF1	ZEB1	
	MMP2			MAPK8			
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						

Validated targets of miRNAs							
TFs	E2F1			NR3C1	FOXM1	FOXO1	KAT2B
	E2F3			RUNX1			
	KAT2B						
	MYC						
	RB1						
	RUNX1						
	STAT3						
Genes	E2F1		HRAS	CTGF		FLNA	CTGF
	MMP2			EDF1		TGFBR2	SMAD4
	MYC			ATM			TGFBR2
	SMAD4			HIF1A			DNMT1
	TGFBR2			HMGCS1			
	HIF1A			SMAD4			
	DNMT1			TGFBR2			
	IGFBP3			DNMT1			

miRNAs	miR-19b-1	miR-200b	miR-200c	miR-20a	miR-22	miR-29a	miR-29b
Predicted targets of miRNAs							
TFs		KLF6		E2F1	FOXO1	ETS1	MYBL2
		SP3		E2F3	HNRNPK	KAT2B	
				EZH2			
				PPARA			
				RB1			
				STAT3			
				KAT2B			
Genes		NCF2		CALD1	CD68		DNMT1
		MAPK8		CCNG2	SOS1		FBN1
		SP3		E2F1	UTRN		EDF1
				HIF1A	VCAM1		
				SMAD4	WRN		
				MMP2			
				MAPK8			
				SOS1			
				TGFBR2			
				KLF11			
				TXNIP			

Validated targets of miRNAs							
TFs	KAT2B	E2F3	MYB	E2F1	PPARA	KLF4	SP1
	NR3C1	ETS1	ETS1	E2F3		AHR	STAT3
		MYB	SP1	MYC		MYC	SP1
		SP1	E2F3	RB1			STAT3
		EZH2	FOXO1	RUNX1			MYC
			E2F3	STAT3			
Genes	CTGF	CREB1	FLNA	CCNB1	HIF1A	MMP2	COL1A1
	FMR1	FN1	FN1	E2F1		DNMT1	DNMT1
	ATM	KLF11	KLF11	FLNA		FBN1	MMP2
	HMGCS1	ZEB1	ZEB1	HIF1A		MYC	FBN1
	SMAD4	DNMT1	NCAM1	MYC			MYC
	TGFBR2		CYP1B1	SMAD4			
	DNMT1			TGFBR2			
				DNMT1			

miRNAs	miR-342-3p	miR-630	miR-874	miR-92a-1	let-7a	let-7b	let-7g
Predicted targets of miRNAs							
TFs	E2F3	KLF6	POU2F1		EZH2	EZH2	EZH2
		EZH2	STAT3		POU2F1	POU2F1	POU2F1
					RB1	RB1	RB1
					TP53	TP53	TP53
Genes	DNMT1		FBN1	COL1A1	FAS	FAS	FAS
	ZEB1		FMR1	DACT3	COL1A1	COL1A1	COL1A1
			SIGIRR		IL6	IL6	IL6
					MAPK8	MAPK8	MAPK8
					UTRN	UTRN	UTRN
Validated targets of miRNAs							
TFs	FOSL2	SNAI2	PARP1	HDAC1	E2F1	CTCF	MYC
	E2F1	FOXM1	HDAC1	HDGF	EZH2	E2F3	
			STAT3	KAT2B	MYC	EZH2	
			E2F3	MYBL2	NFKB1	MYC	
				NFKB1	PARP1	SOX9	
				STAT3	SP1	SP1	
				HDAC2	STAT3		
				KLF4			
				IKZF1			
Genes	DNMT1	SNAI2		ATM	MYC	BIRC5	MYC
	E2F1			CCNB1	HRAS	CCNB1	FN1
				EPB41L3	E2F1	EPB41L3	
				FLNA	IL6	FLNA	
				HMGCS1		HIF1A	
				SMAD4		HMGCS1	
				TGFBR2		MYC	
				TYMP		UTRN	
				MAPK8		HRAS	
				DNMT1			

miRNAs	let-7i

Predicted targets of miRNAs

TFs	EZH2
	POU2F1
	RB1
	TP53
Genes	FAS
	CHUK
	COL1A1
	IL6
	MAPK8
	UTRN

Validated targets of miRNAs

TFs	
Genes	

H19-PPARA-KLF11

miRNAs	miR-106a	miR-130b-3p	miR-138-5p	miR-139	miR-141	miR-152-3p	miR-152-5p
Predicted targets of miRNAs							
TFs	RUNX1	FOSL2	EZH2	ETS1	CREBBP	KLF6	KLF6
	E2F1	MYB	POU2F1		POU2F1	KLF4	E2F3
	PPARA	STAT3	RELA				KLF4
	RB1		SP1				
	SP1						
	STAT3						
	KAT2B						
Genes	CALD1	FMR1	HIF1A	FMR1	FMR1	CHUK	DNMT1
	CCNG2	MET	KLF11	MAPK8		DNMT1	FBN1
	E2F1	TGFBR2		ZEB1		FBN1	FMR1
	HIF1A					FMR1	SOS1
	SMAD4					SOS1	
	MMP2						
	MAPK8						
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						

Validated targets of miRNAs							
TFs	E2F1	AHR	EZH2	NFKB1	E2F3	KLF4	
	MYB	E2F1	NFKB1		PPARA		
	RB1	NR3C1	SNAI2		HDGF		
	RUNX1	PPARA	SOX9				
	STAT3	RB1	TWIST2				
		STAT3					
Genes	E2F1	E2F1	HIF1A	HRAS	ZEB1	DNMT1	
	FAS	KLF11	SNAI2	MET	EIF4E	ADAM17	
	TGFBR2	SMAD4			KLF11		
	ATM	TGFBR2			ZEB1		
	HIF1A	ZEB1					
		FMR1					
		MMP2					

miRNAs	miR-17	miR-181d-3p	miR-181d-5p	miR-18a	miR-194-5p	miR-196a	miR-19a
Predicted targets of miRNAs							
TFs	RUNX1		RUNX1	RUNX1	E2F3	ERG	
	E2F1		KLF6	KLF6	FLI1	FLI1	
	RB1		ETS1	NR3C1	SP3		
	STAT3		NR3C1	POU2F1			
	KAT2B		KAT2B				
Genes	CALD1		ATM	ATM	ACP5	FAS	FMR1
	CCNG2		SOS1	CTGF	FMR1	COL1A1	IL18
	E2F1		VCAM1	HIF1A	SP3	MAPK8	
	HIF1A		EPB41L3	HMGCS1	RSF1	ZEB1	
	MMP2			MAPK8			
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						

Validated targets of miRNAs							
TFs	E2F1			NR3C1	FOXM1	FOXO1	KAT2B
	E2F3			RUNX1			
	KAT2B						
	MYC						
	RB1						
	RUNX1						
	STAT3						
Genes	E2F1		HRAS	CTGF		FLNA	CTGF
	MMP2			EDF1		TGFBR2	SMAD4
	MYC			ATM			TGFBR2
	SMAD4			HIF1A			DNMT1
	TGFBR2			HMGCS1			
	HIF1A			SMAD4			
	DNMT1			TGFBR2			
	IGFBP3			DNMT1			

miRNAs	miR-19b-1	miR-200b	miR-200c	miR-20a	miR-22	miR-29a	miR-29b
Predicted targets of miRNAs							
TFs		KLF6		E2F1	FOXO1	ETS1	MYBL2
		SP3		E2F3	HNRNPK	KAT2B	
				EZH2			
				PPARA			
				RB1			
				STAT3			
				KAT2B			
Genes		NCF2		CALD1	CD68		DNMT1
		MAPK8		CCNG2	SOS1		FBN1
		SP3		E2F1	UTRN		EDF1
				HIF1A	VCAM1		
				SMAD4	WRN		
				MMP2			
				MAPK8			
				SOS1			
				TGFBR2			
				KLF11			
				TXNIP			

Validated targets of miRNAs							
TFs	KAT2B	E2F3	MYB	E2F1	PPARA	KLF4	SP1
	NR3C1	ETS1	ETS1	E2F3		AHR	STAT3
		MYB	SP1	MYC		MYC	SP1
		SP1	E2F3	RB1			STAT3
		EZH2	FOXO1	RUNX1			MYC
			E2F3	STAT3			
Genes	CTGF	CREB1	FLNA	CCNB1	HIF1A	MMP2	COL1A1
	FMR1	FN1	FN1	E2F1		DNMT1	DNMT1
	ATM	KLF11	KLF11	FLNA		FBN1	MMP2
	HMGCS1	ZEB1	ZEB1	HIF1A		MYC	FBN1
	SMAD4	DNMT1	NCAM1	MYC			MYC
	TGFBR2		CYP1B1	SMAD4			
	DNMT1			TGFBR2			
				DNMT1			

miRNAs	miR-342-3p	miR-630	miR-874	miR-92a-1	let-7a	let-7b	let-7g

Predicted targets of miRNAs

TFs	E2F3	KLF6	POU2F1		EZH2	EZH2	EZH2
		EZH2	STAT3		POU2F1	POU2F1	POU2F1
					RB1	RB1	RB1
					TP53	TP53	TP53
Genes	DNMT1		FBN1	COL1A1	FAS	FAS	FAS
	ZEB1		FMR1	DACT3	COL1A1	COL1A1	COL1A1
			SIGIRR		IL6	IL6	IL6
					MAPK8	MAPK8	MAPK8
					UTRN	UTRN	UTRN

Validated targets of miRNAs

TFs	FOSL2	SNAI2	PARP1	HDAC1	E2F1	CTCF	MYC
	E2F1	FOXM1	HDAC1	HDGF	EZH2	E2F3	
			STAT3	KAT2B	MYC	EZH2	
			E2F3	MYBL2	NFKB1	MYC	
				NFKB1	PARP1	SOX9	
				STAT3	SP1	SP1	
				HDAC2	STAT3		
				KLF4			
				IKZF1			
Genes	DNMT1	SNAI2		ATM	MYC	BIRC5	MYC
	E2F1			CCNB1	HRAS	CCNB1	FN1
				EPB41L3	E2F1	EPB41L3	
				FLNA	IL6	FLNA	
				HMGCS1		HIF1A	
				SMAD4		HMGCS1	
				TGFBR2		MYC	
				TYMP		UTRN	
				MAPK8		HRAS	
				DNMT1			

miRNAs	let-7i

Predicted targets of miRNAs

TFs	EZH2
	POU2F1
	RB1
	TP53
Genes	FAS
	CHUK
	COL1A1
	IL6
	MAPK8
	UTRN

Validated targets of miRNAs

TFs	
Genes	

H19-SP1-TGFBR2

miRNAs	miR-106a	miR-130b-3p	miR-138-5p	miR-139	miR-141	miR-152-3p	miR-152-5p
Predicted targets of miRNAs							
TFs	RUNX1	FOSL2	EZH2	ETS1	CREBBP	KLF6	KLF6
	E2F1	MYB	POU2F1		POU2F1	KLF4	E2F3
	PPARA	STAT3	RELA				KLF4
	RB1		SP1				
	SP1						
	STAT3						
	KAT2B						
Genes	CALD1	FMR1	HIF1A	FMR1	FMR1	CHUK	DNMT1
	CCNG2	MET	KLF11	MAPK8		DNMT1	FBN1
	E2F1	TGFBR2		ZEB1		FBN1	FMR1
	HIF1A					FMR1	SOS1
	SMAD4					SOS1	
	MMP2						
	MAPK8						
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						

Validated targets of miRNAs							
TFs	E2F1	AHR	EZH2	NFKB1	E2F3	KLF4	
	MYB	E2F1	NFKB1		PPARA		
	RB1	NR3C1	SNAI2		HDGF		
	RUNX1	PPARA	SOX9				
	STAT3	RB1	TWIST2				
		STAT3					
Genes	E2F1	E2F1	HIF1A	HRAS	ZEB1	DNMT1	
	FAS	KLF11	SNAI2	MET	EIF4E	ADAM17	
	TGFBR2	SMAD4			KLF11		
	ATM	TGFBR2			ZEB1		
	HIF1A	ZEB1					
		FMR1					
		MMP2					

miRNAs	miR-17	miR-181d-3p	miR-181d-5p	miR-18a	miR-194-5p	miR-196a	miR-19a
Predicted targets of miRNAs							
TFs	RUNX1		RUNX1	RUNX1	E2F3	ERG	
	E2F1		KLF6	KLF6	FLI1	FLI1	
	RB1		ETS1	NR3C1	SP3		
	STAT3		NR3C1	POU2F1			
	KAT2B		KAT2B				
Genes	CALD1		ATM	ATM	ACP5	FAS	FMR1
	CCNG2		SOS1	CTGF	FMR1	COL1A1	IL18
	E2F1		VCAM1	HIF1A	SP3	MAPK8	
	HIF1A		EPB41L3	HMGCS1	RSF1	ZEB1	
	MMP2			MAPK8			
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						

Validated targets of miRNAs							
TFs	E2F1			NR3C1	FOXM1	FOXO1	KAT2B
	E2F3			RUNX1			
	KAT2B						
	MYC						
	RB1						
	RUNX1						
	STAT3						
Genes	E2F1		HRAS	CTGF		FLNA	CTGF
	MMP2			EDF1		TGFBR2	SMAD4
	MYC			ATM			TGFBR2
	SMAD4			HIF1A			DNMT1
	TGFBR2			HMGCS1			
	HIF1A			SMAD4			
	DNMT1			TGFBR2			
	IGFBP3			DNMT1			

miRNAs	miR-19b-1	miR-200b	miR-200c	miR-20a	miR-22	miR-29a	miR-29b
Predicted targets of miRNAs							
TFs		KLF6		E2F1	FOXO1	ETS1	MYBL2
		SP3		E2F3	HNRNPK	KAT2B	
				EZH2			
				PPARA			
				RB1			
				STAT3			
				KAT2B			
Genes		NCF2		CALD1	CD68		DNMT1
		MAPK8		CCNG2	SOS1		FBN1
		SP3		E2F1	UTRN		EDF1
				HIF1A	VCAM1		
				SMAD4	WRN		
				MMP2			
				MAPK8			
				SOS1			
				TGFBR2			
				KLF11			
				TXNIP			

Validated targets of miRNAs							
TFs	KAT2B	E2F3	MYB	E2F1	PPARA	KLF4	SP1
	NR3C1	ETS1	ETS1	E2F3		AHR	STAT3
		MYB	SP1	MYC		MYC	SP1
		SP1	E2F3	RB1			STAT3
		EZH2	FOXO1	RUNX1			MYC
			E2F3	STAT3			
Genes	CTGF	CREB1	FLNA	CCNB1	HIF1A	MMP2	COL1A1
	FMR1	FN1	FN1	E2F1		DNMT1	DNMT1
	ATM	KLF11	KLF11	FLNA		FBN1	MMP2
	HMGCS1	ZEB1	ZEB1	HIF1A		MYC	FBN1
	SMAD4	DNMT1	NCAM1	MYC			MYC
	TGFBR2		CYP1B1	SMAD4			
	DNMT1			TGFBR2			
				DNMT1			

miRNAs	miR-342-3p	miR-630	miR-874	miR-92a-1	let-7a	let-7b	let-7g
Predicted targets of miRNAs							
TFs	E2F3	KLF6	POU2F1		EZH2	EZH2	EZH2
		EZH2	STAT3		POU2F1	POU2F1	POU2F1
					RB1	RB1	RB1
					TP53	TP53	TP53
Genes	DNMT1		FBN1	COL1A1	FAS	FAS	FAS
	ZEB1		FMR1	DACT3	COL1A1	COL1A1	COL1A1
			SIGIRR		IL6	IL6	IL6
					MAPK8	MAPK8	MAPK8
					UTRN	UTRN	UTRN

Validated targets of miRNAs							
TFs	FOSL2	SNAI2	PARP1	HDAC1	E2F1	CTCF	MYC
	E2F1	FOXM1	HDAC1	HDGF	EZH2	E2F3	
			STAT3	KAT2B	MYC	EZH2	
			E2F3	MYBL2	NFKB1	MYC	
				NFKB1	PARP1	SOX9	
				STAT3	SP1	SP1	
				HDAC2	STAT3		
				KLF4			
				IKZF1			
Genes	DNMT1	SNAI2		ATM	MYC	BIRC5	MYC
	E2F1			CCNB1	HRAS	CCNB1	FN1
				EPB41L3	E2F1	EPB41L3	
				FLNA	IL6	FLNA	
				HMGCS1		HIF1A	
				SMAD4		HMGCS1	
				TGFBR2		MYC	
				TYMP		UTRN	
				MAPK8		HRAS	
				DNMT1			

miRNAs	let-7i

Predicted targets of miRNAs

TFs	EZH2
	POU2F1
	RB1
	TP53
Genes	FAS
	CHUK
	COL1A1
	IL6
	MAPK8
	UTRN

Validated targets of miRNAs

TFs	
Genes	

H19-STAT3-KLF11

miRNAs	miR-106a	miR-130b-3p	miR-138-5p	miR-139	miR-141	miR-152-3p	miR-152-5p	miR-17
Predicted targets of miRNAs								
TFs	RUNX1	FOSL2	EZH2	ETS1	CREBBP	KLF6	KLF6	RUNX1
	E2F1	MYB	POU2F1		POU2F1	KLF4	E2F3	E2F1
	PPARA	STAT3	RELA				KLF4	RB1
	RB1		SP1					STAT3
	SP1							KAT2B
	STAT3							
	KAT2B							
Genes	CALD1	FMR1	HIF1A	FMR1	FMR1	CHUK	DNMT1	CALD1
	CCNG2	MET	KLF11	MAPK8		DNMT1	FBN1	CCNG2
	E2F1	TGFBR2		ZEB1		FBN1	FMR1	E2F1
	HIF1A					FMR1	SOS1	HIF1A
	SMAD4					SOS1		MMP2
	MMP2							SOS1
	MAPK8							TGFBR2
	SOS1							KLF11
	TGFBR2							TXNIP
	KLF11							
	TXNIP							
Validated targets of miRNAs								
TFs	E2F1	AHR	EZH2	NFKB1	E2F3	KLF4		E2F1
	MYB	E2F1	NFKB1		PPARA			E2F3
	RB1	NR3C1	SNAI2		HDGF			KAT2B
	RUNX1	PPARA	SOX9					MYC
	STAT3	RB1	TWIST2					RB1
		STAT3						RUNX1
								STAT3
Genes	E2F1	E2F1	HIF1A	HRAS	ZEB1	DNMT1		E2F1
	FAS	KLF11	SNAI2	MET	EIF4E	ADAM17		MMP2
	TGFBR2	SMAD4			KLF11			MYC
	ATM	TGFBR2			ZEB1			SMAD4
	HIF1A	ZEB1						TGFBR2
		FMR1						HIF1A
		MMP2						DNMT1
								IGFBP3

miRNAs	miR-181d-3p	miR-181d-5p	miR-18a	miR-194-5p	miR-196a	miR-19a	miR-19b-1
Predicted targets of miRNAs							
TFs		RUNX1	RUNX1	E2F3	ERG		
		KLF6	KLF6	FLI1	FLI1		
		ETS1	NR3C1	SP3			
		NR3C1	POU2F1				
		KAT2B					
Genes		ATM	ATM	ACP5	FAS	FMR1	
		SOS1	CTGF	FMR1	COL1A1	IL18	
		VCAM1	HIF1A	SP3	MAPK8		
		EPB41L3	HMGCS1	RSF1	ZEB1		
			MAPK8				
Validated targets of miRNAs							
TFs			NR3C1	FOXM1	FOXO1	KAT2B	KAT2B
			RUNX1				NR3C1
Genes		HRAS	CTGF		FLNA	CTGF	CTGF
			EDF1		TGFBR2	SMAD4	FMR1
			ATM			TGFBR2	ATM
			HIF1A			DNMT1	HMGCS1
			HMGCS1				SMAD4
			SMAD4				TGFBR2
			TGFBR2				DNMT1
			DNMT1				

miRNAs	miR-200b	miR-200c	miR-20a	miR-22	miR-29a	miR-29b	miR-342-3p
Predicted targets of miRNAs							
TFs	KLF6		E2F1	FOXO1	ETS1	MYBL2	E2F3
	SP3		E2F3	HNRNPK	KAT2B		
			EZH2				
			PPARA				
			RB1				
			STAT3				
			KAT2B				
Genes	NCF2		CALD1	CD68		DNMT1	DNMT1
	MAPK8		CCNG2	SOS1		FBN1	ZEB1
	SP3		E2F1	UTRN		EDF1	
			HIF1A	VCAM1			
			SMAD4	WRN			
			MMP2				
			MAPK8				
			SOS1				
			TGFBR2				
			KLF11				
			TXNIP				

Validated targets of miRNAs							
TFs	E2F3	MYB	E2F1	PPARA	KLF4	SP1	FOSL2
	ETS1	ETS1	E2F3		AHR	STAT3	E2F1
	MYB	SP1	MYC		MYC	SP1	
	SP1	E2F3	RB1			STAT3	
	EZH2	FOXO1	RUNX1			MYC	
		E2F3	STAT3				
Genes	CREB1	FLNA	CCNB1	HIF1A	MMP2	COL1A1	DNMT1
	FN1	FN1	E2F1		DNMT1	DNMT1	E2F1
	KLF11	KLF11	FLNA		FBN1	MMP2	
	ZEB1	ZEB1	HIF1A		MYC	FBN1	
	DNMT1	NCAM1	MYC			MYC	
		CYP1B1	SMAD4				
			TGFBR2				
			DNMT1				

miRNAs	miR-630	miR-874	miR-92a-1	let-7a	let-7b	let-7g	let-7i

Predicted targets of miRNAs

TFs	KLF6	POU2F1		EZH2	EZH2	EZH2	EZH2
	EZH2	STAT3		POU2F1	POU2F1	POU2F1	POU2F1
				RB1	RB1	RB1	RB1
				TP53	TP53	TP53	TP53
Genes		FBN1	COL1A1	FAS	FAS	FAS	FAS
		FMR1	DACT3	COL1A1	COL1A1	COL1A1	CHUK
		SIGIRR		IL6	IL6	IL6	COL1A1
				MAPK8	MAPK8	MAPK8	IL6
				UTRN	UTRN	UTRN	MAPK8
							UTRN

Validated targets of miRNAs

TFs	SNAI2	PARP1	HDAC1	E2F1	CTCF	MYC	
	FOXM1	HDAC1	HDGF	EZH2	E2F3		
		STAT3	KAT2B	MYC	EZH2		
		E2F3	MYBL2	NFKB1	MYC		
			NFKB1	PARP1	SOX9		
			STAT3	SP1	SP1		
			HDAC2	STAT3			
			KLF4				
			IKZF1				
Genes	SNAI2		ATM	MYC	BIRC5	MYC	
			CCNB1	HRAS	CCNB1	FN1	
			EPB41L3	E2F1	EPB41L3		
			FLNA	IL6	FLNA		
			HMGCS1		HIF1A		
			SMAD4		HMGCS1		
			TGFBR2		MYC		
			TYMP		UTRN		
			MAPK8		HRAS		
			DNMT1				

H19-NFYB-SP3

miRNAs	miR-106a	miR-130b-3p	miR-138-5p	miR-139	miR-141	miR-152-3p	miR-152-5p
Predicted targets of miRNAs							
TFs	RUNX1	FOSL2	EZH2	ETS1	CREBBP	KLF6	KLF6
	E2F1	MYB	POU2F1		POU2F1	KLF4	E2F3
	PPARA	STAT3	RELA				KLF4
	RB1		SP1				
	SP1						
	STAT3						
	KAT2B						
Genes	CALD1	FMR1	HIF1A	FMR1	FMR1	CHUK	DNMT1
	CCNG2	MET	KLF11	MAPK8		DNMT1	FBN1
	E2F1	TGFBR2		ZEB1		FBN1	FMR1
	HIF1A					FMR1	SOS1
	SMAD4					SOS1	
	MMP2						
	MAPK8						
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						
targets of miRNAs							
TFs	E2F1	AHR	EZH2	NFKB1	E2F3	KLF4	
	MYB	E2F1	NFKB1		PPARA		
	RB1	NR3C1	SNAI2		HDGF		
	RUNX1	PPARA	SOX9				
	STAT3	RB1	TWIST2				
		STAT3					
Genes	E2F1	E2F1	HIF1A	HRAS	ZEB1	DNMT1	
	FAS	KLF11	SNAI2	MET	EIF4E	ADAM17	
	TGFBR2	SMAD4			KLF11		
	ATM	TGFBR2			ZEB1		
	HIF1A	ZEB1					
		FMR1					
		MMP2					

miRNAs	miR-17	miR-181d-3p	miR-181d-5p	miR-18a	miR-194-5p	miR-196a	miR-19a
Predicted targets of miRNAs							
TFs	RUNX1		RUNX1	RUNX1	E2F3	ERG	
	E2F1		KLF6	KLF6	FLI1	FLI1	
	RB1		ETS1	NR3C1	SP3		
	STAT3		NR3C1	POU2F1			
	KAT2B		KAT2B				
Genes	CALD1		ATM	ATM	ACP5	FAS	FMR1
	CCNG2		SOS1	CTGF	FMR1	COL1A1	IL18
	E2F1		VCAM1	HIF1A	SP3	MAPK8	
	HIF1A		EPB41L3	HMGCS1	RSF1	ZEB1	
	MMP2			MAPK8			
	SOS1						
	TGFBR2						
	KLF11						
	TXNIP						

targets of miRNAs							
TFs	E2F1			NR3C1	FOXM1	FOXO1	KAT2B
	E2F3			RUNX1			
	KAT2B						
	MYC						
	RB1						
	RUNX1						
	STAT3						
Genes	E2F1		HRAS	CTGF		FLNA	CTGF
	MMP2			EDF1		TGFBR2	SMAD4
	MYC			ATM			TGFBR2
	SMAD4			HIF1A			DNMT1
	TGFBR2			HMGCS1			
	HIF1A			SMAD4			
	DNMT1			TGFBR2			
	IGFBP3			DNMT1			

miRNAs	miR-19b-1	miR-200b	miR-200c	miR-20a	miR-22	miR-29a	miR-29b
Predicted targets of miRNAs							
TFs		KLF6		E2F1	FOXO1	ETS1	MYBL2
		SP3		E2F3	HNRNPK	KAT2B	
				EZH2			
				PPARA			
				RB1			
				STAT3			
				KAT2B			
Genes		NCF2		CALD1	CD68		DNMT1
		MAPK8		CCNG2	SOS1		FBN1
		SP3		E2F1	UTRN		EDF1
				HIF1A	VCAM1		
				SMAD4	WRN		
				MMP2			
				MAPK8			
				SOS1			
				TGFBR2			
				KLF11			
				TXNIP			

targets of miRNAs							
TFs	KAT2B	E2F3	MYB	E2F1	PPARA	KLF4	SP1
	NR3C1	ETS1	ETS1	E2F3		AHR	STAT3
		MYB	SP1	MYC		MYC	SP1
		SP1	E2F3	RB1			STAT3
		EZH2	FOXO1	RUNX1			MYC
			E2F3	STAT3			
Genes	CTGF	CREB1	FLNA	CCNB1	HIF1A	MMP2	COL1A1
	FMR1	FN1	FN1	E2F1		DNMT1	DNMT1
	ATM	KLF11	KLF11	FLNA		FBN1	MMP2
	HMGCS1	ZEB1	ZEB1	HIF1A		MYC	FBN1
	SMAD4	DNMT1	NCAM1	MYC			MYC
	TGFBR2		CYP1B1	SMAD4			
	DNMT1			TGFBR2			
				DNMT1			

miRNAs	miR-342-3p	miR-630	miR-874	miR-92a-1	let-7a	let-7b	let-7g
Predicted targets of miRNAs							
TFs	E2F3	KLF6	POU2F1		EZH2	EZH2	EZH2
		EZH2	STAT3		POU2F1	POU2F1	POU2F1
					RB1	RB1	RB1
					TP53	TP53	TP53
Genes	DNMT1		FBN1	COL1A1	FAS	FAS	FAS
	ZEB1		FMR1	DACT3	COL1A1	COL1A1	COL1A1
			SIGIRR		IL6	IL6	IL6
					MAPK8	MAPK8	MAPK8
					UTRN	UTRN	UTRN
targets of miRNAs							
TFs	FOSL2	SNAI2	PARP1	HDAC1	E2F1	CTCF	MYC
	E2F1	FOXM1	HDAC1	HDGF	EZH2	E2F3	
			STAT3	KAT2B	MYC	EZH2	
			E2F3	MYBL2	NFKB1	MYC	
				NFKB1	PARP1	SOX9	
				STAT3	SP1	SP1	
				HDAC2	STAT3		
				KLF4			
				IKZF1			
Genes	DNMT1	SNAI2		ATM	MYC	BIRC5	MYC
	E2F1			CCNB1	HRAS	CCNB1	FN1
				EPB41L3	E2F1	EPB41L3	
				FLNA	IL6	FLNA	
				HMGCS1		HIF1A	
				SMAD4		HMGCS1	
				TGFBR2		MYC	
				TYMP		UTRN	
				MAPK8		HRAS	
				DNMT1			

miRNAs	let-7i

Predicted targets of miRNAs

TFs	EZH2
	POU2F1
	RB1
	TP53
Genes	FAS
	CHUK
	COL1A1
	IL6
	MAPK8
	UTRN

targets of miRNAs

TFs	
Genes	

Table S6. Primers for qRT-PCR experiment

Gene	Forward sequence	Reverse sequence
GAPDH	5'-CCACTCCTCCACCTTTGAC-3'	5'-ACCCTGTTGCTGTAGCCA-3'
H19	5'-GTGGACTTGGTGACGCTGTA-3'	5'-CACCATCCTCCCTCCTGAGA-3'
SP1	5'-TGGCAGCAGTACCAATGGC-3'	5'-CCAGGTAGTCCTGTCAGAACTT-3'
ETS1	5'-GATAGTTGTGATCGCCTCACC-3'	5'-GTCCTCTGAGTCGAAGCTGTC-3'
STAT3	5'-ACCAGCAGTATAGCCGCTTC-3'	5'-GCCACAATCCGGGCAATCT-3'
TGFBR2	5'-GTAGCTCTGATGAGTGCAATGAC-3'	5'-CAGATATGGCAACTCCCAGTG-3'
KLF11	5'-GTTGCGGATAAGACCCCTCAC-3'	5'-TGGAATCTGTTACTTGGGGAGA-3'