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Artificial intelligence-driven pan-cancer analysis reveals miRNA signatures for cancer stage prediction

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Summary

The ability to detect cancer at an early stage in patients who would benefit from effective therapy is a key factor in increasing survivability. This work proposes an evolutionary supervised learning method called Cancer*Sig* to identify cancer stage-specific microRNA (miRNA) signatures for early cancer predictions. Cancer*Sig* established a compact panel of miRNA signatures as potential markers from 4,667 patients with 15 different types of cancers for the cancer stage prediction, and achieved a mean performance: 10-fold cross-validation accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve of 84.27% ± 6.31%, 0.81 ± 0.12, 0.80 ± 0.10, and 0.80 ± 0.06, respectively. The pan-cancer analysis of miRNA signatures suggested that three miRNAs, hsa-let-7i-3p, hsa-miR-362-3p, and hsa-miR-3651, contributed significantly toward stage prediction across 8 cancers, and each of the 67 miRNAs of the panel was a biomarker of stage prediction in more than one cancer. Cancer*Sig* may serve as the basis for cancer screening and therapeutic selection..

Introduction

Cancer is one of the major health problems in the world and causes millions of deaths every year. According to the Cancer Statistics, in 2019, there were 1,806,590 new cancer cases and 606,520 cancer deaths that were estimated to occur in the United States alone.[1] The cure for this complex disease remains elusive. Detecting cancer at an early stage in patients who would benefit from effective therapy is a key factor to increase survival. As regulators of gene expression in health and disease, microRNAs (miRNAs) may have potential roles as predictive biomarkers in cancer.[2]

MicroRNAs are a class of noncoding RNAs involved in the regulation of gene expression and control a number of diverse biological processes, including but not limited to differentiation, development, and growth, and are expressed in wide variety of organisms. These RNAs are transcribed from DNA sequences and consist of an average length of 22 nucleotides. Currently, there are 48,860 known mature miRNA sequences from 271 organisms, including 2,654 mature miRNA sequences from humans listed in miRBase,[3] although the functions of many of these miRNAs have yet to be discovered.

Next-generation sequencing has made it possible to examine the expression levels of numerous miRNAs in various cancers and investigate their association with cancer development and progression. Over the last two decades, crucial evidence has demonstrated that miRNAs and miRNA biogenesis mechanisms are involved in the development of various cancers.[4–6] There is considerable evidence that the expression of miRNAs has been linked to a number of human cancers.[4–6] Depending on their target genes and under certain conditions, miRNAs either have oncogenic or tumor suppressor properties. MicroRNA expression profiles can also define cancer subtypes and are associated with varying treatment responses[7] and overall survival.[8] Identifying cancer-specific miRNA signatures and corresponding changes in gene expression over time is important for understanding the molecular basis of cancer and detecting early-stage cancers.

Accumulating evidence suggests that miRNA biomarkers can be effective in predicting early stages of cancer. For instance, miR-205, miR-210, and miR-708 have been used for early-stage detection of squamous cell lung cancer,[9] and 34 miRNAs as a signature for early-stage detection in breast cancer.[10,11] However, numerous miRNAs are expressed in cancers, and variability among different patients makes it challenging to determine true association between cancer and miRNA from spurious associations. Artificial Intelligence/machine learning methods may surmount these challenges by integrating and analyzing large datasets from numerous sources. Previously, we developed various machine learning-based cancer prediction models that contributed to survival prediction[8,12–14] and early-stage detection[10] in different cancer types.

Here, in pursuit of identifying the miRNA signatures that could aid in early-stage detection and may serve as general biomarkers for multiple cancer types, we present an evolutionary learning method called Cancer*Sig*. Cancer*Sig* is a

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machine learning method using an inheritable bi-objective combinatorial genetic algorithm (IBCGA)[15] to identify cancer stage-specific miRNA signatures from 15 cancer types. Consequently, the miRNAs in each signatures were ranked based on their contribution to the prediction of early and advanced stages, and the top-ranked miRNAs analyzed using Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and Gene Ontology (GO) annotations to evaluate the biological significance of these connections. Pan-cancer analysis revealed similarities and differences in miRNA signatures across the 15 cancer types. Cancer*Sig* established a compact panel of 242 significant miRNAs across the 15 cancer types with a mean cross-validation accuracy of 84.27%. Analysis of the identified panel of miRNAs may serve as a predictive measure for early-stage diagnosis of cancer and have important implications in biomarker-based cancer therapeutics.

Material and methods

MicroRNA expression profiles

The dataset was retrieved from TCGA. We initially considered all 33 cancer types available in the TCGA database; however, the amount of miRNA data and clinical information for certain cancer types was limited and therefore excluded. Cancer types with a minimum number of 80 patients with miRNA expression profiles were included for analysis and limited the number of cancer types to 15 for further analysis. With this criterion, our dataset contained 6,578 clinical samples with miRNA expression profiles across 15 cancer types. After removing the samples without cancer staging information and miRNA sequence data, each cancer type contained an average of 311 clinical samples with 311 corresponding miRNA expression profiles where each miRNA profile contained an average of 474.46 miRNAs. Overall, there were 4,667 clinical samples with miRNA expression profiles, which included 7,117 miRNAs (with duplication) for 15 cancer types. Normalized mature miRNA sequence data for analysis was obtained using the Illumina HiSeq 2000 platform. For prediction purposes, the dataset was divided into early (stages I and II) and advanced stages (stages III and IV) based on stage information. The number of samples and miRNAs for each cancer type are shown in Table 1.

Artificial intelligence-based prediction method Cancer*Sig*

The novel cancer stage prediction method Cancer*Sig* identifies miRNA signatures to distinguish the early stage from advanced stage of various cancer types using their miRNA expression profiles with stage labels as input data. The output of Cancer*Sig* is the cancer-specific miRNA signatures and the panel of miRNA biomarkers for predicting cancer stages of multiple cancers. High performance of Cancer*Sig* arises mainly from an optimal feature selection algorithm IBCGA[15] incorporated with a support vector machine (SVM) classifier,[16,17] and pan-analysis of the miRNA signature. A brief summary of the methods is presented in the following paragraphs. The schematic diagram of Cancer*Sig* method is shown in Figure 1.

Identifying a minimal set of m miRNAs, i.e., a miRNA signature from a large set of n candidate miRNAs while maximizing the prediction performance, is a bi-objective combinatorial optimization problem C(n, m) where the best value of m is not known in advance. The feature selection algorithm IBCGA uses an intelligent evolutionary algorithm[18] to solve a large combinatorial optimization problem and an inheritance mechanism to efficiently identify a robust set of m features in a single run. IBCGA uses an orthogonal array crossover operation with a systematic reasoning ability to reproduce better offspring instead of random recombination used for traditional crossover operations. Accumulated evidence has indicated that IBCGA is good at identifying informative signatures in various cancers[8,10,12,13,19] and other bioinformatics problems.[20,21]

SVM is a well-known powerful classifier, which has been applied to a wide variety of biological applications.[17] SVM uses nonlinear transformation to map data from an input space to a higher-dimensional space to establish an accurate prediction model, especially when the training sample size is relatively small. We utilized the LibSVM[22] package with the radial basis function kernel to implement Cancer*Sig*. The scoring function of the RBF kernel is computed in the feature space between the two data points, x_i and x_j, defined as follows:

$$K(x_i, x_j) = \exp\left(-\gamma \|x_i - x_j\|\right)^2 \qquad \text{(Equation 1)}$$

To identify the miRNA signature and design an optimal classifier, the feature selection of IBCGA and parameter setting (cost C and kernel γ) of SVM play a vital role in modeling. IBCGA solves the problem C(n, m) for each cancer type independently. Taking bladder urothelial carcinoma (BLCA) with 477-miRNA expression profiles as an example, $n = 477$, and the value of m and the corresponding m miRNAs are determined by IBCGA. The parameter setting of IBCGA was $r_{start} = 10$ and $r_{end} = 50$ meaning that the search for the m value is from 10 to 50. The fitness function is to maximize prediction accuracy of 10-fold cross-validation (10-CV). The tuning parameters of the Cancer*Sig* were independent for the each cancer type. The detailed description of parameters and IBCGA algorithm can refer to the studies.[10,12] The main steps of IBCGA for identifying a signature of m miRNAs and the SVM classifier are as follows.

Step 1 Randomly generate a population of N_{pop} individuals. In this work, $N_{pop} = 50$, $G_{max} = 60$, $r_{start} = 10$, $r_{end} = 50$, $r = r_{start.}$

Step 2 Evaluate the fitness value of all individuals using the fitness function.

Step 3 Use a tournament selection method that selects the winner from two randomly selected individuals to generate a mating pool.

Step 4 Select two parents from the mating pool to perform an orthogonal array crossover operation.

Step 5 Apply a conventional mutation operator to the randomly selected individuals in the new population. To prevent the highest fitness value from deteriorating, mutation is not applied to the best individuals.

Step 6 If the stopping condition of G_{max} generation is satisfied, the best individual is the solution S_r. Otherwise, go to step 2.

Step 7 If $r < r_{end}$, randomly change one bit in the binary genes for each individual from 0 to 1; increase the number r by one, and go to step 2. Otherwise, output the solution S_m with m miRNAs as a signature where S_m is the most accurate solution among the S_r solutions and stop the algorithm.

Table 1. TCGA datasets considered and used for miRNA and cancer stage association analyses after filtration

Dataset	Abbreviation	Original samples	Final samples	miRNAs
Bladder urothelial carcinoma	BLCA	412	407	477
Breast invasive carcinoma	BRCA	1097	386	503
Colon adenocarcinoma	COAD	458	221	444
Esophageal carcinoma	ESCA	185	162	459
Head and neck squamous cell carcinoma	HNSC	528	420	498
Kidney renal clear cell carcinoma	KIRC	537	256	420
Kidney renal papillary cell carcinoma	KIRP	291	261	438
Liver hepatocellular carcinoma	LIHCC	377	348	540
Lung adenocarcinoma	LUAD	522	452	477
Lung squamous cell carcinoma	LUSC	504	339	494
Skin cutaneous melanoma	SKCM	470	389	483
Stomach adenocarcinoma	STAD	443	381	459
Thyroid carcinoma	THCA	503	500	474
Rectum adenocarcinoma	READ	171	66	465
Uveal melanoma	UVM	80	79	486

Robust signature

The selection of a robust signature is necessary when using the nondeterministic algorithm IBCGA in which the solutions of multiple runs are not always the same. For each cancer type, the robust signature among $R = 30$ solutions S_m had the largest appearance score using the following procedure.

Step 1 Perform R independent runs of IBCGA to obtain R signatures. There are P_t features (or miRNAs) in the t-th signatures, $t = 1, \ldots, R$.

Step 2 The appearance score of a signature is calculated as follows:

a) Calculate the feature frequency score $f(p)$ for each miRNA p that ever appears in the R signatures.

b) Calculate the score F_t, $t = 1, \ldots, R$ where S_{ti} is the i-th miRNA in the t-th signature:

$$F_t = \sum_{i=1}^{P_t} f(S_{ti}) / P_t \qquad \text{(Equation 3)}$$

Step 3 Output the t-th signature with the largest appearance score F_t as the robust signature.

KEGG pathway and GO annotation analysis

We utilized the DIANA-miRPath web-based server to analyze the miRNA signatures for downstream biological pathway analyses using KEGG and GO.[23] Plausible miRNA targets identified from the DIANA-TarBase/microT-CDs algorithm analyzed via hypergeometric distribution method using Fisher's exact test for enrichment analysis. A p value of <0.05 was used as the threshold to describe statistical significance. To estimate the specificity of the results, we performed another pathway analysis for all identified miRNA signatures across the 15 cancer types. The GO annotations of the miRNA signatures were analyzed to identify miRNAs belonging to the specific GO categories of biological process, cellular components, and molecular function.

Results

Identification of miRNA signatures across cancers

To identify the miRNA signatures associated with early and advanced stages across cancers, we obtained miRNA expression profiles from the clinical samples of 6,578 patients with cancers from TCGA. The TCGA network contains clinical and molecular information on 33 cancer types from tumor samples collected from 68 primary sites. After preprocessing the data, which included removal of duplicate samples, samples without stage information, and miRNAs that were not expressed in more than 80% of samples, the final dataset consisted of 4,667 clinical samples with cancer stage information. The clinical samples, miRNAs, and cancer types used in this study are summarized in Table 1.

To distinguish between early-stage and advanced-stage cancers via miRNA expression profiles, we proposed an evolutionary learning method, Cancer*Sig*, based on the feature selection algorithm IBCGA and SVM. Identifying a minimum number of features from a large number of candidate features while maximizing the prediction performance is a bi-objective combinatorial optimization problem that is effectively solved by IBCGA.[20,24] Because IBCGA is a nondeterministic method, we performed 30 independent runs and measured the appearance frequency of selected features to select one robust feature set of miRNAs as an miRNA signature for each of 15 cancers.[10] The schematic diagram of the Cancer*Sig* method is depicted in Figure 1.

The prediction performance of Cancer*Sig* across 15 cancer types is shown in Table 2. Cancer*Sig* identified 15 signatures with an average size of 21.93 miRNAs from

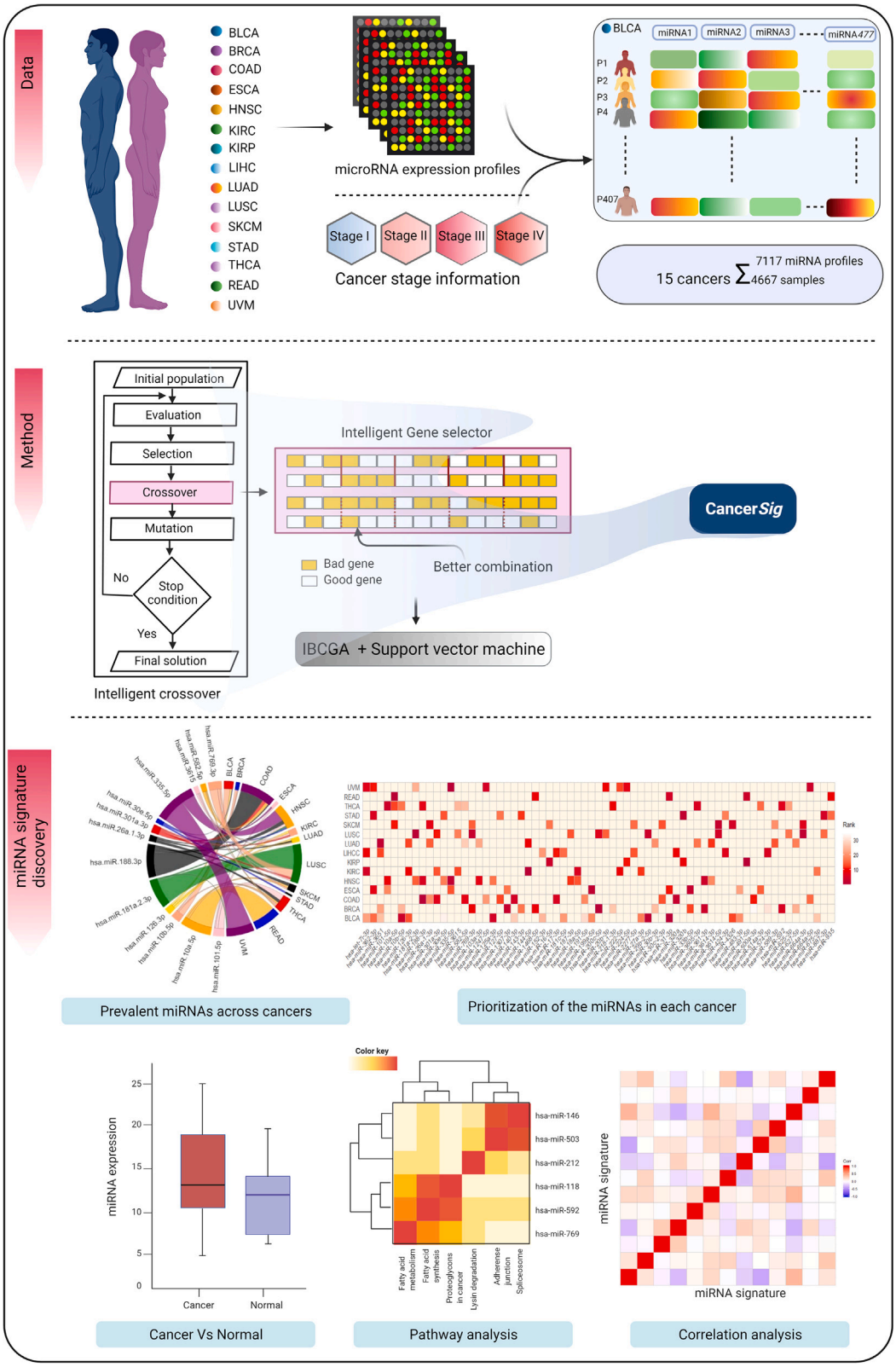

Figure 1. Schematic diagram of the Cancer*Sig* method and analysis of the panel of miRNAs
MicroRNA expression profiles of 15 cancer types along with cancer stage information are input in the workflow of the Cancer*Sig* method to identify miRNA signatures.

Table 2. Prediction performance of Cancer*Sig* across 15 cancers

	Dataset	miRNA signature	10-CV accuracy	Sensitivity	Specificity	MCC	AUC
1	BLCA	35	84.40 ± 1.27	0.64 ± 0.04	0.93 ± 0.01	0.65 ± 0.02	0.82 ± 0.01
2	BRCA	34	80.38 ± 1.55	0.79 ± 2.7	0.81 ± 2.26	0.60 ± 0.03	0.81 ± 0.02
3	COAD	21	86.67 ± 2.40	0.89 ± 0.02	0.82 ± 0.03	0.73 ± 0.04	0.81 ± 0.02
4	ESCA	22	87.97 ± 2.35	0.93 ± 0.02	0.78 ± 0.06	0.75 ± 0.04	0.78 ± 0.03
5	HNSC	20	85.20 ± 1.4	0.52 ± 0.06	0.95 ± 0.01	0.57 ± 0.05	0.71 ± 0.03
6	KIRC	18	87.14 ± 1.76	0.85 ± 0.02	0.87 ± 0.02	0.75 ± 0.03	0.87 ± 0.01
7	KIRP	12	89.43 ± 2.01	0.96 ± 0.01	0.73 ± 0.06	0.76 ± 0.04	0.87 ± 0.03
8	LIHCC	23	89.56 ± 1.27	0.94 ± 0.01	0.73 ± 0.03	0.71 ± 0.03	0.86 ± 0.02
9	LUAD	29	74.29 ± 1.33	0.80 ± 0.02	0.65 ± 0.03	0.53 ± 0.02	0.7 ± 0.01
10	LUSC	18	79.11 ± 2.28	0.74 ± 0.06	0.81 ± 0.02	0.61 ± 0.03	0.80 ± 0.02
11	SKCM	27	78.71 ± 2.47	0.79 ± 0.03	0.76 ± 0.04	0.60 ± 0.03	0.75 ± 0.02
12	STAD	20	77.03 ± 1.9	0.70 ± 0.03	0.79 ± 0.13	0.58 ± 0.03	0.78 ± 0.03
13	THCA	26	76.37 ± 1.20	0.86 ± 0.02	0.61 ± 0.04	0.55 ± 0.02	0.71 ± 0.01
14	READ	11	94.57 ± 2.8	0.90 ± 0.05	0.97 ± 0.02	0.88 ± 0.05	0.95 ± 0.03
15	UVM	13	93.33 ± 3.5	0.93 ± 0.04	0.90 ± 0.13	0.86 ± 0.06	0.85 ± 0.03
	Mean ± SD	21.93 ± 7.30	84.27 ± 6.31	0.81 ± 0.12	0.80 ± 0.10	0.67 ± 0.11	0.80 ± 0.06

10-CV, 10-fold cross-validations; MCC, Matthews correlation coefficient; AUC, area under the ROC curve; SD, standard deviation.

the profiles with an average of 474.5 miRNAs. Cancer*Sig* achieved a mean performance: 10-CV accuracy, sensitivity, specificity, Matthews correlation coefficient (MCC), and area under the receiver operating characteristic (ROC) area under the curve (AUC) of 84.27% ± 6.31%, 0.81 ± 0.12, 0.80 ± 0.10, 0.67 ± 0.11, and 0.80 ± 0.06, respectively. The prediction performance was evaluated using ROC curves and AUC in the range of 0.70–0.95 for 15 cancers, as shown in Figure 2A.

We compared the prediction performance of Cancer*Sig* with various machine learning algorithms using the same number of features based on feature importance. LightGBM[25] achieved a mean performance: 10-CV accuracy, sensitivity, specificity, and AUC of 72.22 ± 0.04, 0.83 ± 0.06, 0.51 ± 0.14, and 0.72 ± 0.06, respectively, while distinguishing early and advanced stages of BLCA. XGBoost[26] achieved a mean 10-CV accuracy, sensitivity, specificity, and AUC of 72.70 ± 0.06, 0.88 ± 0.06, 0.41 ± 0.16, and 0.73 ± 0.05, respectively. Random Forest[27] achieved a mean 10-CV accuracy, sensitivity, specificity, and AUC of 70.98 ± 0.05, 0.77 ± 0.07, 0.59 ± 0.16, and 0.74 ± 0.05, respectively. CatBoost[28] achieved a mean 10-CV accuracy, sensitivity, specificity, and AUC of 73.93 ± 0.06, 0.91 ± 0.07, 0.39 ± 0.12, and 0.74 ± 0.05, respectively. Extra Trees achieved a mean 10-CV accuracy, sensitivity, specificity, and AUC of 72.72 ± 0.04, 0.78 ± 0.07, 0.63 ± 0.11, and 0.74 ± 0.06, respectively. Cancer*Sig* achieved a mean 10-CV accuracy, sensitivity, specificity, and AUC of 84.40 ± 1.27, 0.64 ± 0.04, 0.93 ± 0.01, and 0.82 ± 0.01, respectively, shown in Table S1. The prediction performance of Cancer*Sig* is better than other machine learning methods in predicting cancer stage of BLCA. In addition, the prediction performance of the optimizing technique in distinguishing breast invasive carcinoma (BRCA) and liver hepatocellular carcinoma (LIHCC) was compared with other machine learning methods in our previous studies.[10,29]

A panel of miRNAs across 15 cancers

A panel is designed as a compact set of informative miRNAs obtained from the 15 miRNA signatures, which has 329 miRNAs in total. After removing duplication, the union has 242 informative miRNAs in the designed cancer-stage panel. The panel can predict the cancer stage across 15 cancer types. In predicting the stage of a specific cancer, the same prediction model with the corresponding signature in the panel can be used. Therefore, the prediction performance using the panel of miRNAs for predicting the 15 cancers achieved 10-CV accuracy, sensitivity, specificity, MCC, and AUCs of 84.27% ± 6.31%, 0.81 ± 0.12, 0.80 ± 0.10, 0.67 ± 0.11, and 0.80 ± 0.06, respectively, as shown in Table 2.

Prioritization of the miRNA signatures

Each cancer type had an average of about 22 miRNAs in a signature. To rank the miRNAs of a signature according to the degree of contribution to prediction performance, a main effect difference (MED) analysis[8,30] was performed. A higher MED score represents a greater contribution of the specific miRNA to the stage prediction. The miRNAs with the greatest predictive ability can be ranked highest in the signature. The identified miRNA signatures, ranks

of their miRNAs, and corresponding MED scores are listed

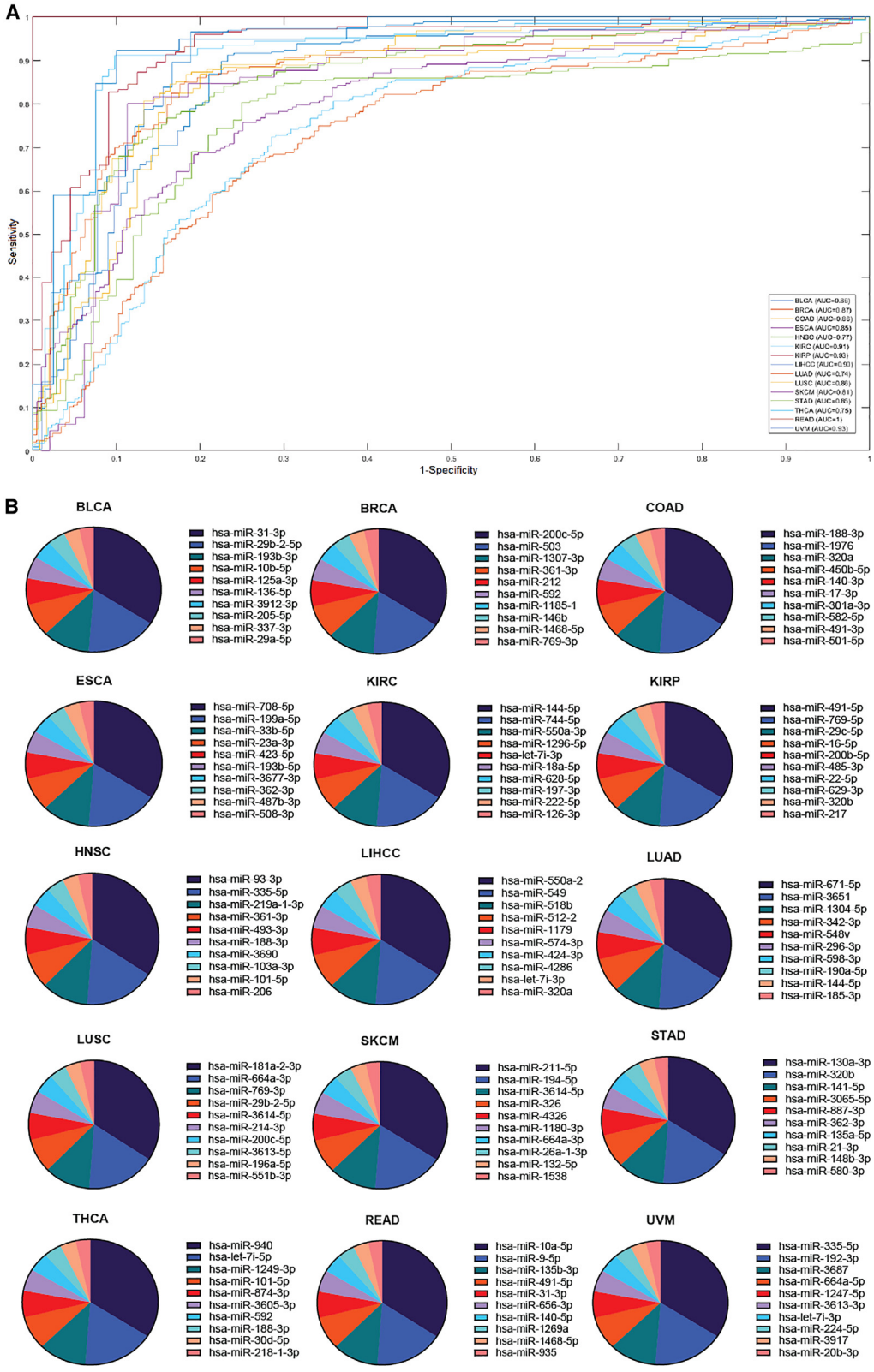

Figure 2. Cancer*Sig* prediction performance across cancers

(A) Evaluating the prediction performance of Cancer*Sig* using receiver operating characteristic (ROC) across 15 cancers. Cancer*Sig* obtained a mean area under the curve (AUC) of 0.80 across all cancers.

(B) Ranking of the relative miRNAs within the signature using MED analysis.

in Tables S2.1–S2.15. The top 10 ranked miRNAs across 15 cancers are shown in Figure 2B.

Prevalent miRNAs across cancers

Next, we determined if there are any similarities among the miRNAs of each signature in addition to distinguishing stages across the 15 cancers. In this context, we identified some common miRNAs that were found to be expressed in more than one cancer. Three miRNAs, hsa-let-7i-3p, hsa-miR-362-3p, and hsa-miR-3651, contributed more toward stage prediction across eight cancer types (BLCA, BRCA, esophageal carcinoma [ESCA], kidney renal clear cell carcinoma [KIRC], LIHCC, lung adenocarcinoma [LUAD], stomach adenocarcinoma [STAD], and uveal melanoma [UVM]) than any other miRNAs. According to the MED analysis, hsa-let-7i-3p ranked 5th, 7th, 9th, and 22nd in predicting cancer stage in KIRC, UVM, LIHCC, and BLCA, respectively; hsa-miR-362-3p ranked 6th, 8th, 11th, and 16th in STAD, ESCA, UVM, and BLCA, respectively; and hsa-miR-3651 ranked 2nd, 13th, 22nd, and 26th in LUAD, LIHCC, BRCA, and BLCA, respectively. These miRNAs were annotated with miRBase accession numbers and used in subsequent pathway analyses.

The three target miRNAs were first analyzed via prediction interaction networks supported by Cytoscape v.3.7[31] to explore the proposed target gene interactions. From the three miRNA target prediction databases, miRTarBase, MicroCosm, and TargetScan, 1,839 predicted miRNA-target interactions were identified. The predicted miRNA-gene target network is shown in Figure S1. In addition to the three primary miRNAs, 64 additional miRNAs were identified in the signatures where each was involved in more than one cancer. Among the 64 miRNAs, each of 14 miRNAs was involved in 3 cancers while each of the remaining 50 miRNAs was involved in 2 cancers. These prevalent miRNAs and their contribution in predicting the stage across cancers are depicted in Figures 3A–3C.

To confirm that the expression levels of the identified target miRNAs differ significantly between tumor and non-tumor samples for each cancer type, we compared the relative expression difference of the three miRNAs, hsa-let-7i-3p, hsa-miR-362-3p, and hsa-miR-3651. Significant differences in expression levels between tumor samples and normal samples for all miRNAs analyzed were reported for BRCA, lung squamous cell carcinoma (LUSC), and STAD. Hsa-let-7i-3p and hsa-miR-362-3p were significantly expressed in BLCA, KIRC, LIHCC, and LUAD, while hsa-miR-362-3p and hsa-miR-3651 had significant differences in head and neck squamous cell carcinoma. A statistically significant difference in expression level for kidney renal papillary cell carcinoma (KIRP) was only detected for hsa-miR-362-3p; similarly, significant differences in expression for hsa-miR-3651 were only noted for ESCA and thyroid carcinoma. The relative expression levels of these miRNAs and corresponding comparisons are shown in Table S3.

As the MED analysis, the top-ranked miRNAs are potential predictors of cancer stage. However, some miRNAs had low ranks in some cancers yet high ranks in other cancer types. For instance, hsa-let-7i-3p ranked 22nd in BLCA but ranked 5th in KIRC meaning that its contribution to cancer stage was higher for KIRC. This analysis revealed a panel of 242 miRNAs that are associated with the cancer stage in more than 1 cancer. The heatmap of the most prevalent miRNA rankings across the 15 cancer types is depicted in Figure 3D.

Co-expression analysis of the miRNA signatures

Though IBCGA identified critical miRNA signatures for cancer stage prediction, the algorithm might exclude some informative miRNAs from the signatures to select a small set of candidate miRNAs to enhance prediction performance. To ensure a robust set of miRNAs selected by IBCGA, co-expression analysis was performed via series of correlational analyses. First, correlation coefficient (R) between the miRNAs in the signatures was measured and then the coefficients between all the miRNAs (an average 474.46) and individual miRNAs in the signature for each cancer type were measured. The miRNAs pairs with $R \geq 0.80$ were considered for further analysis. There were 154 miRNA pairs that co-expressed with the miRNAs of 15 cancer stage-specific miRNA signatures. Of the signatures analyzed by cancer type, the miRNA signature for LUSC did not have co-expressed miRNAs with $R \geq 0.8$. The correlation heatmap of miRNAs in each of the 15 signatures is shown in Figure S2, and the correlation coefficients of the154 miRNA pairs for the 15 miRNA signatures are listed in Table S4.

Significance of the identified miRNA signatures in cancers

We evaluated the significance of the identified miRNAs for each cancer type based on experimentally validated literature and, of these miRNAs, only the top 10 ranked miRNAs of each signature were considered, as shown in Tables S5–S19. Among the identified 15 cancer stage-specific miRNA signatures, most of have experimentally validated evidence to support their dysregulation and potential role in various cancers. However, of the 15 miRNA signatures, the role of 34 miRNAs was not reported in the earlier literature leading us to believe that these 34 miRNAs are novel biomarkers for predicting the cancer stage (listed in Table S20). The roles of these miRNAs in cancer stage detection need to be validated to further determine their significance.

To confirm that the selected miRNAs had differing expression levels by stage within each cancer, we measured the expression differences of the identified top 10 ranked miRNAs between the early- and advanced-stage groups across 15 cancers, as shown in Figure S3. All of the identified miRNA signatures are significantly different between early- and late-stage cancers, which supports the use of these miRNAs in predicting early-stage cancers.

Biological relevance of miRNA signatures across cancers

Employing KEGG analysis, we found that each miRNA signature was involved in several cancers and signaling

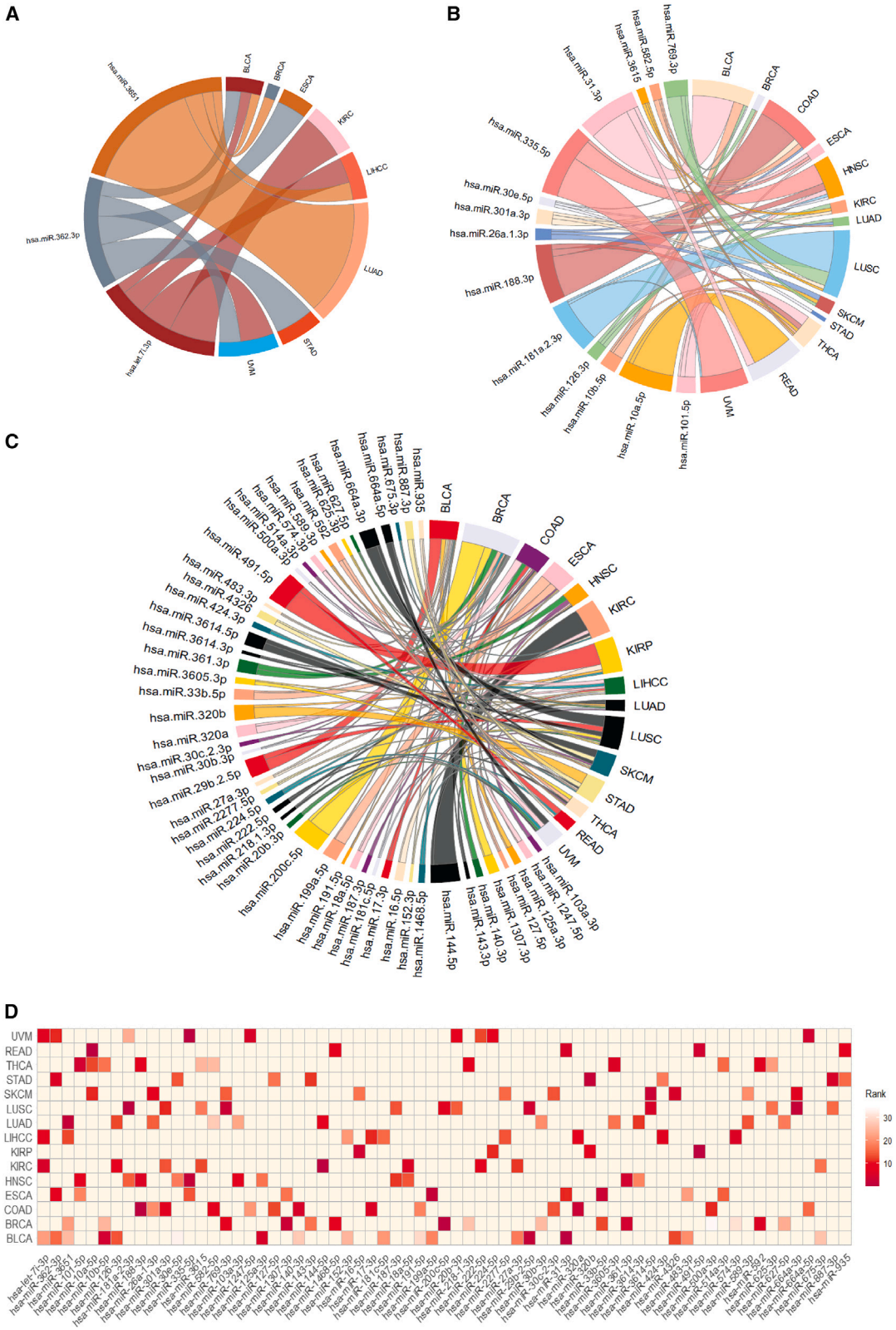

Figure 3. The predictive ability of miRNAs as a biomarker for cancer stage across cancer types

(A) Three signature miRNAs and their contributions to stage prediction across eight cancer types. Each miRNA contributed to at least four cancers. The size of the line is proportional to the percent contribution toward the stage prediction.

(B) Fourteen miRNAs contributed across cancers, and each miRNA contributed to at least three cancers.

(C) Fifty miRNAs contributed to at least two cancers.

(D) Heatmap showing 67 miRNAs and their ranks based on their predictive ability across 15 cancer types.

Table 3. KEGG pathways commonly appearing in more than five cancers

KEGG pathways	No. of cancers
Proteoglycans in cancer	15
Signaling pathways regulating pluripotency of stem cells	14
Beta signaling pathway	13
Axon guidance	11
Glioma	10
Hippo signaling pathway	10
Renal cell carcinoma	10
ErbB signaling pathway	9
FoxO signaling pathway	9
Pathways in cancer	9
Prion diseases	9
Rap1 signaling pathway	9
Long-term depression	8
Ras signaling pathway	8
Circadian rhythm	7
Focal adhesion	7
Thyroid hormone signaling pathway	7
Adherens junction	6
Colorectal cancer	6
ECM-receptor interaction	6
Estrogen signaling pathway	6
Melanoma	6
Morphine addiction	6
Adrenergic signaling in cardio myocytes	5
Choline metabolism in cancer	5
Fatty acid biosynthesis	5
Mucin type O-glycan biosynthesis	5
Oxytocin signaling pathway	5
Phosphatidylinositol signaling system	5
Prolactin signaling pathway	5
Prostate cancer	5
Wnt signaling pathway	5

pathways, including transforming growth factor β, hippo, and the thyroid hormone signaling pathways as well as signaling pathways related to axon guidance (see Table S21). Of the cancer types analyzed, the proteoglycans in cancer pathway was observed in all 15 cancer types, which is consistent with the role of proteoglycans and extracellular matrix components in cancer development and progression.[32–41] In addition, the second KEGG pathway commonly found in 14 cancers was "Signaling pathways regulating the pluripotency of stem cells," which has a wide range of applications in regenerative medicine and significance in cancer.[42] A summary of the miRNA signatures that appeared in more than five cancer types and were identified as having potential involvement in biological pathways by KEGG pathway analysis is provided in Table 3. The identified miRNA signatures enriched in KEGG pathways across the 15 cancer types are shown in Figures S4.1–S4.15.

To support the biological validity of our findings, we performed GO enrichment analysis and identified GO terms that were enriched by the identified miRNA signatures. Among the 15 cancer types analyzed, 9 GO terms consistently appeared. The most frequent and significant GO terms that appeared were biosynthetic process, cellular component assembly, cellular nitrogen compound metabolic process, cellular protein modification process, epidermal growth factor receptor signaling pathway, Fc-epsilon receptor signaling pathway, gene expression, neurotrophin TRK receptor signaling pathway, transcription, and DNA template synthesis, listed in Tables 4 and S22. The identified miRNA signatures enriched in the various GO categories across 15 cancers are shown in Figures S5.1–S5.15.

Discussion

Due to the different types of cancers and the frequent emergence of cancer symptoms at advanced stages, it is challenging to detect cancer at an early stage. Identifying broad and reliable biomarkers for cancer detection and prediction in the early stage may provide timely treatment for patients.

In this study, we describe the development and preliminary predictive ability of cancer stage prediction method Cancer*Sig* using SVM combined with an optimal feature selection algorithm IBCGA to identify miRNA signatures associated with staging across various cancers. Cancer*Sig* identified 15 cancer stage-specific miRNA signatures for 15 different cancer types that are associated with the stage of patients with cancers. There were 242 miRNAs that showed promising predictive ability as a panel for stage detection across the 15 cancer types. Rankings of miRNAs via MED analysis highlighted the contribution of each miRNA to stage prediction. Of these, three miRNAs, hsa-let-7i-3p, hsa-miR-362-3p, and hsa-miR-3651, consistently had statistically significantly different expression levels between tumor and non-tumor samples and by cancer stage within the 15 cancer types analyzed. The biological plausibility of these miRNAs as reliable predictors of cancer development and progression are supported by the following evidences in the literature. Hu et al., Cai et al., and Zhao et al. reported that the hsa-let-7 family of miRNAs are dysregulated in several cancer types, such as, breast,[43] ovarian,[44] and non-small cell lung cancer.[45] Hsa-miR-362-3p and hsa-miR-3651 are also found to be regulated in different cancer types.[46,47]

Analysis of prevalent miRNAs within the total set of 242 miRNAs highlighted 67 miRNAs that contributed to 2 or more cancers. Out of the 67 miRNAs, 3 miRNAs each

Table 4. GO category frequency in more than five cancers

GO category	No. of cancers
Biosynthetic process	15
Cellular component assembly	15
Cellular nitrogen compound metabolic process	15
Cellular protein modification process	15
Epidermal growth factor receptor signaling pathway	15
Fc-epsilon receptor signaling pathway	15
Gene expression	15
Neurotrophin TRK receptor signaling pathway	15
Transcription, DNA template	15
Catabolic process	14
Cytosol	14
Enzyme binding	14
Ion binding	14
Nucleic acid binding transcription factor activity	14
Nucleoplasm	14
Organelle	14
Protein binding transcription factor activity	14
Protein complex	14
Small-molecule metabolic process	14
Blood coagulation	13
Cytoskeletal protein binding	13
Symbiosis, encompassing mutualism through parasitism	13
Viral process	13
Macromolecular complex assembly	12
Fibroblast growth factor receptor signaling pathway	11
Response to stress	11
Cell death	10
Phosphatidylinositol-mediated signaling	10
Nucleobase-containing compound catabolic process	9
Synaptic transmission	9
Mitotic cell cycle	7
Protein complex assembly	7
Enzyme regulator activity	6
Transcription initiation from RNA polymerase II promoter	6

contributed to four cancers, 14 miRNAs each contributed to 3 cancers, and 50 miRNAs each contributed to 2 cancers. The 15 miRNA signatures were all significantly involved in various signaling pathways, extracellular matrix-associated signaling, and stem cell pluripotency according to KEGG pathway analysis and GO term assignment post-enrichment analysis. One hundred and fifty-four miRNAs co-expressed with the miRNA signatures across cancers were associated with cancer progression and early-stage detection. Of the miRNAs detected within the signature and associated with cancer stage, 34 miRNAs that we describe here have not been reported before. Further research of these miRNAs may provide new avenues for therapeutic and diagnostic test development.

Across all cancer types, miRNA signatures were enriched for proteins associated with proteoglycans. Proteoglycans are macromolecules and the major component of the extracellular matrix. They act as co-receptors for enhancing proliferative signaling and tumor growth.[34] Notably, the altered expression of proteoglycans correlates with prognosis in various malignant neoplasms.[33,35] In addition, proteoglycan-dependent pathways are involved in promoting metastasis and cell motility in breast cancer.[36,37] The miRNAs regulate enzymes that are directly linked to proteoglycan function and are involved in tumor progression.[38,39] The aberrant expression of miRNAs affects the expression patterns of laminins, proteoglycans, and proteases in the tumor microenvironment[40]; consequently, cell adhesion, migration, and apoptosis and cancer stem cell properties are affected.[41] In addition, multiple roles of miRNAs in pluripotency have been investigated, including but not limited to cell fate during embryogenesis[48] and the regulation of stem cells.[49] The upregulation of miR-495 was observed in breast cancer stem cells,[50] and miR-34a is downregulated and regulates cancer stem cells in prostate cancer.[51] The finding suggests that a specific miRNA signature regulates proteoglycans in the tumor microenvironment and stem cell pluripotency, which may have a profound impact on early-stage cancer detection.

High performance of Cancer*Sig* arises mainly from an optimal feature selection algorithm IBCGA incorporated with an SVM classifier. IBCGA is effective at solving bi-objective combinatorial optimization problems and has been proven to be efficient at identifying suitable biomarkers in various cancers.[8,10,12,13,52] Cancer*Sig* achieved a promising accuracy while predicting the cancer stage across 15 different cancer types; and obtained a mean performance of 10-CV accuracy, sensitivity, specificity, MCC, AUC of 84.27 $\pm$ 6.31, 0.81 $\pm$ 0.12, 0.80 $\pm$ 0.10, 0.67 $\pm$ 0.11, and 0.80 $\pm$ 0.06, respectively. The limitation of the current method is using the TCGA data alone for the experiments due to the availability of similar extraction methods for miRNA expression profiling and clinical information. However, Cancer*Sig* showed better performance on all cancer types irrespective of the data size. This method can be customized based on the availability of miRNA expression data and clinical samples.

In conclusion, identification of the novel miRNA signatures via Cancer*Sig* may serve as the basis for predicting the development and stage of various types of cancer. Use of

this method may aid in early identification of cancer and cancer stage, which would facilitate clinician decision making for treatment plans and provide patients with timely treatment for cancer. The designed novel panel of miRNA signatures across cancers would guide the development of stage detection chips and miRNA-based target therapies to treat cancer.

Data and code availability

All the data used in this analysis can be found in the TCGA data portal: https://portal.gdc.cancer.gov/ CancerSig is available at Github: https://github.com/mingjutsai/CancerSig.

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.xhgg.2023.100190.

Acknowledgments

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Author contributions

S.Y.S. and S.-Y.H. designed the system and carried out the detailed study. S.-Y.S. participated in the design of the system and implemented programs. M.-J.T., S.K.S., S.-Y.H., and S.-Y.S. participated in analysis and discussed the results. All authors participated in the manuscript preparation and approved the final manuscript.

Declaration of interests

The authors declare no competing interests.

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Web resources

Cancer*Sig*, https://github.com/mingjutsai/CancerSig

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HGGA, Volume *4*

Supplemental information

Artificial intelligence-driven pan-cancer analysis reveals miRNA signatures for cancer stage prediction

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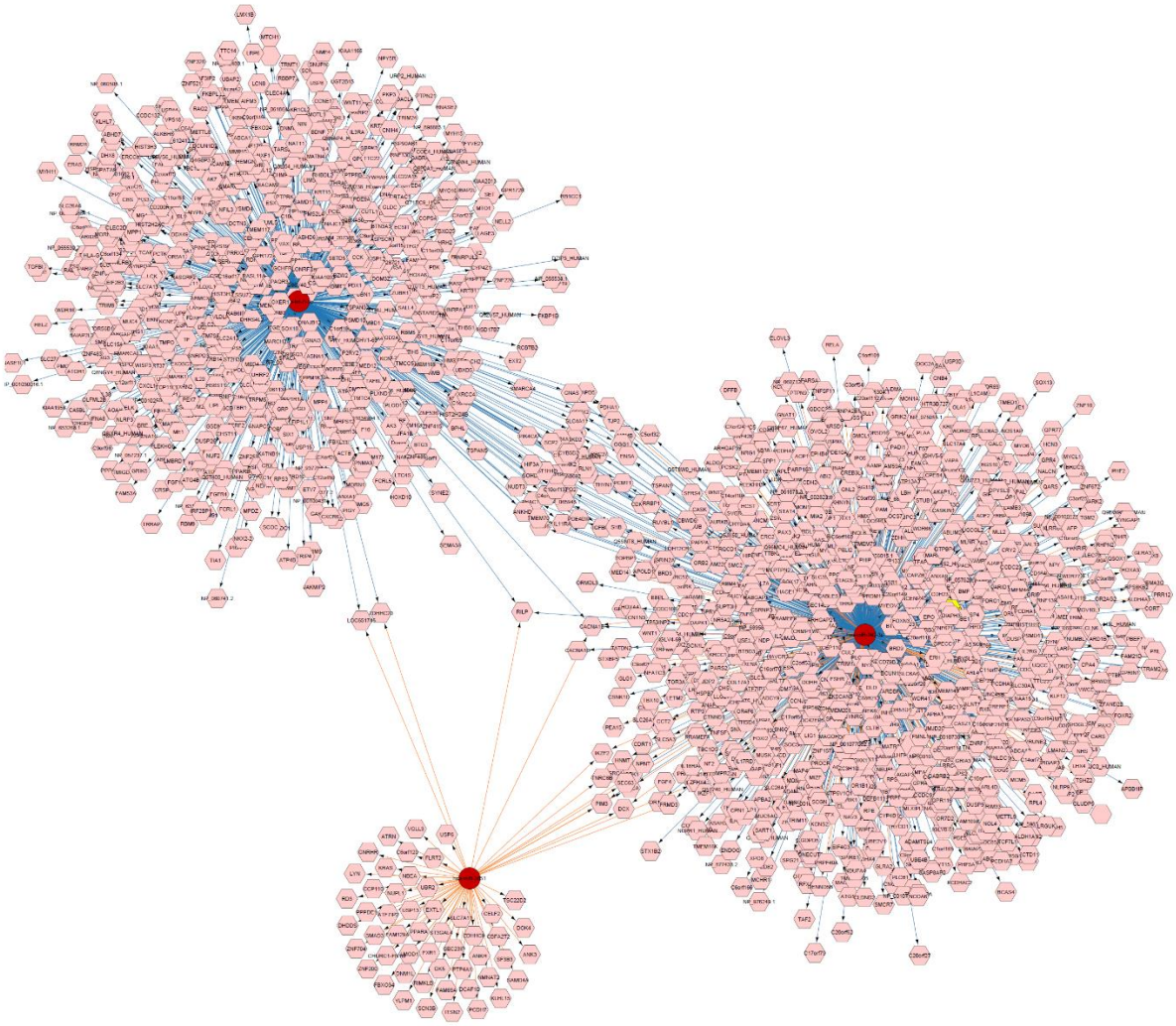
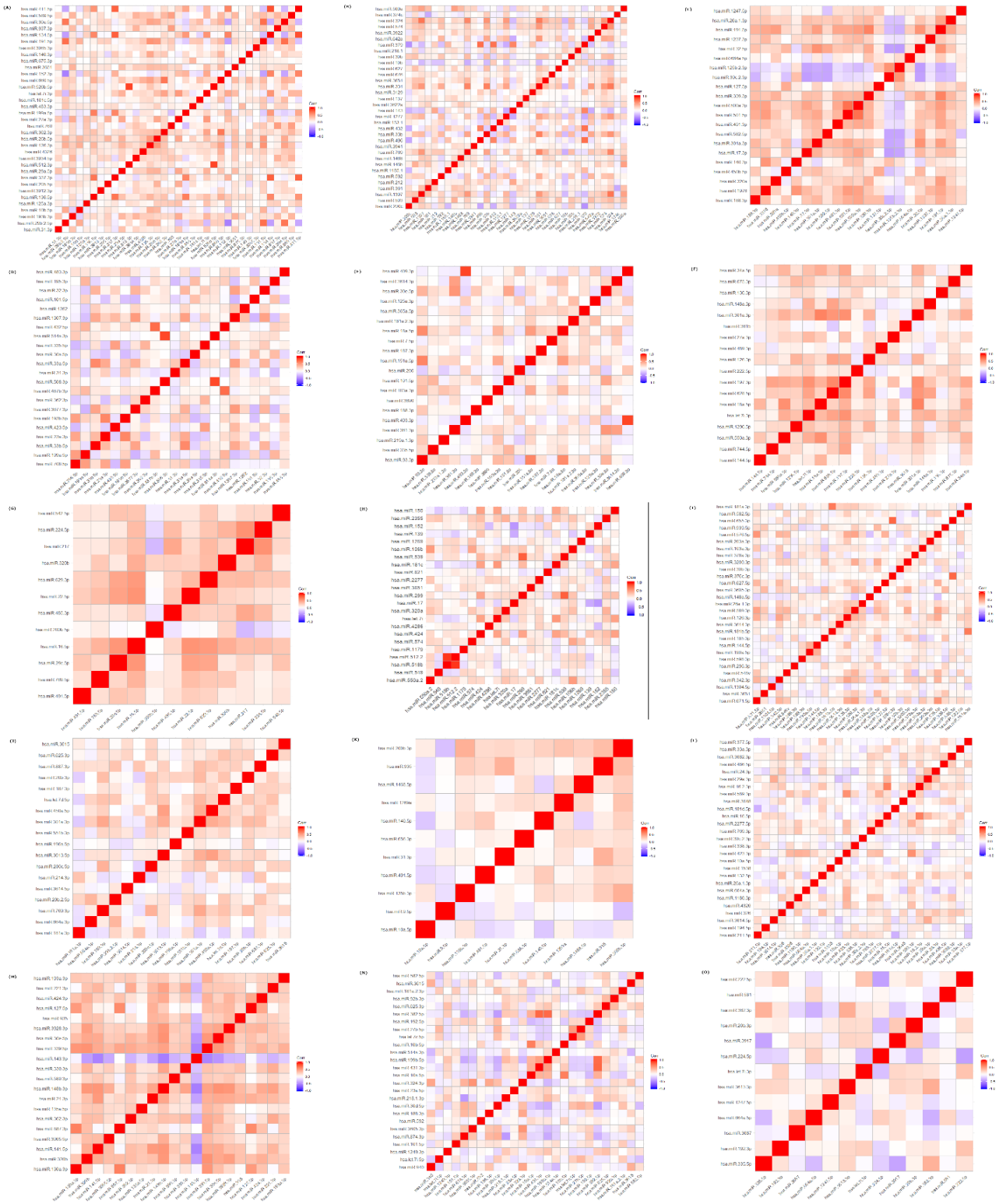
Supplementary information

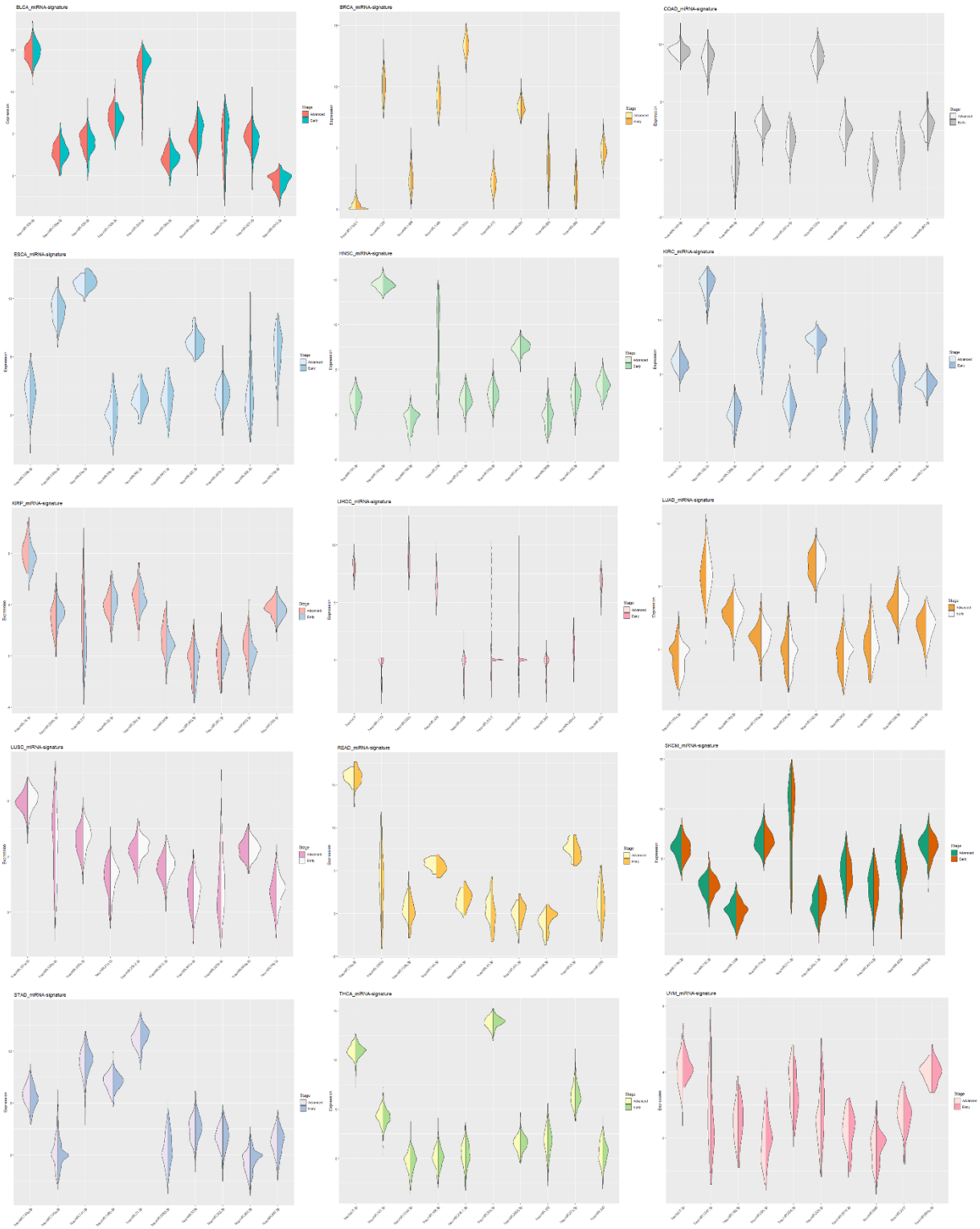
Supplementary Figures



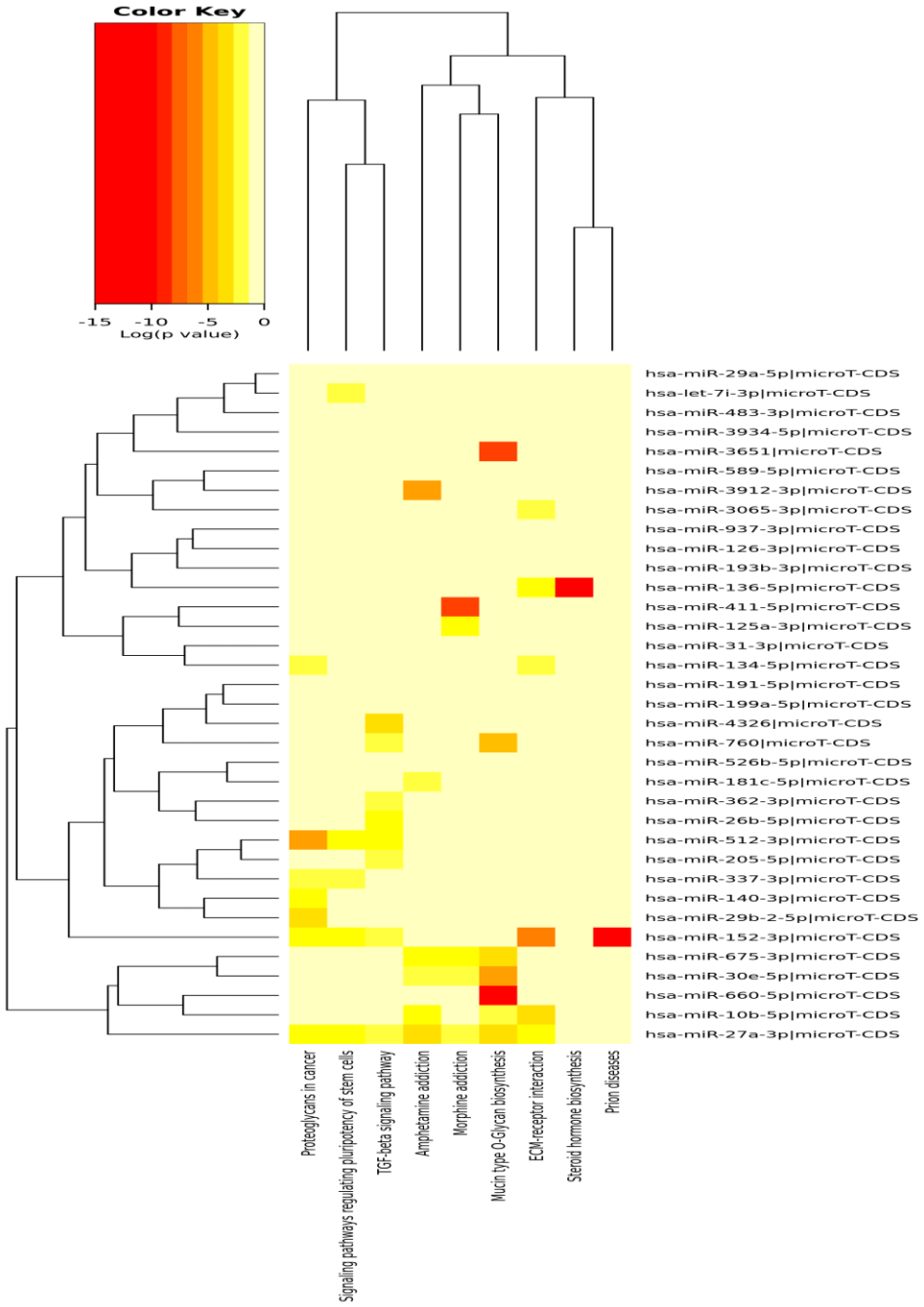
Supplementary Figure S1. Three miRNAs and corresponding target genes predicted using MicroCosm, miRTar base, and TargetScan. In this network microRNAs and target genes are defined as red circles and pink rounded hexagons respectively. The predicted microRNA-Target interactions are visualized in blue and in orange color.



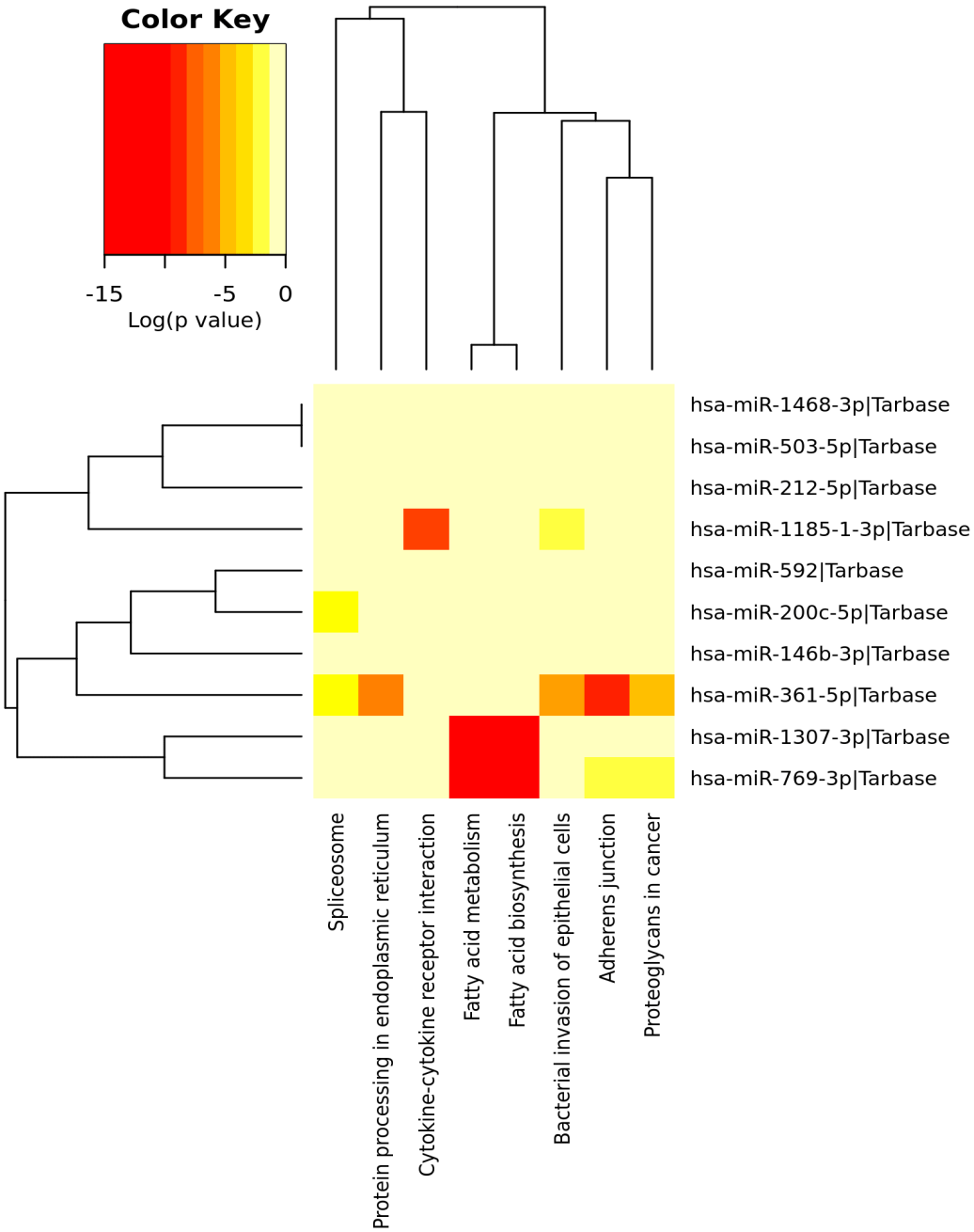
Supplementary Figure S2. Co-expression analysis of miRNA signatures across 15 cancers. (A) BLCA, (B) BRCA, (C) COAD, (D) ESCA, (E) HNSC, (F) KIRC, (G) KIRP, (H) LIHCC, (I) LUAD, (J) LUSC, (K) READ, (L) SKCM, (M) STAD, (N) THCA, and (O) UVM.



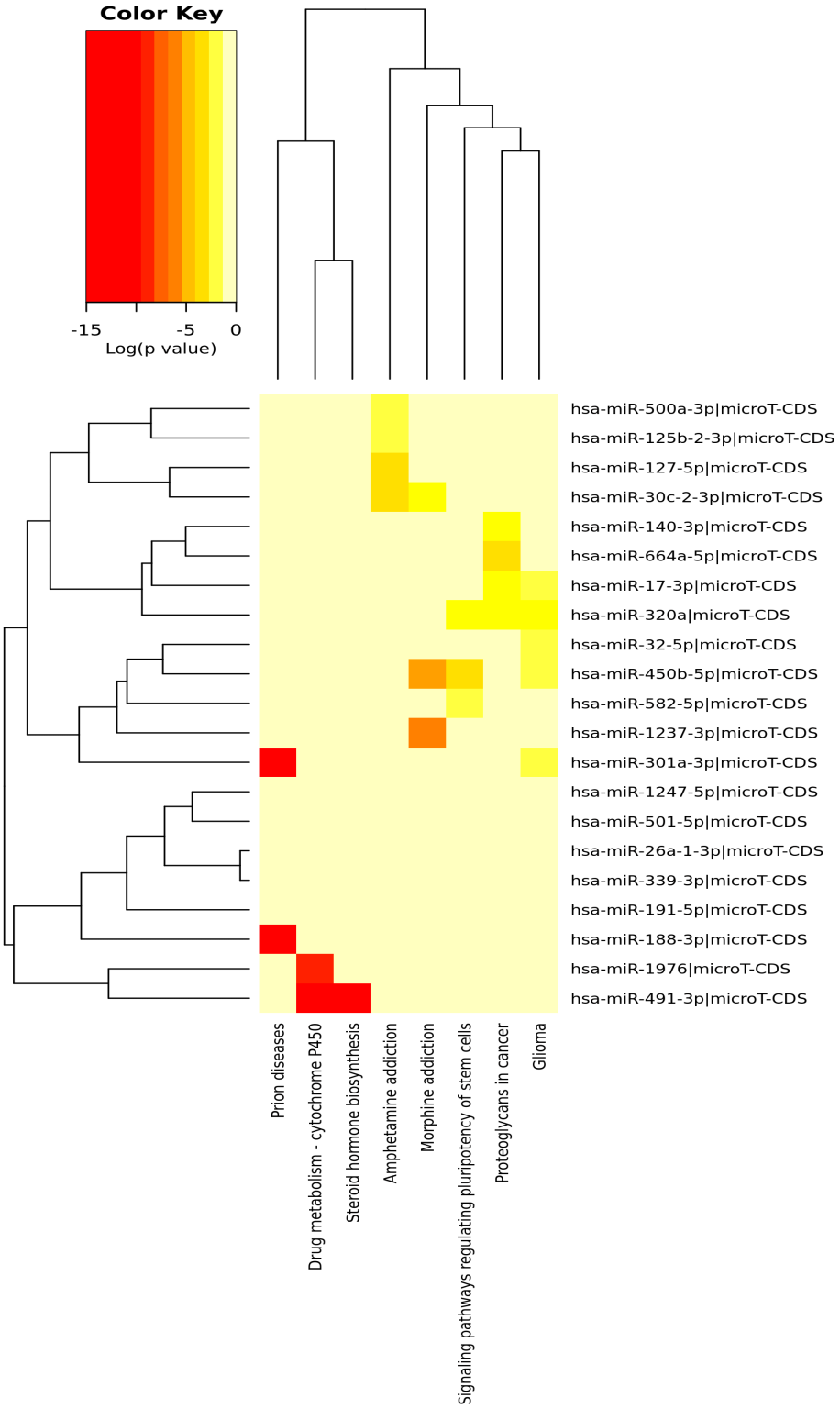
Supplementary Figure S3. **Expression difference analysis of the miRNA signatures across 15 cancers**. Relative expression differences of the miRNA signatures between early and advanced stages across cancers.



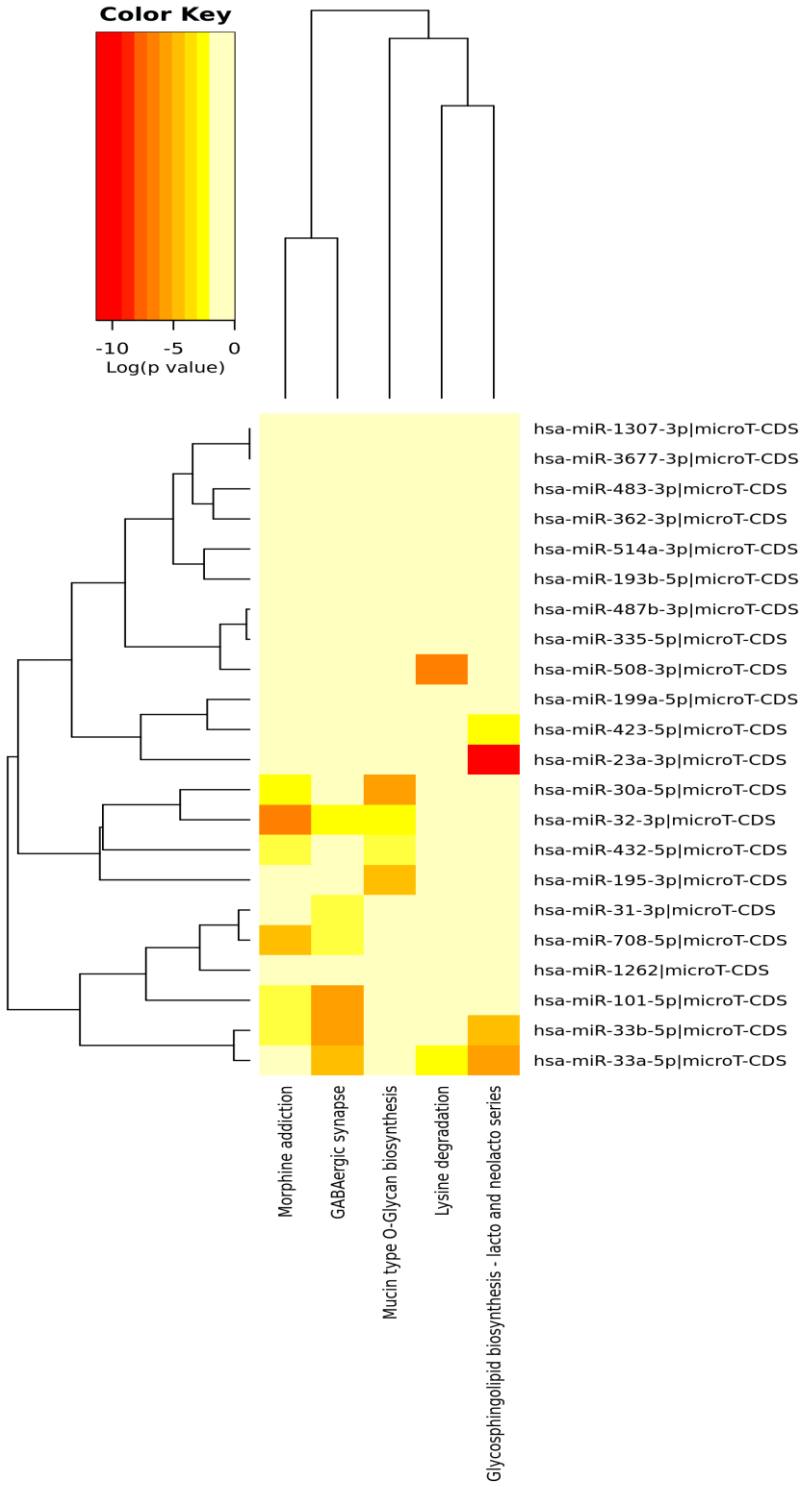
Supplementary Figure S4.1. KEGG pathway enrichment analysis of miRNA signatures in BLCA



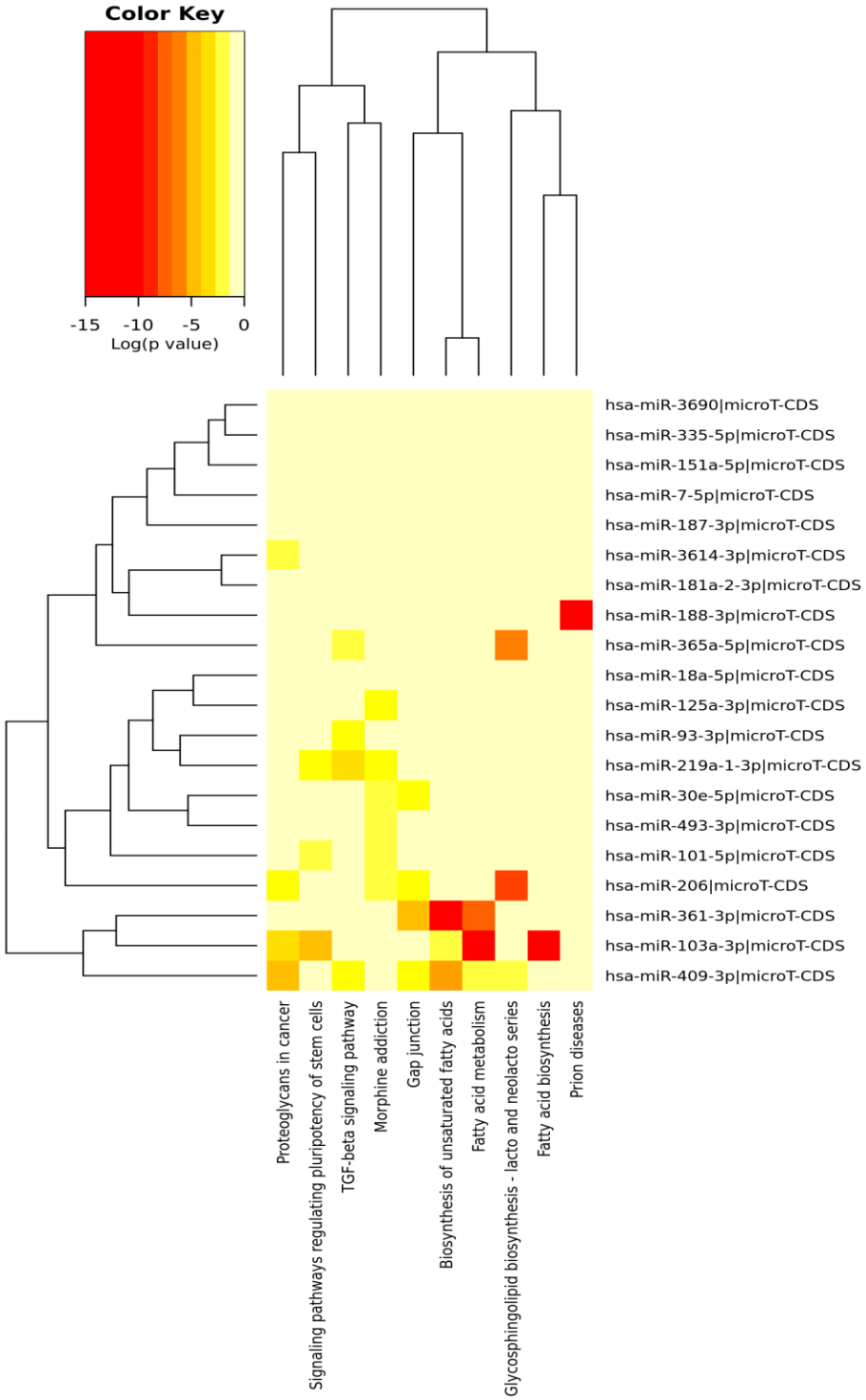
Supplementary Figure S4.2. KEGG pathway enrichment analysis of miRNA signatures in BRCA



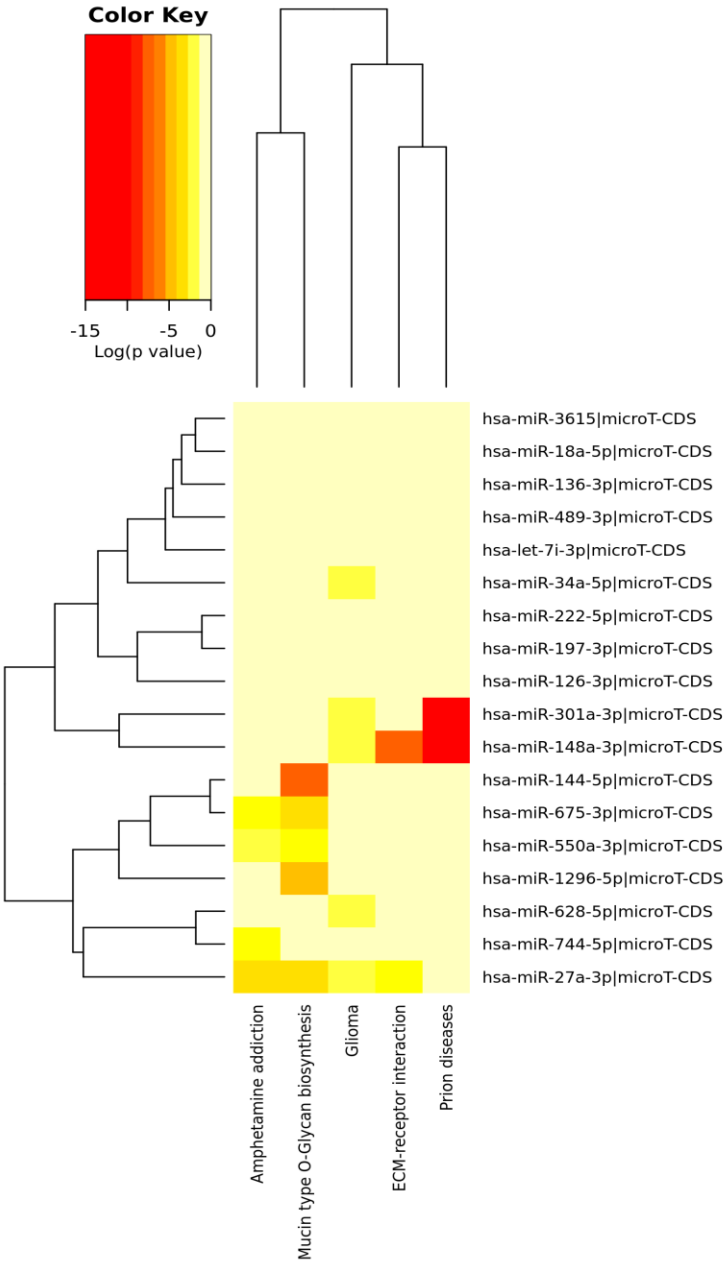
Supplementary Figure S4.3. KEGG pathway enrichment analysis of miRNA signatures in COAD



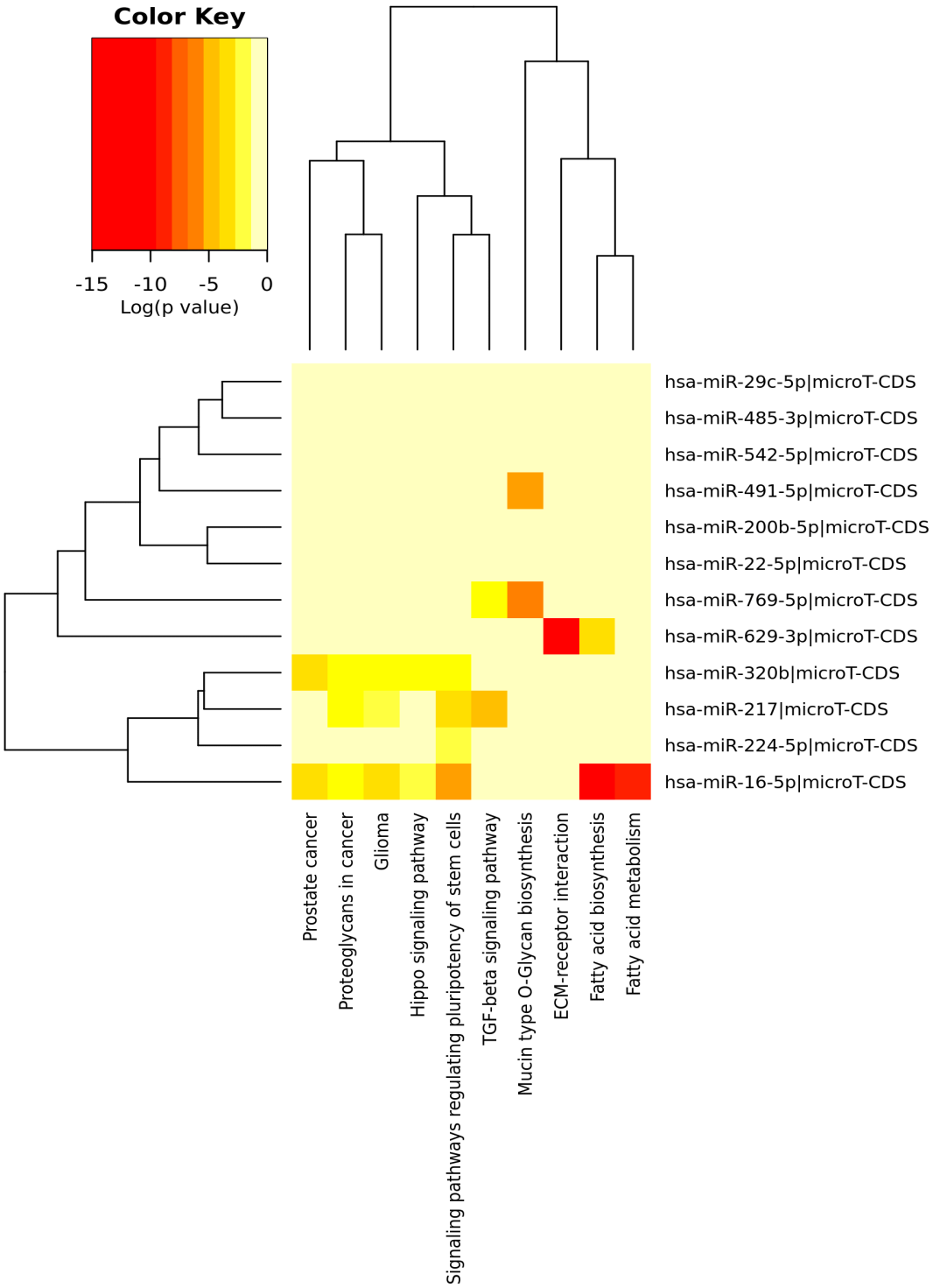
Supplementary Figure S4.4. KEGG pathway enrichment analysis of miRNA signatures in ESCA



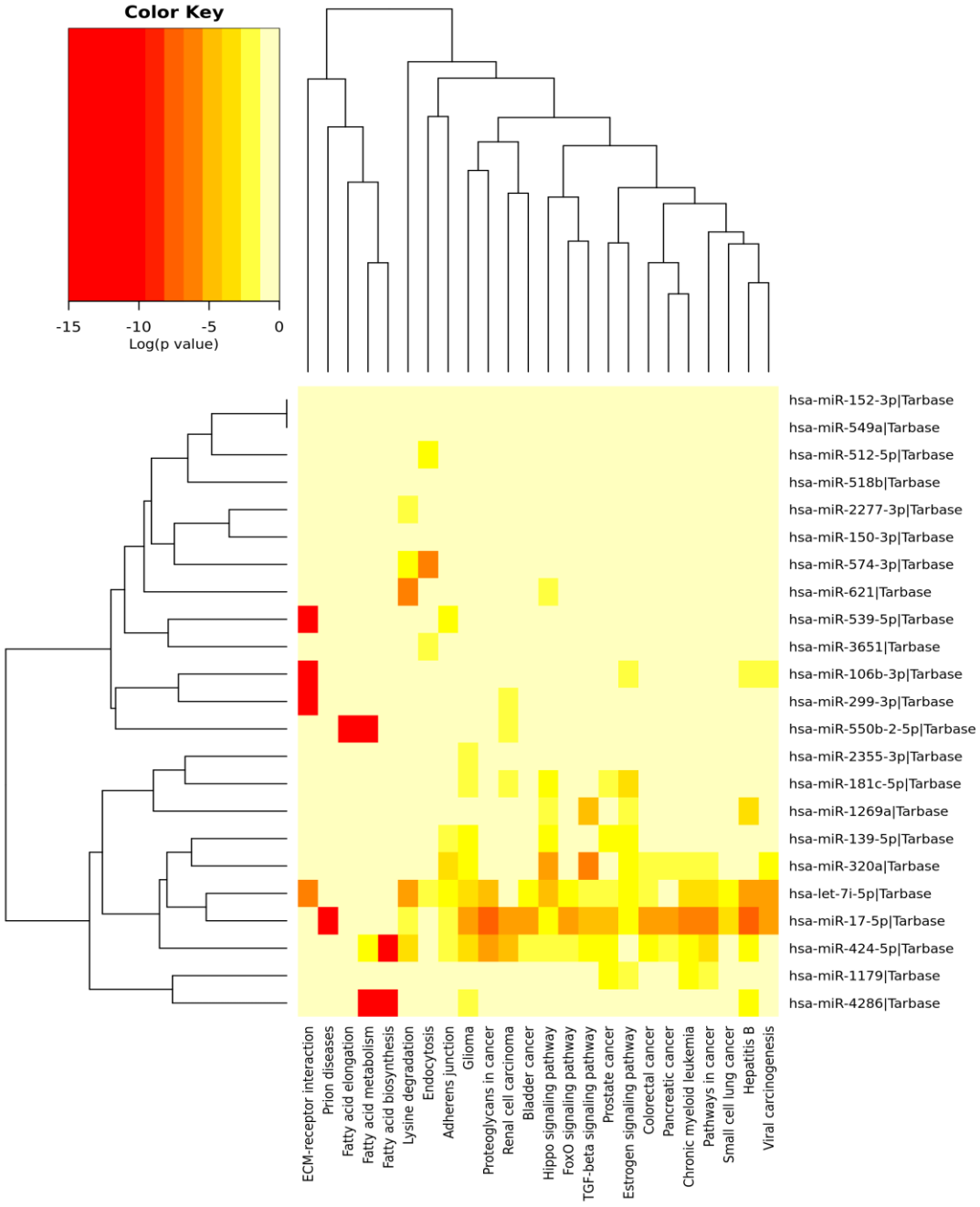
Supplementary Figure S4.5. KEGG pathway enrichment analysis of miRNA signatures in HNSC



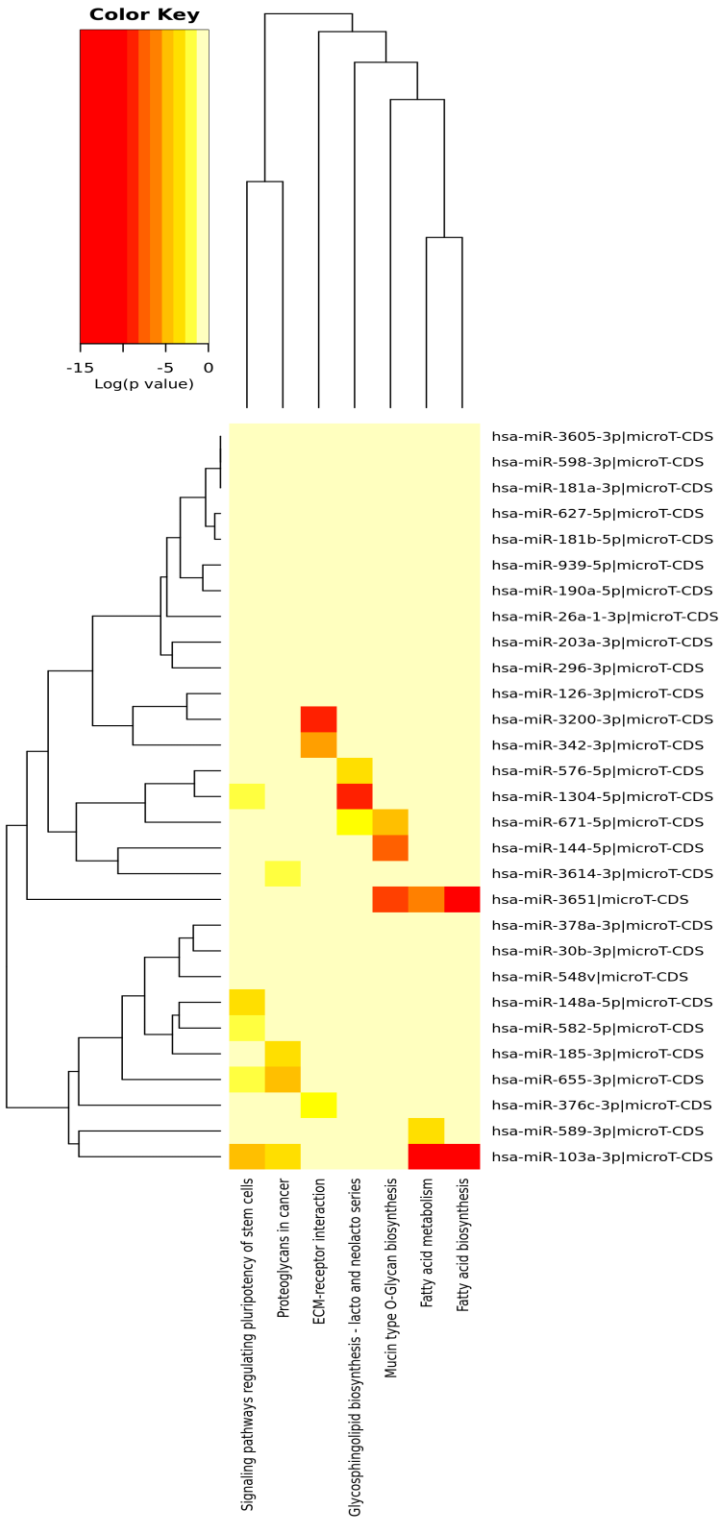
Supplementary Figure S4.6. KEGG pathway enrichment analysis of miRNA signatures in KIRC



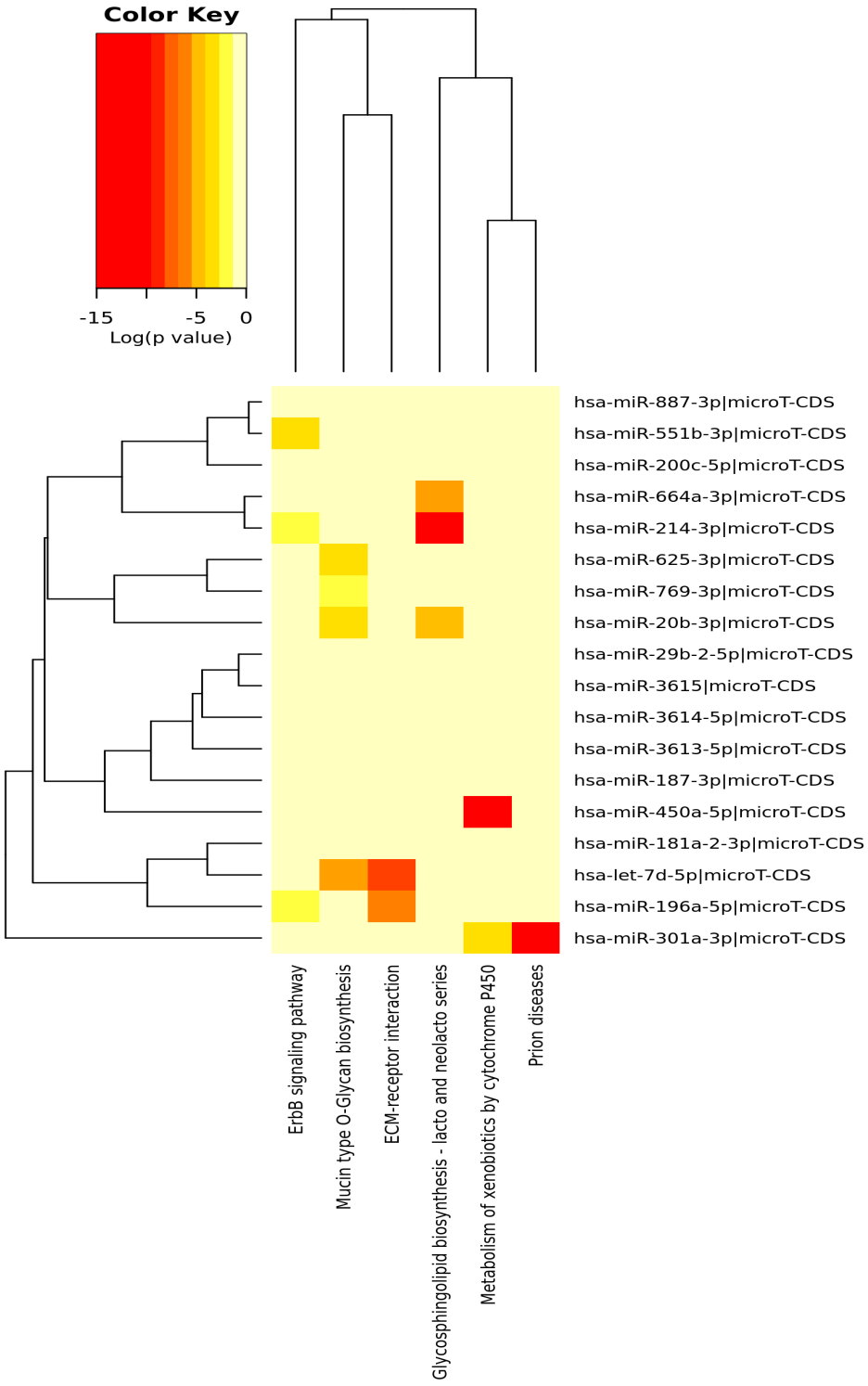
Supplementary Figure S4.7. KEGG pathway enrichment analysis of miRNA signatures in KIRP



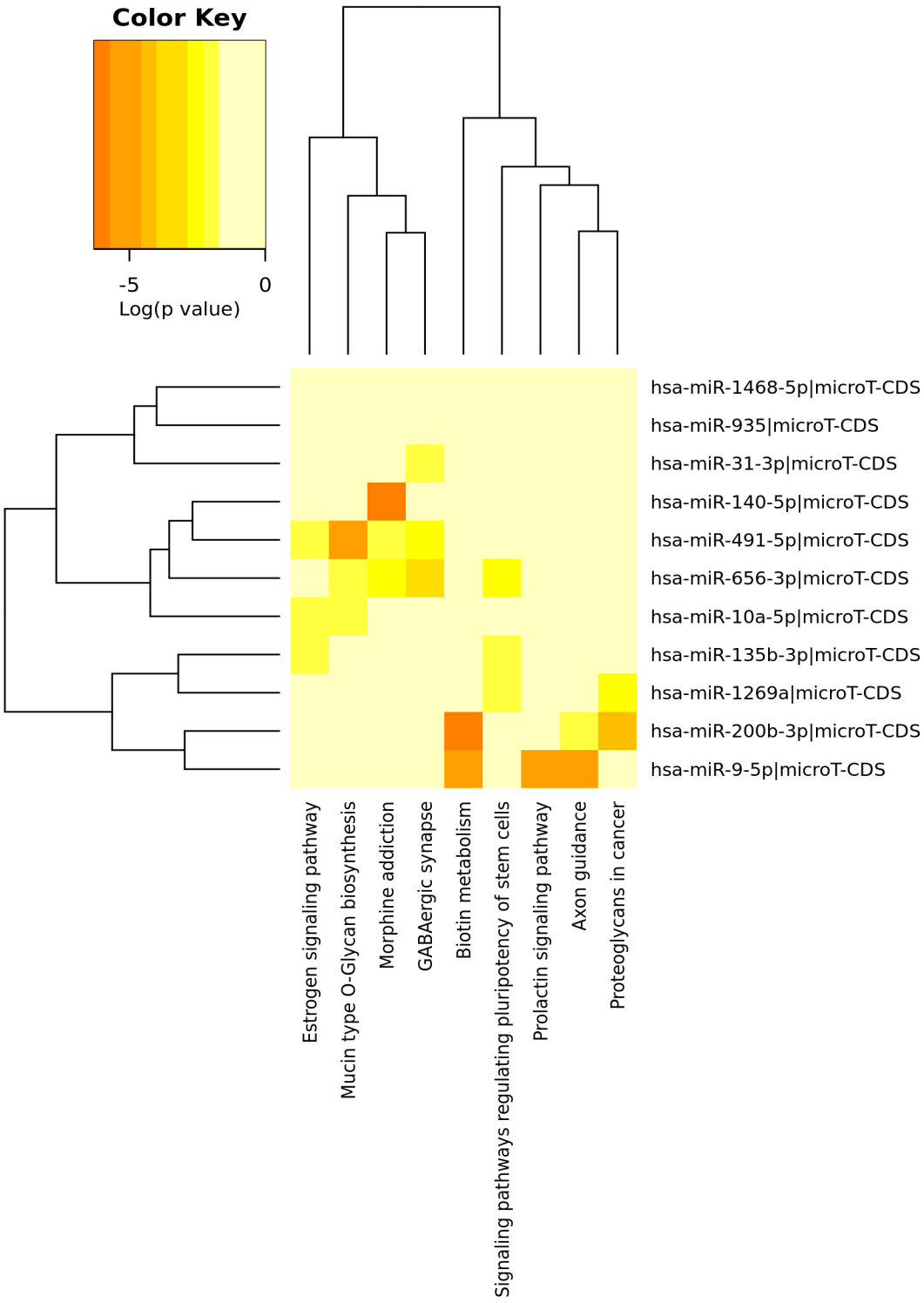
Supplementary Figure S4.8. KEGG pathway enrichment analysis of miRNA signatures in LIHCC



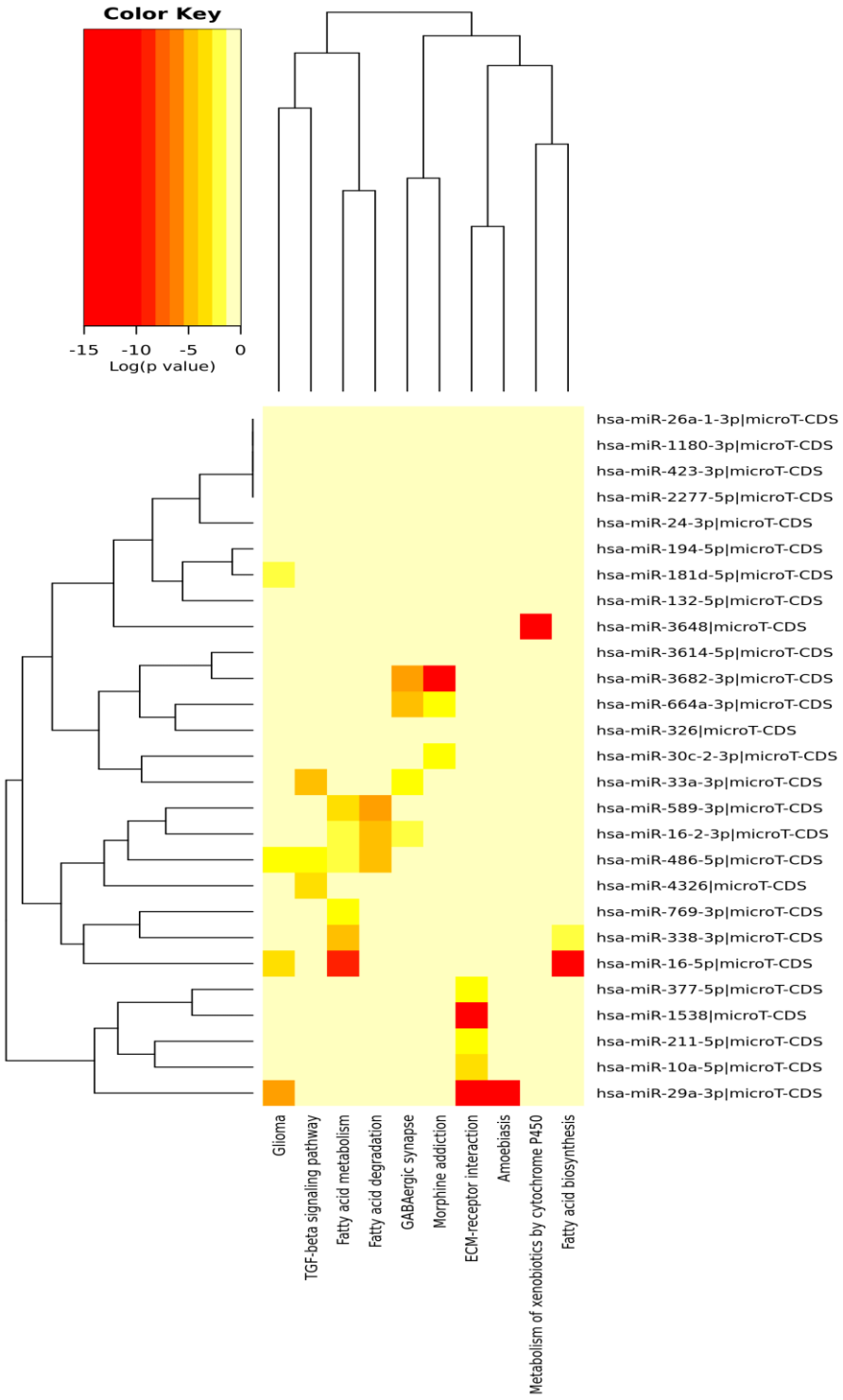
Supplementary Figure S4.9. KEGG pathway enrichment analysis of miRNA signatures in LUAD



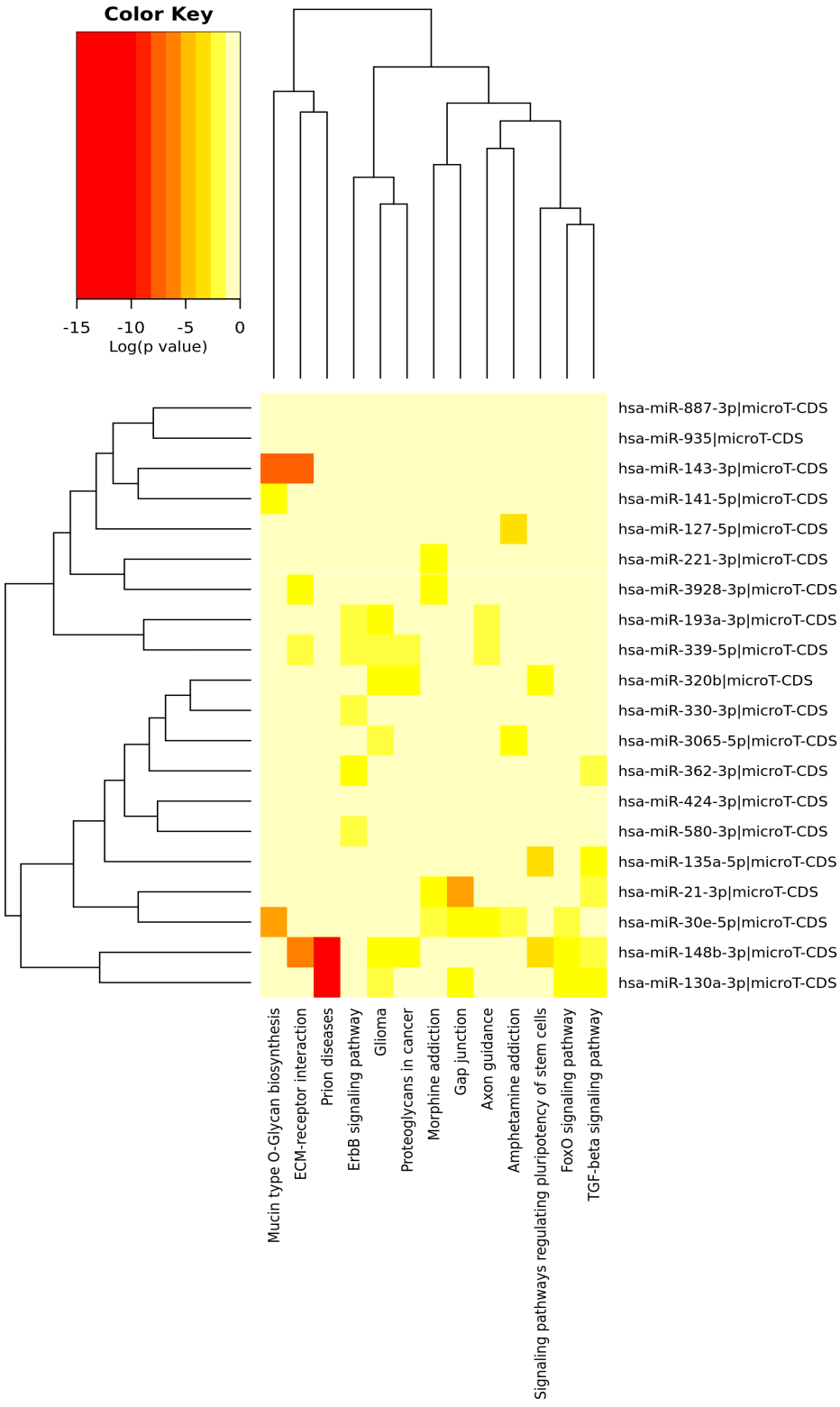
Supplementary Figure S4.10. KEGG pathway enrichment analysis of miRNA signatures in LUSC



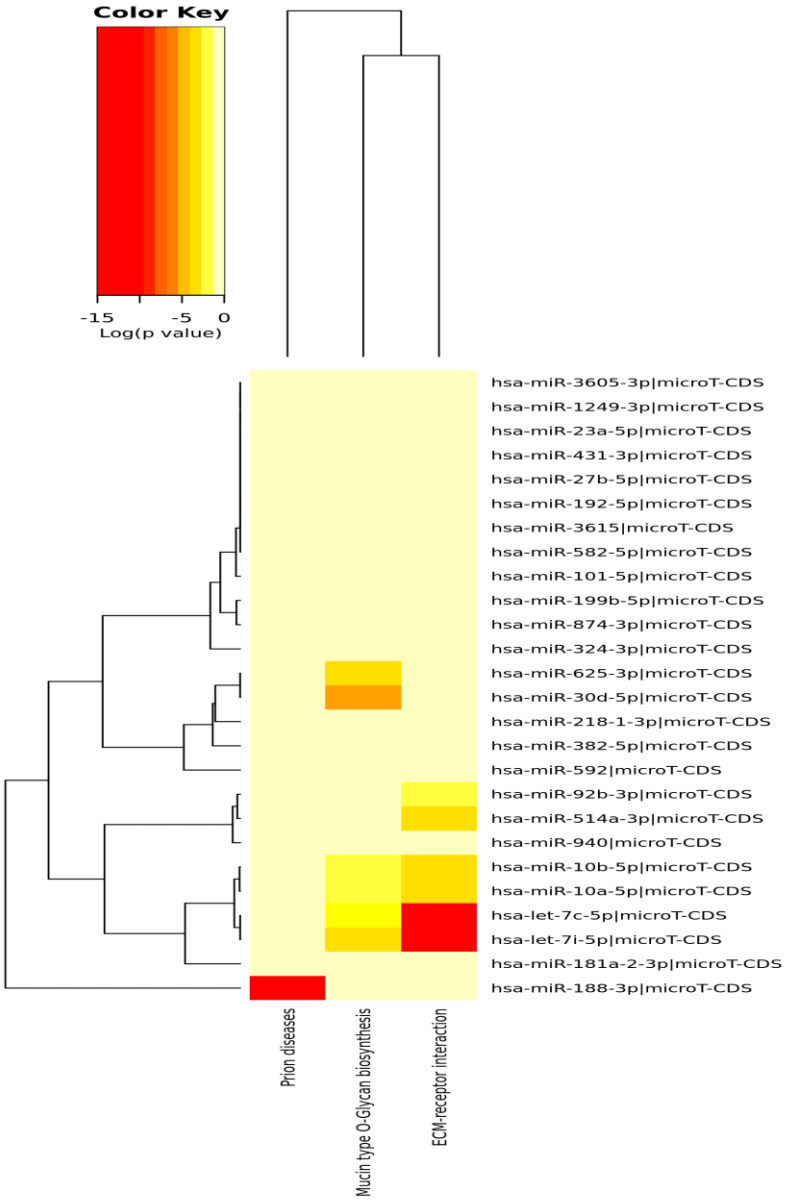
Supplementary Figure S4.11. KEGG pathway enrichment analysis of miRNA signatures in READ



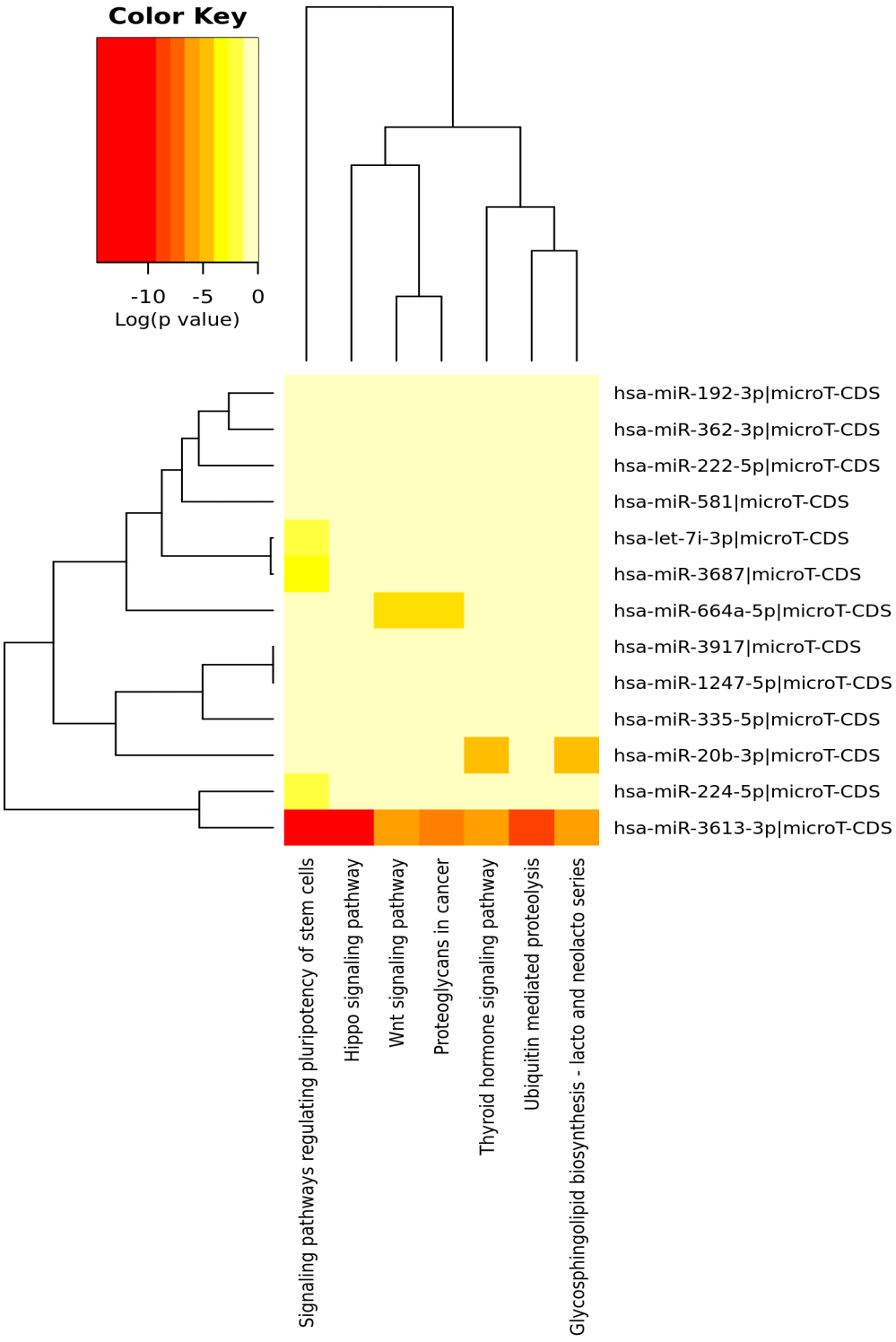
Supplementary Figure S4.12. KEGG pathway enrichment analysis of miRNA signatures in SKCM



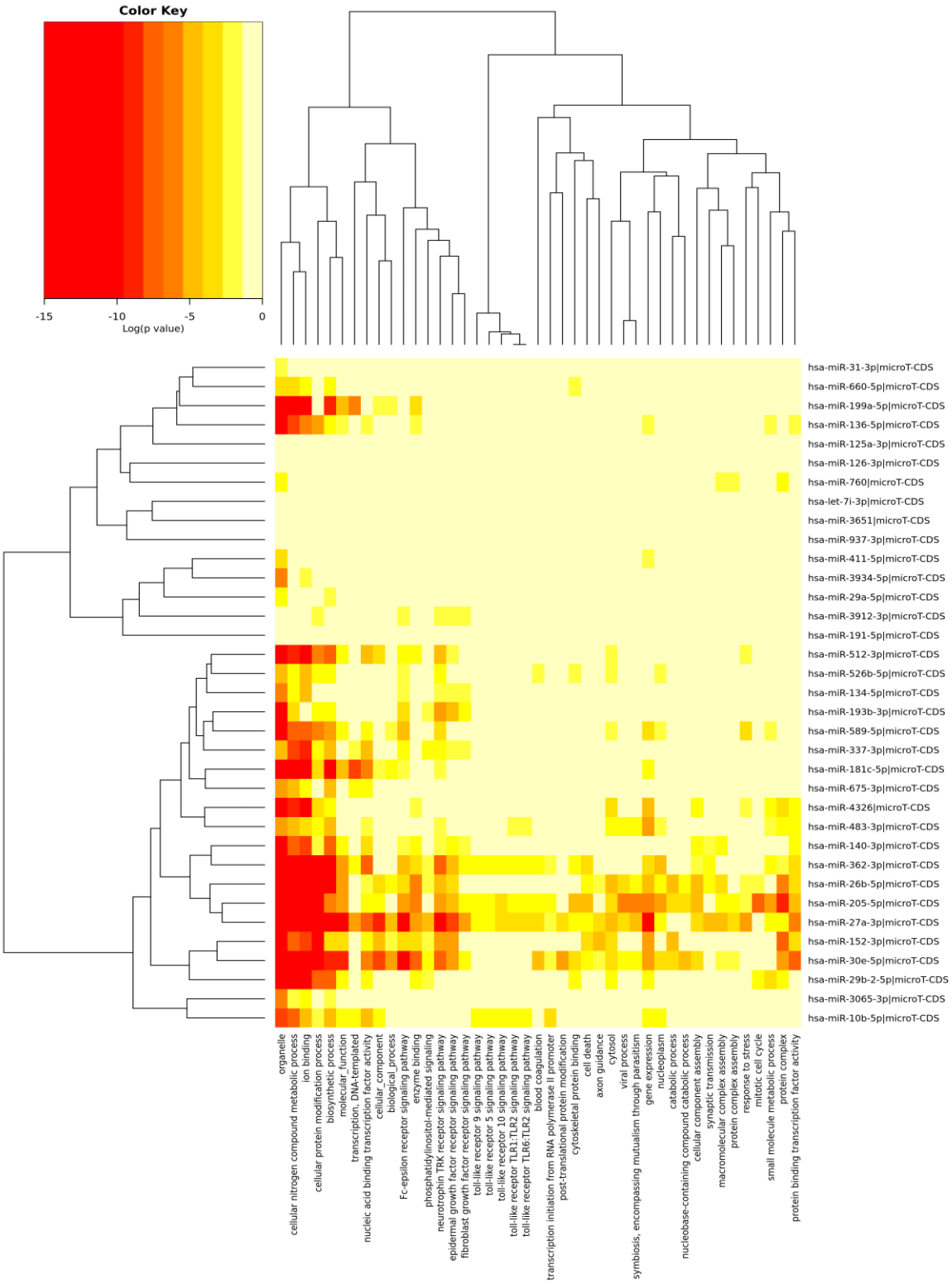
Supplementary Figure S4.13. KEGG pathway enrichment analysis of miRNA signatures in STAD



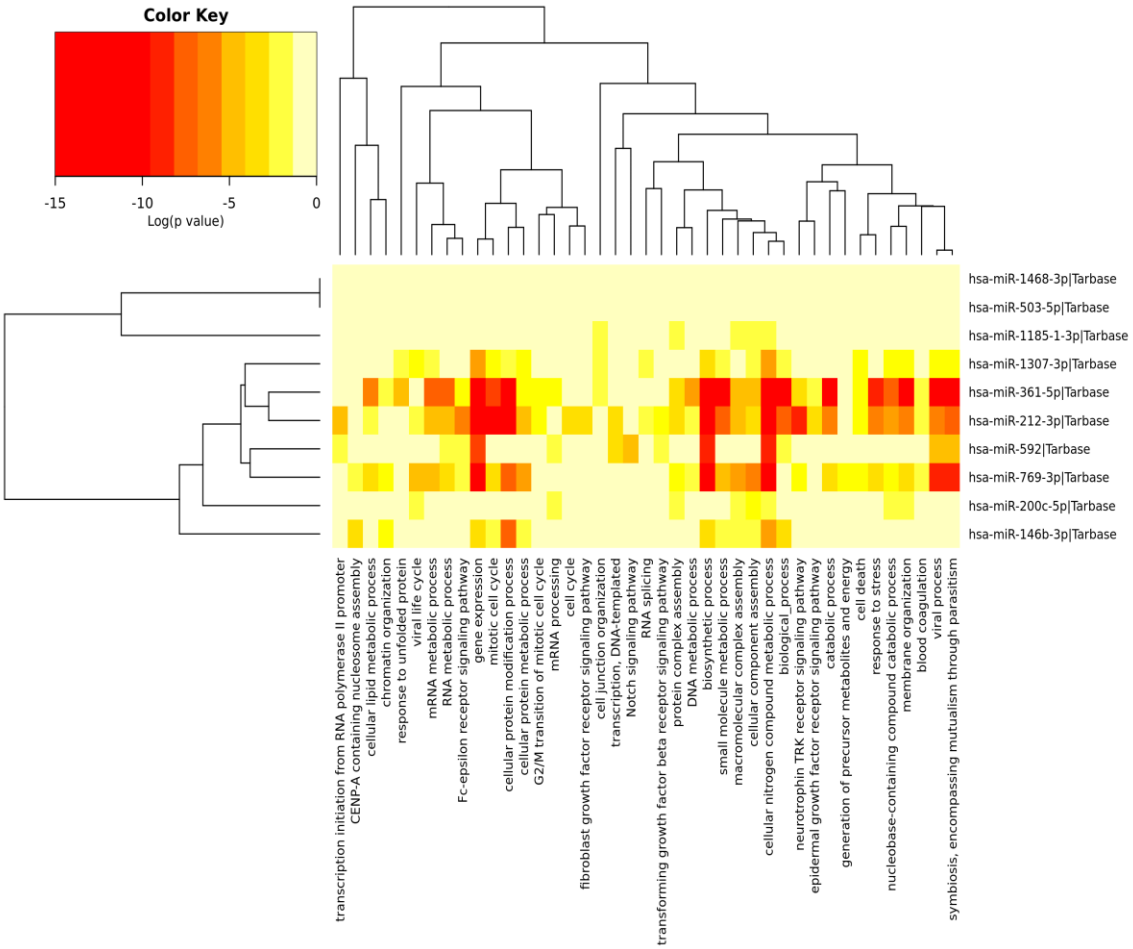
Supplementary Figure S4.14. KEGG pathway enrichment analysis of miRNA signatures in THCA



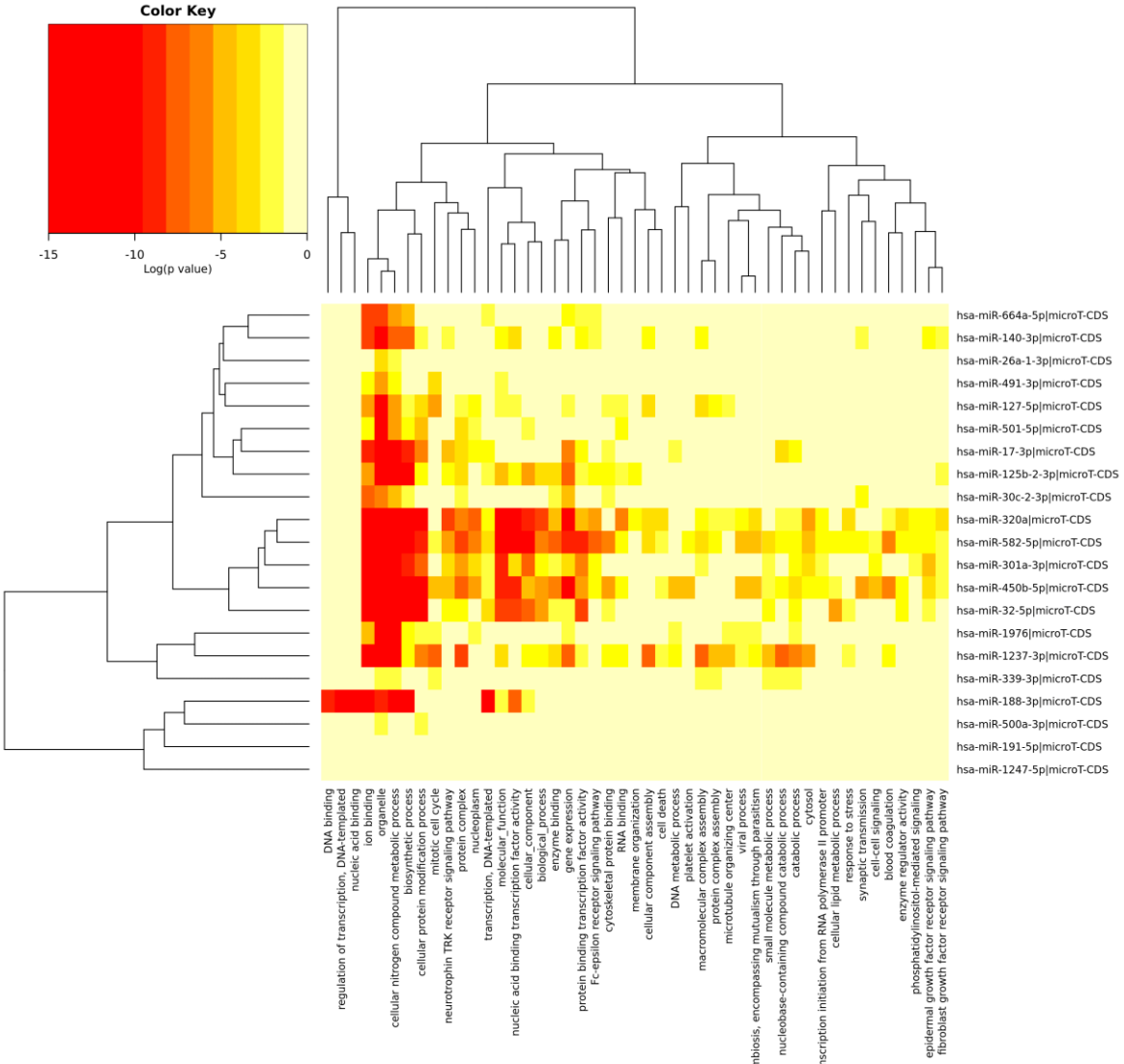
Supplementary Figure S4.15. KEGG pathway enrichment analysis of miRNA signatures in UVM



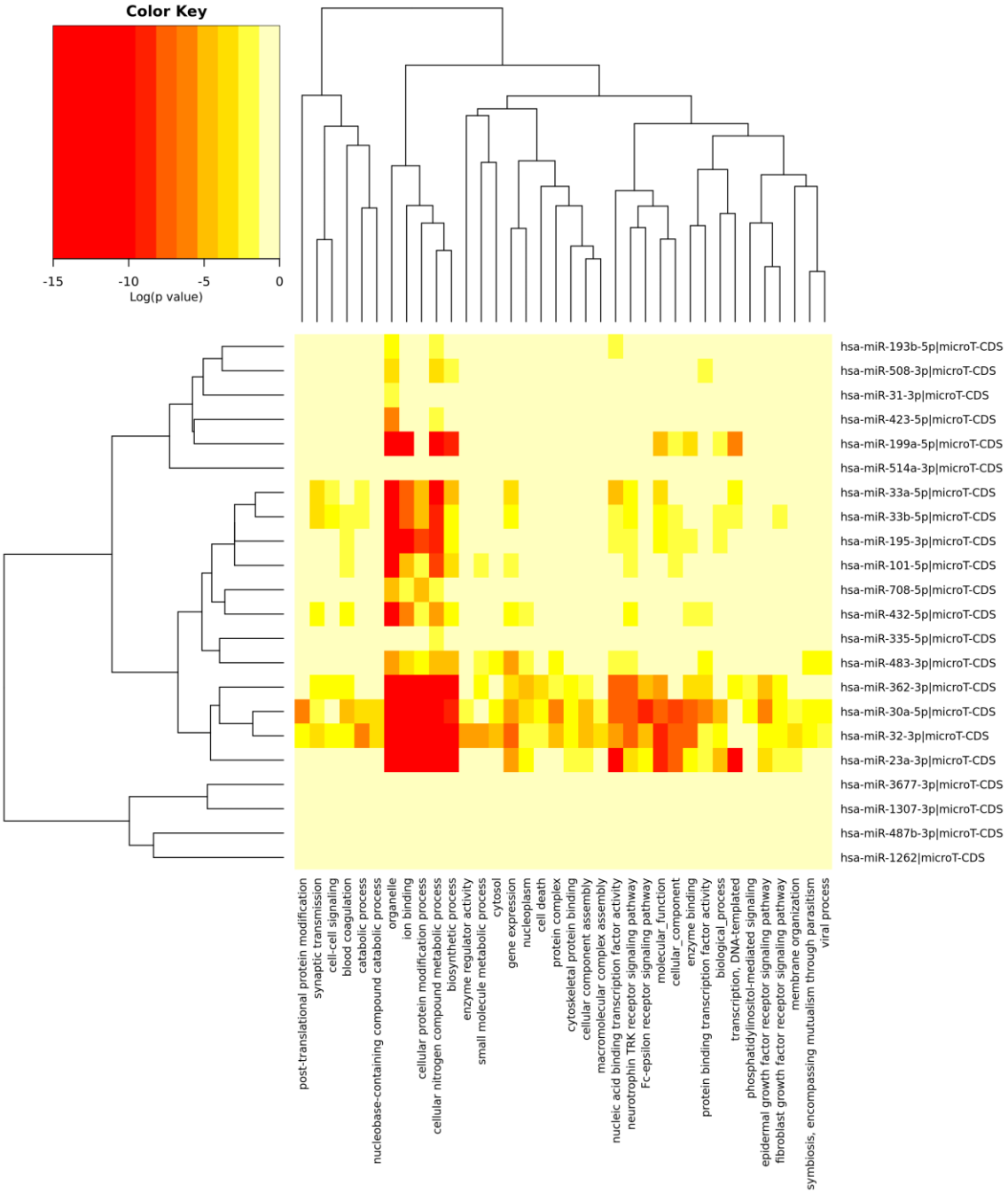
Supplementary Figure S5.1. GO category enrichment analysis of miRNA signatures in BLCA



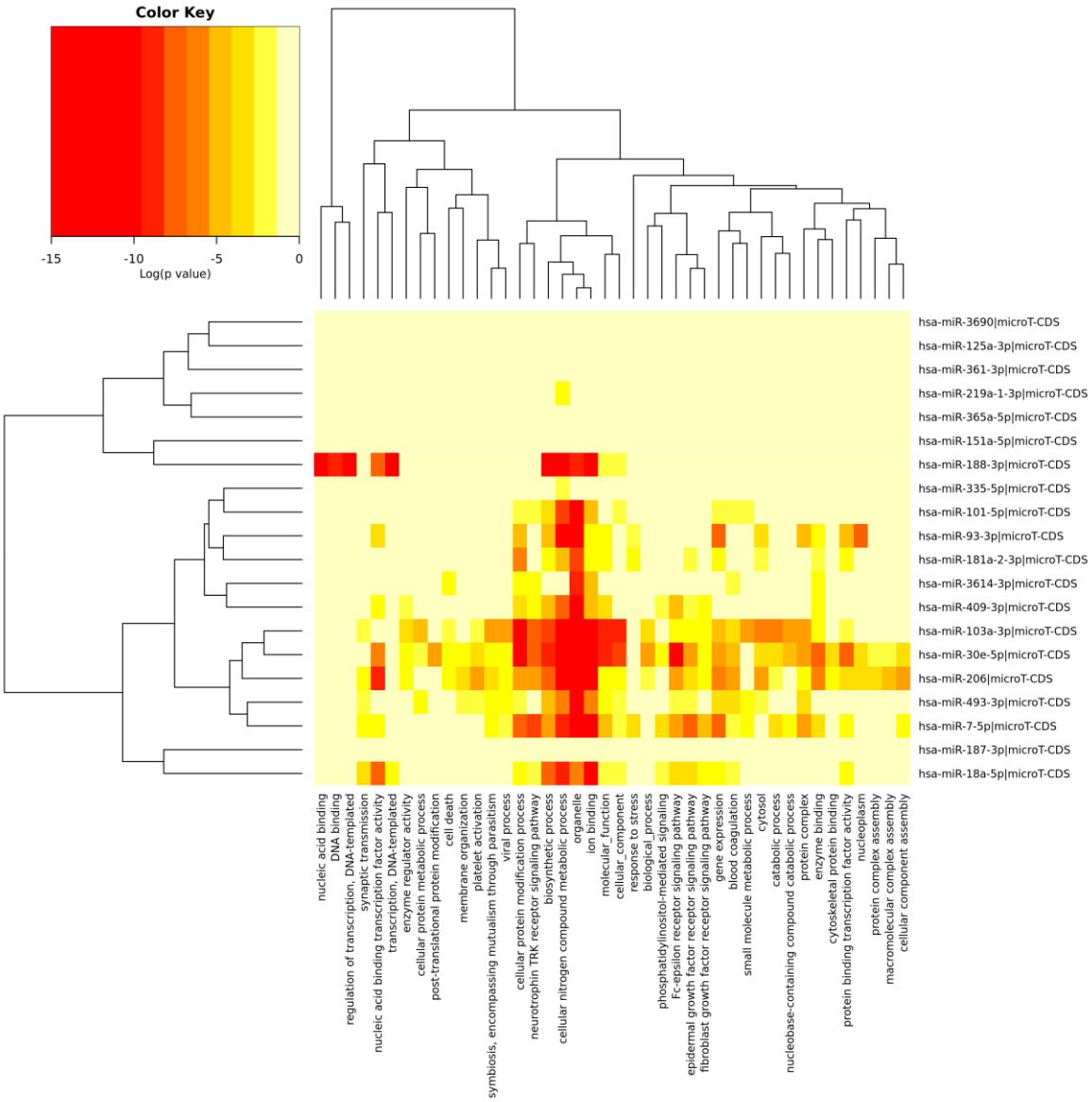
Supplementary Figure S5.2. GO category enrichment analysis of miRNA signatures in BRCA



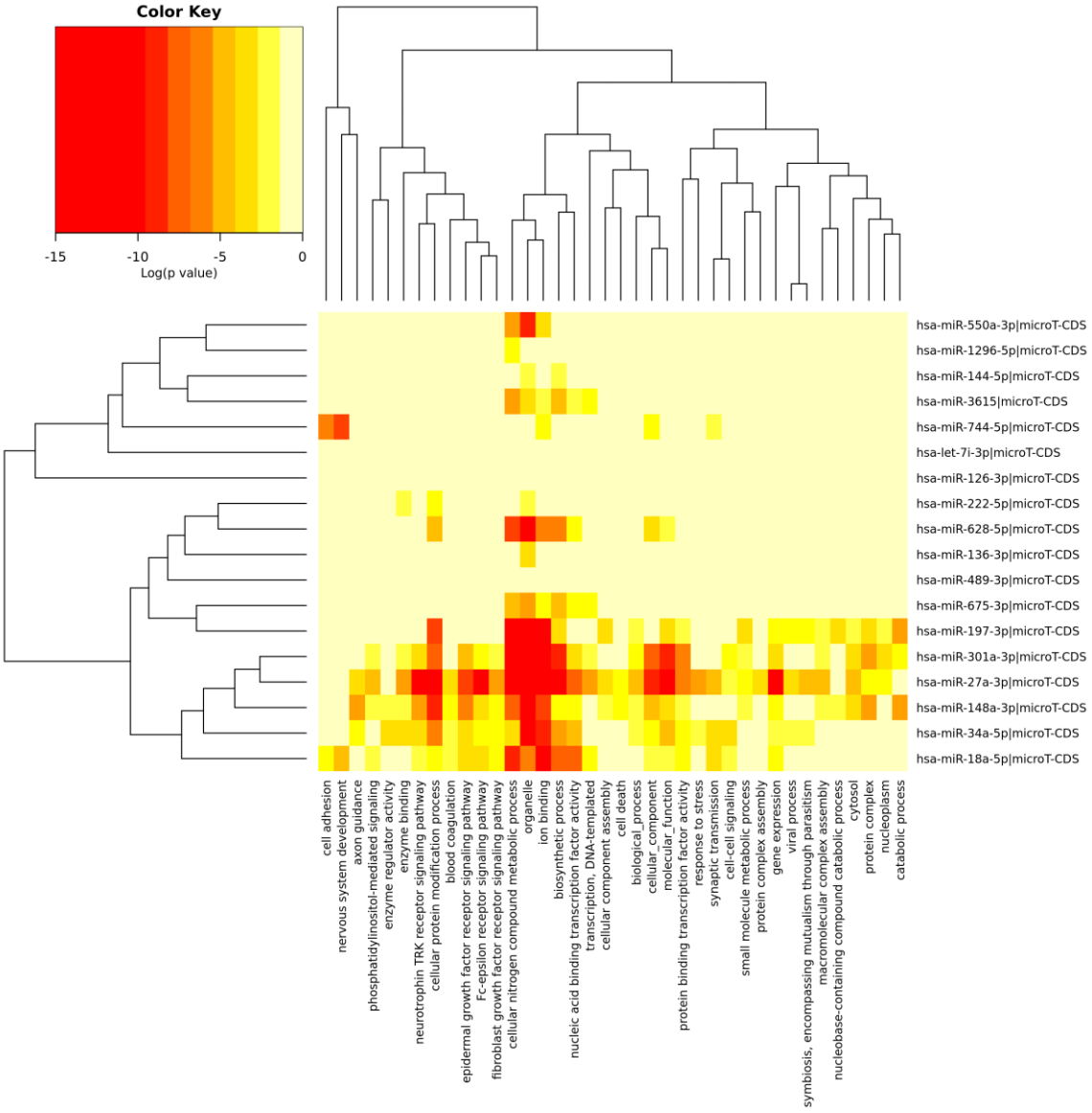
Supplementary Figure S5.3. GO category enrichment analysis of miRNA signatures in COAD



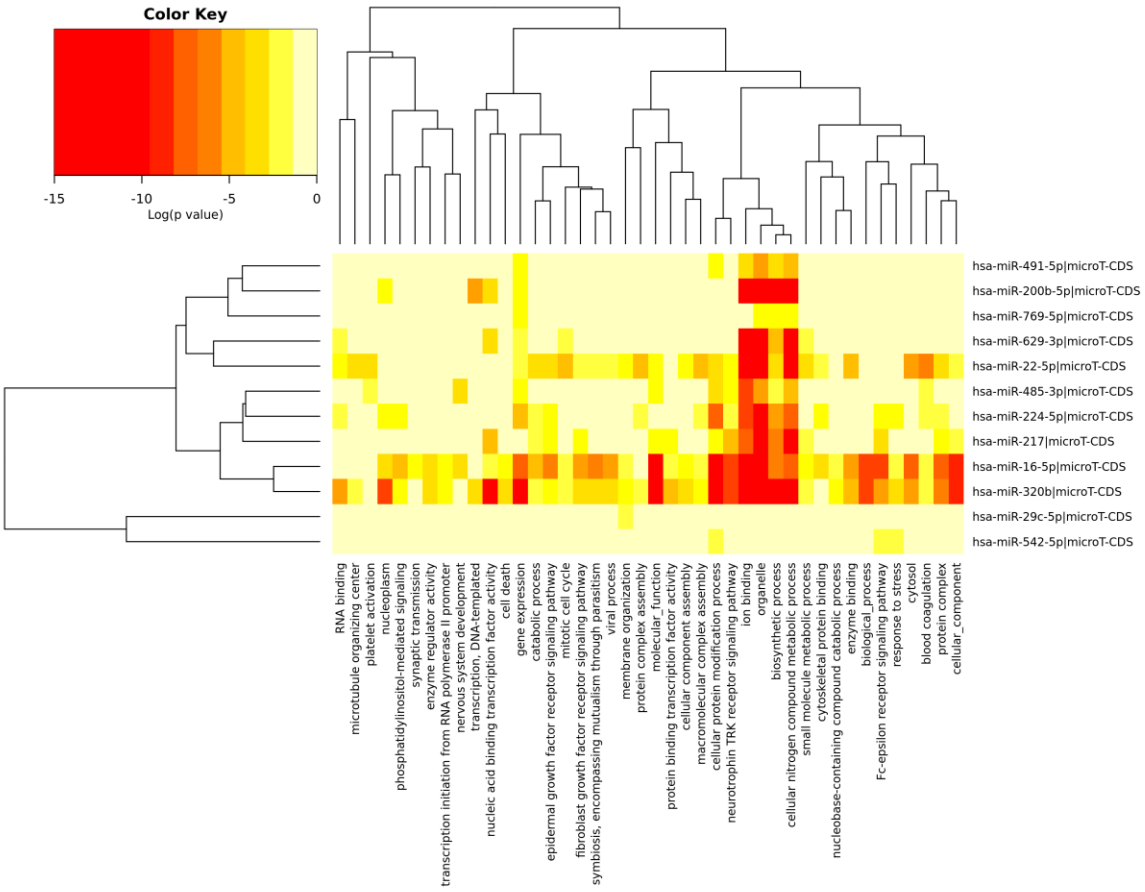
Supplementary Figure S5.4. GO category enrichment analysis of miRNA signatures in ESCA



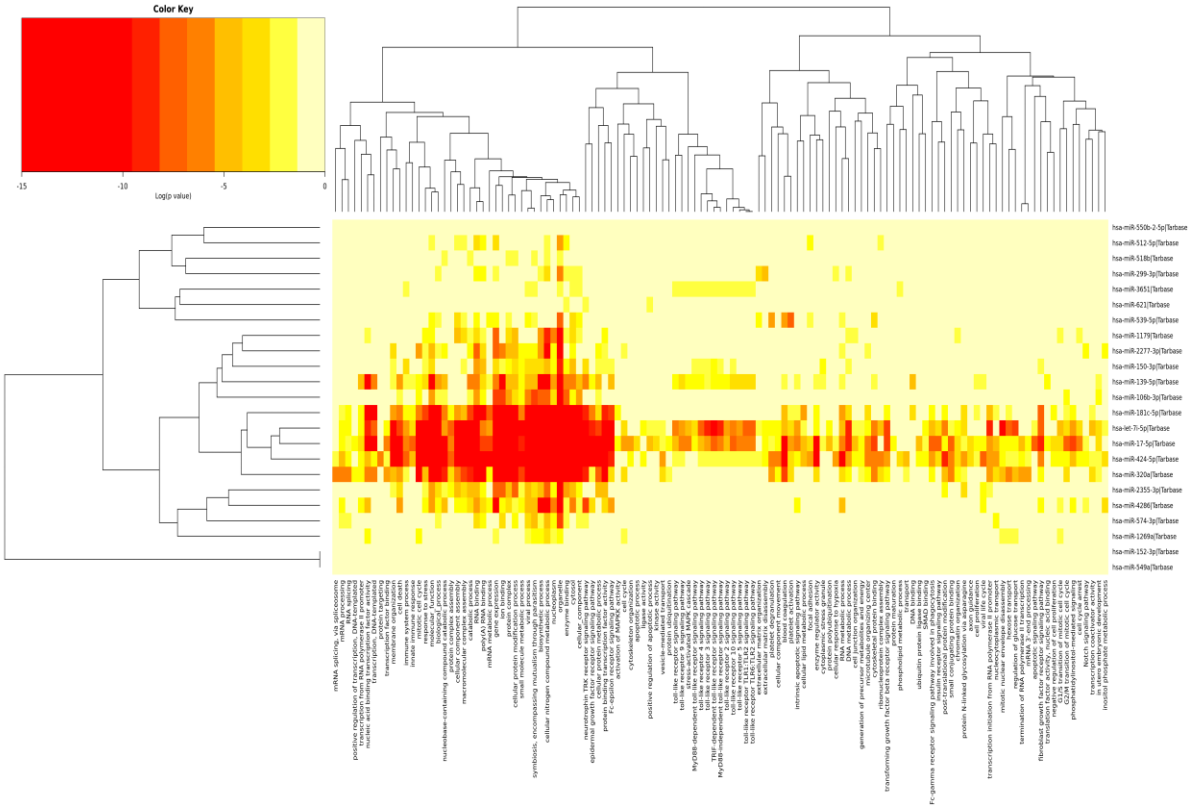
Supplementary Figure S5.5. GO category enrichment analysis of miRNA signatures in HNSC



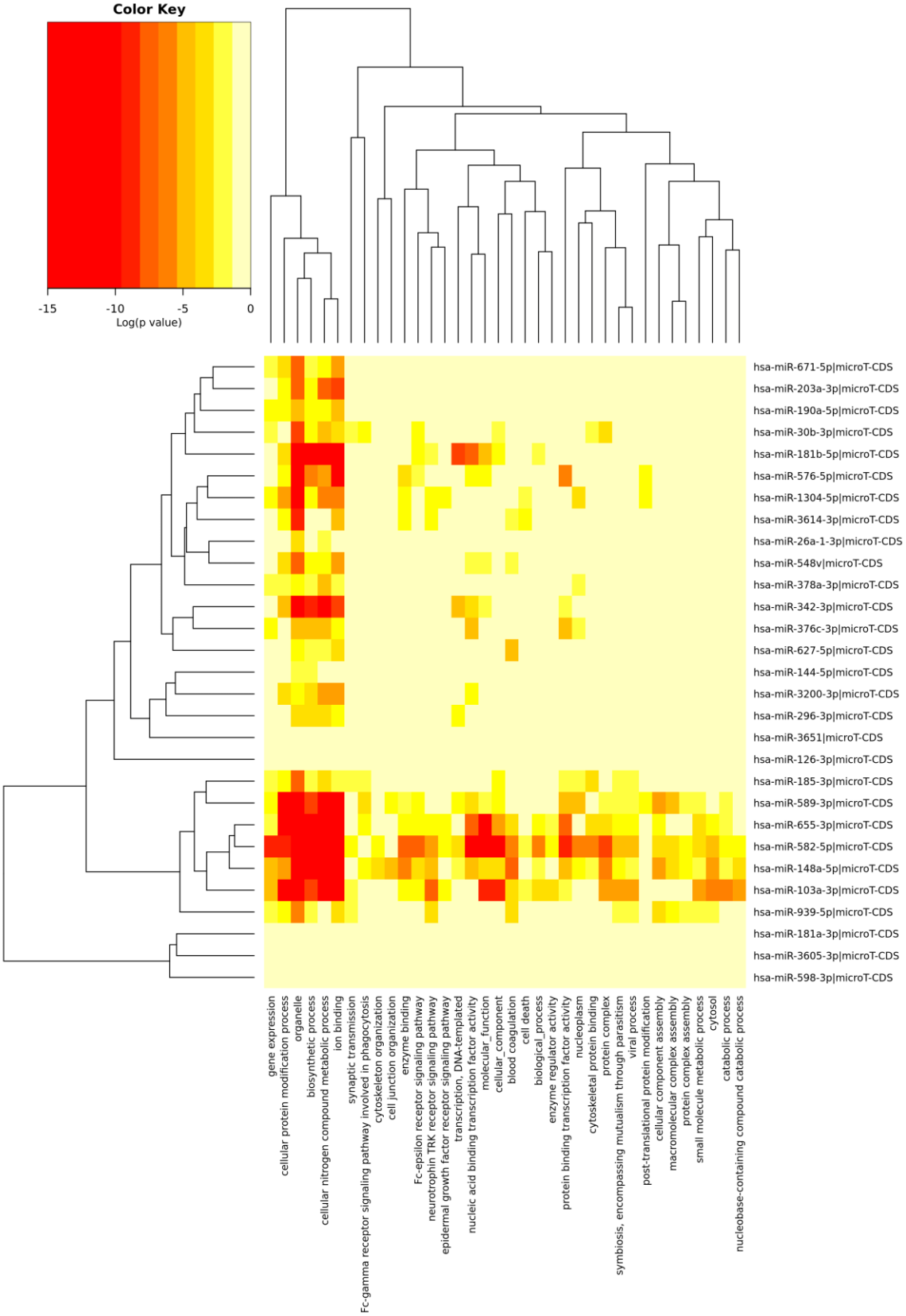
Supplementary Figure S5.6. GO category enrichment analysis of miRNA signatures in KIRC



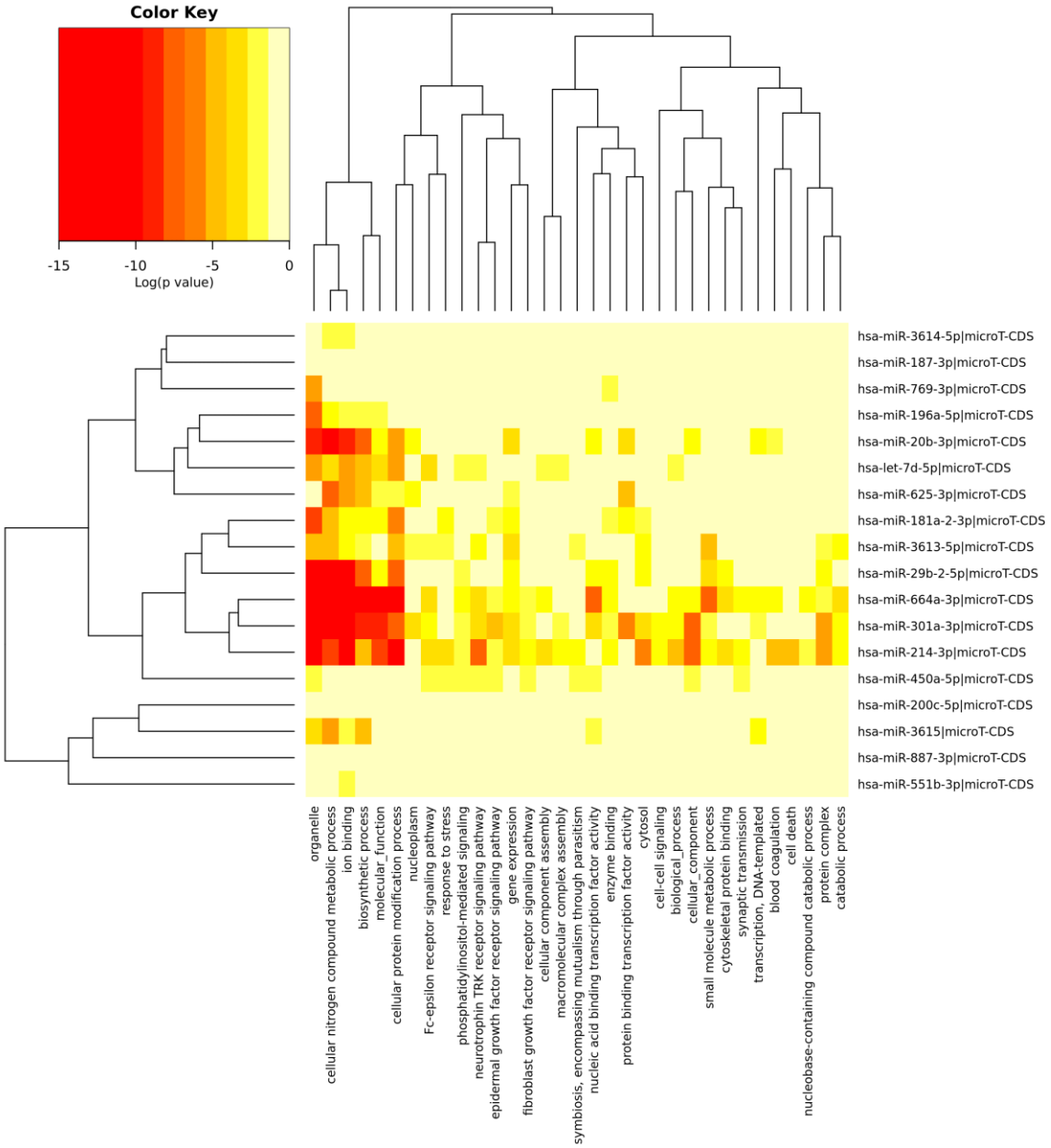
Supplementary Figure S5.7. GO category enrichment analysis of miRNA signatures in KIRP



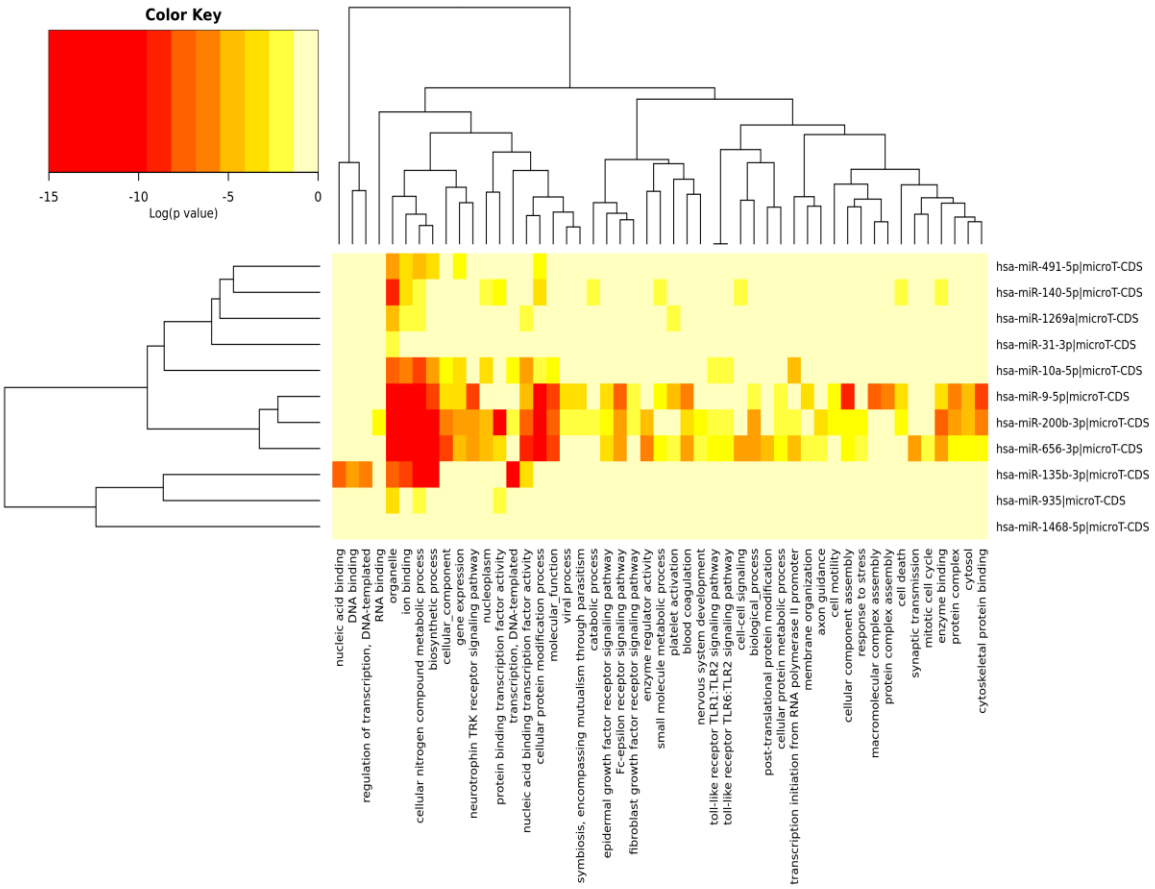
Supplementary Figure S5.8. GO category enrichment analysis of miRNA signatures in LIHCC



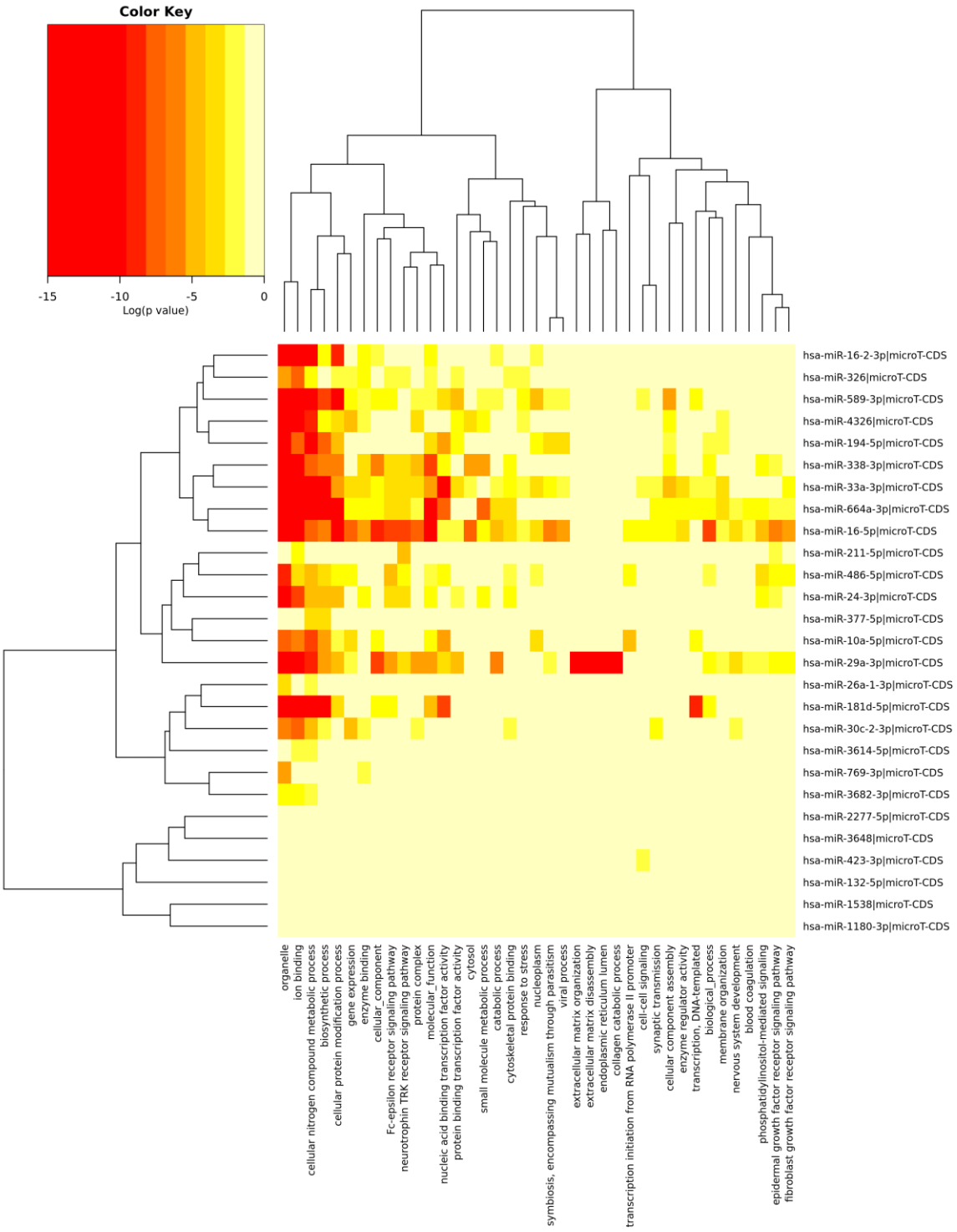
Supplementary Figure S5.9. GO category enrichment analysis of miRNA signatures in LUAD



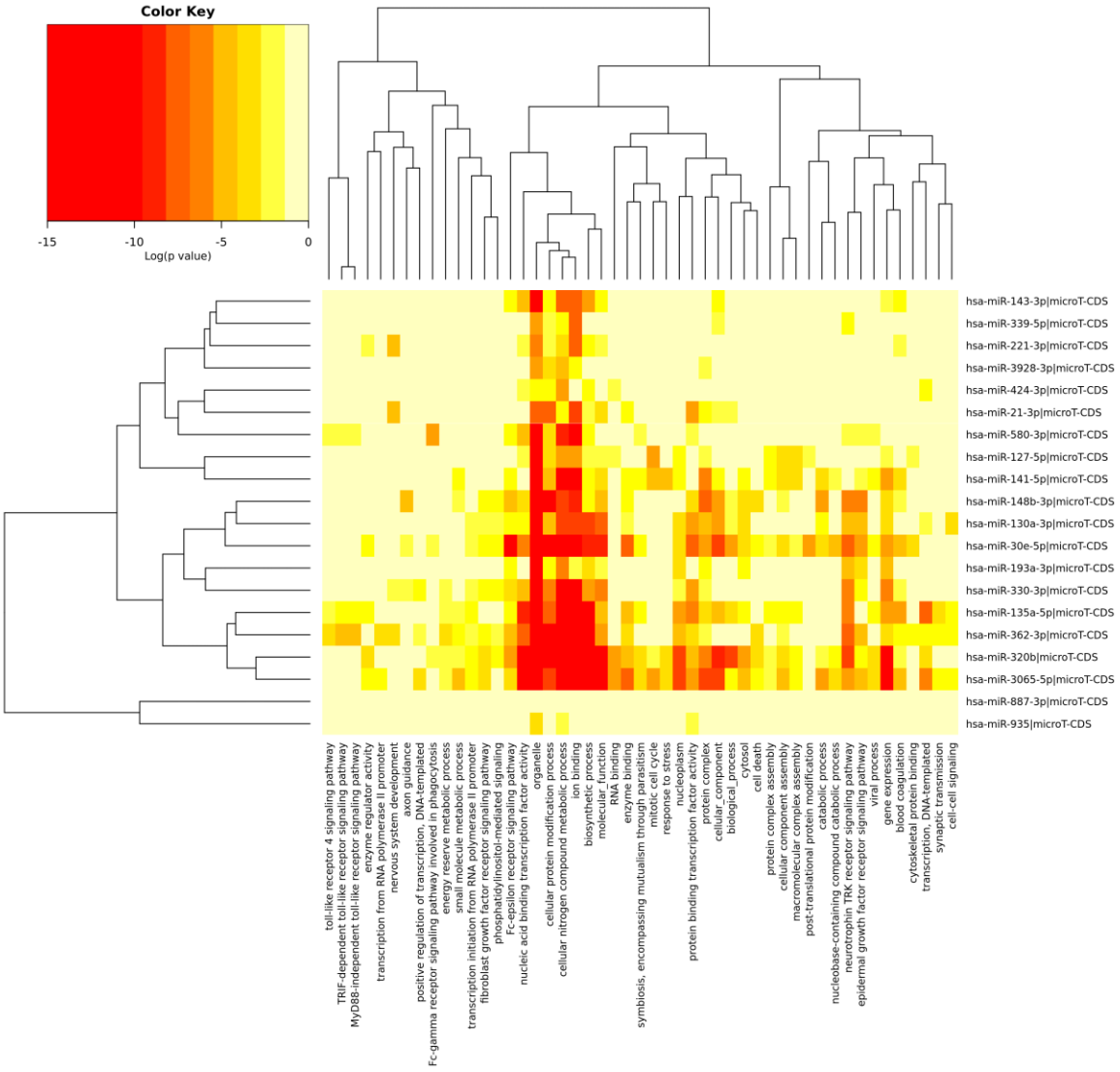
Supplementary Figure S5.10. GO category enrichment analysis of miRNA signatures in LUSC



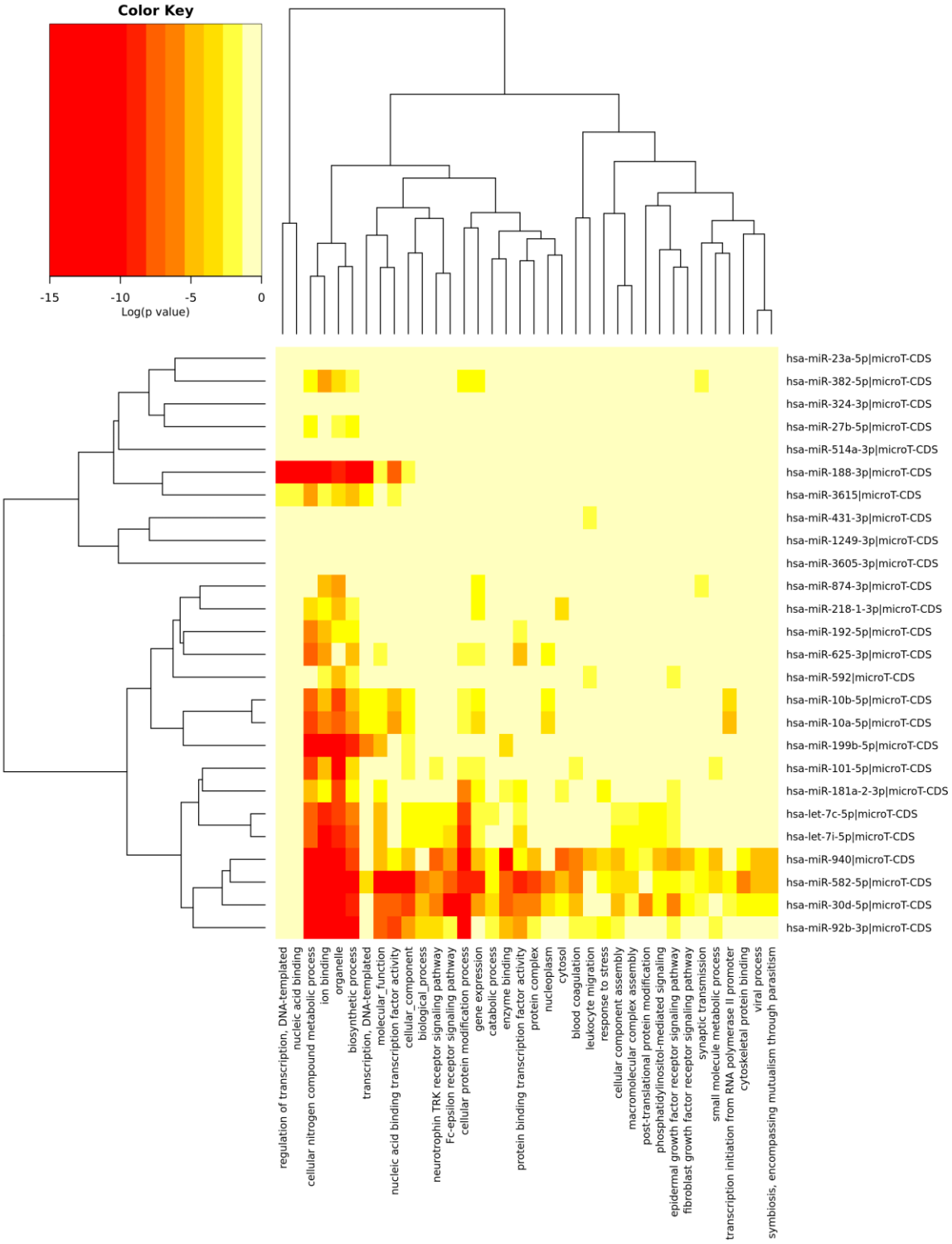
Supplementary Figure S5.11. GO category enrichment analysis of miRNA signatures in READ



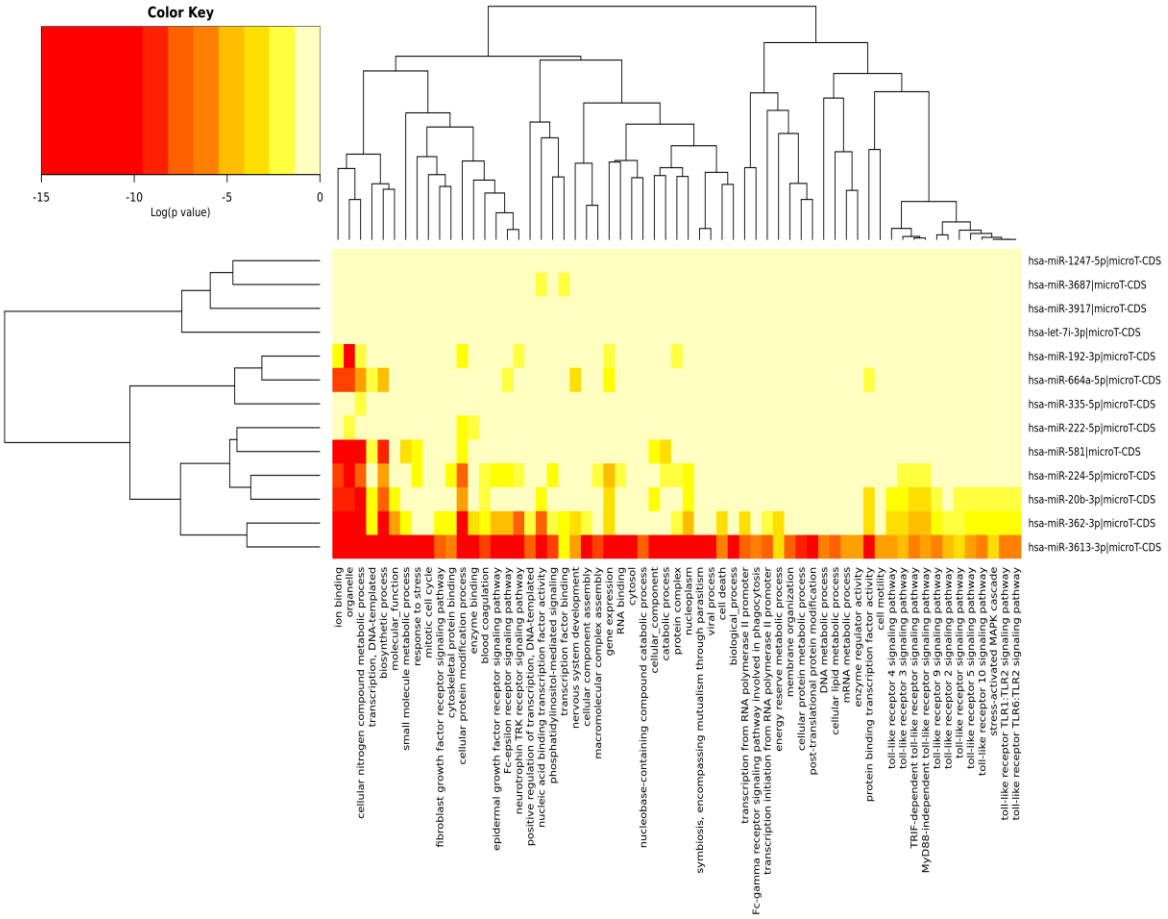
Supplementary Figure S5.12. GO category enrichment analysis of miRNA signatures in SKCM



Supplementary Figure S5.13. GO category enrichment analysis of miRNA signatures in STAD



Supplementary Figure S5.14. GO category enrichment analysis of miRNA signatures in THCA



Supplementary Figure S5.15. GO category enrichment analysis of miRNA signatures in UVM.

Supplementary Tables

Supplementary Table S1. The prediction comparison results of CancerSig with different machine learning methods.

Method	miRNA-signature	10-CV Accuracy	Sensitivity	Specificity	MCC	AUC
CancerSig-BLCA	35	84.40±1.27	0.64±0.04	0.93±0.01	0.65±0.02	0.82±0.01
LightGBM	35	72.22±0.04	0.83±0.06	0.51±0.14	0.35±0.10	0.72±0.06
XGBoost	35	72.70±0.06	0.88±0.06	0.41±0.16	0.33±0.18	0.73±0.05
Random Forest	35	70.98±0.05	0.77±0.07	0.59±0.16	0.35±0.13	0.74±0.05
CatBoost	35	73.93±0.06	0.91±0.07	0.39±0.12	0.37±0.15	0.74±0.05
Extra Trees	35	72.72±0.04	0.78±0.07	0.63±0.11	0.40±0.09	0.74±0.06

Supplementary Table S2.1. Contribution of individual miRNAs using MED analysis in BLCA

Rank	miRNA	MIMAT-ID	MED-Score
1	hsa-miR-31-3p	MIMAT0004504	45.21
2	hsa-miR-29b-2-5p	MIMAT0004515	40.29
3	hsa-miR-193b-3p	MIMAT0002819	31.45
4	hsa-miR-10b-5p	MIMAT0000254	30.47
5	hsa-miR-125a-3p	MIMAT0004602	28.01
6	hsa-miR-136-5p	MIMAT0000448	20.15
7	hsa-miR-3912-3p	MIMAT0018186	19.16
8	hsa-miR-205-5p	MIMAT0000266	17.69
9	hsa-miR-337-3p	MIMAT0000754	17.69
10	hsa-miR-29a-5p	MIMAT0004503	17.20
11	hsa-miR-512-3p	MIMAT0002823	14.74
12	hsa-miR-3934-5p	MIMAT0018349	14.25
13	hsa-miR-4326	MIMAT0016888	14.25
14	hsa-miR-126-3p	MIMAT0000445	12.29
15	hsa-miR-26b-5p	MIMAT0000083	12.29
16	hsa-miR-362-3p	MIMAT0004683	10.32
17	hsa-miR-760	MIMAT0004957	10.32
18	hsa-miR-27a-3p	MIMAT0000084	6.39
19	hsa-miR-199a-5p	MIMAT0000231	5.90
20	hsa-miR-483-3p	MIMAT0002173	4.91
21	hsa-miR-181c-5p	MIMAT0000258	3.93
22	hsa-let-7i-3p	MIMAT0004585	3.93

23	hsa-miR-526b-5p	MIMAT0002835	3.93
24	hsa-miR-660-5p	MIMAT0003338	3.93
25	hsa-miR-152-3p	MIMAT0000438	3.44
26	hsa-miR-3651	MIMAT0018071	3.44
27	hsa-miR-675-3p	MIMAT0006790	2.46
28	hsa-miR-140-3p	MIMAT0004597	1.97
29	hsa-miR-3065-3p	MIMAT0015378	1.47
30	hsa-miR-191-5p	MIMAT0000440	1.47
31	hsa-miR-134-5p	MIMAT0000447	0.49
32	hsa-miR-937-3p	MIMAT0004980	0.49
33	hsa-miR-30e-5p	MIMAT0000692	0.49
34	hsa-miR-589-5p	MIMAT0004799	0.00
35	hsa-miR-411-5p	MIMAT0003329	0.00

Supplementary Table S2.2. Contribution of individual miRNAs using MED analysis in BRCA

Rank	**miRNA**	**MIMAT-ID**	**MED-Score**
1	hsa-miR-200c-5p	MIMAT0004657	69.69
2	hsa-miR-503	MIMAT0002874	65.03
3	hsa-miR-1307-3p	MIMAT0005951	48.45
4	hsa-miR-361-3p	MIMAT0004682	47.93
5	hsa-miR-212	MIMAT0022695	46.89
6	hsa-miR-592	MIMAT0003260	46.89
7	hsa-miR-1185-1	MIMAT0022838	43.26
8	hsa-miR-146b	MIMAT0004766	43.26
9	hsa-miR-1468-5p	MIMAT0006789	34.46
10	hsa-miR-769-3p	MIMAT0003887	30.83
11	hsa-miR-3941	MIMAT0018357	30.31
12	hsa-miR-496	MIMAT0002818	25.65
13	hsa-miR-33b-5p	MIMAT0003301	23.58
14	hsa-miR-432-3p	MIMAT0002815	20.98
15	hsa-miR-153-1	MIMAT0000439	19.43
16	hsa-miR-1277	MIMAT0005933	16.32
17	hsa-miR-143-3p	MIMAT0000435	12.69
18	hsa-miR-3622a	MIMAT0018004	12.69
19	hsa-miR-137	MIMAT0000429	11.14
20	hsa-miR-3129	MIMAT0019202	11.14
21	hsa-miR-331	MIMAT0000760	8.03
22	hsa-miR-3651	MIMAT0018071	6.48
23	hsa-miR-676	MIMAT0018203	5.44
24	hsa-miR-627-5p	MIMAT0003296	4.40
25	hsa-miR-10b-5p	MIMAT0000254	3.89
26	hsa-miR-30b-3p	MIMAT0004589	2.03
27	hsa-miR-218-1-3p	MIMAT0004565	2.03
28	hsa-miR-379	MIMAT0000733	1.69
29	hsa-miR-642a	MIMAT0003312	1.36

30	hsa-miR-3922	MIMAT0019227	0.88
31	hsa-miR-574-3p	MIMAT0003239	0.34
32	hsa-miR-324-5p	MIMAT0000761	0.32
33	hsa-miR-374c	MIMAT0018443	0.30
34	hsa-miR-500a-3p	MIMAT0002871	0.29

Supplementary Table S2.3. Contribution of individual miRNAs using MED analysis in COAD

Rank	**miRNA**	**MIMAT-ID**	**MED-Score**
1	hsa-miR-188-3p	MIMAT0004613	73.46
2	hsa-miR-1976	MIMAT0009451	70.62
3	hsa-miR-320a	MIMAT0000510	63.98
4	hsa-miR-450b-5p	MIMAT0004909	51.66
5	hsa-miR-140-3p	MIMAT0004597	35.55
6	hsa-miR-17-3p	MIMAT0000071	34.60
7	hsa-miR-301a-3p	MIMAT0000688	33.65
8	hsa-miR-582-5p	MIMAT0003247	28.91
9	hsa-miR-491-3p	MIMAT0004765	27.01
10	hsa-miR-501-5p	MIMAT0002872	26.07
11	hsa-miR-500a-3p	MIMAT0002871	24.17
12	hsa-miR-339-3p	MIMAT0004702	21.33
13	hsa-miR-127-5p	MIMAT0004604	20.38
14	hsa-miR-30c-2-3p	MIMAT0004550	19.43
15	hsa-miR-125b-2-3p	MIMAT0004603	19.43
16	hsa-miR-664a-5p	MIMAT0005948	11.85
17	hsa-miR-32-5p	MIMAT0000090	10.90
18	hsa-miR-1237-3p	MIMAT0005592	10.90
19	hsa-miR-191-5p	MIMAT0000440	5.21
20	hsa-miR-26a-1-3p	MIMAT0004499	5.21
21	hsa-miR-1247-5p	MIMAT0005899	2.37

Supplementary Table S2.4. Contribution of individual miRNAs using MED analysis in ESCA

Rank	**miRNA**	**MIMAT-ID**	**MED-Score**
1	hsa-miR-708-5p	MIMAT0004926	43.83
2	hsa-miR-199a-5p	MIMAT0000231	43.83
3	hsa-miR-33b-5p	MIMAT0003301	40.12
4	hsa-miR-23a-3p	MIMAT0000078	40.12
5	hsa-miR-423-5p	MIMAT0004748	30.25
6	hsa-miR-193b-5p	MIMAT0004767	29.01
7	hsa-miR-3677-3p	MIMAT0018101	29.01
8	hsa-miR-362-3p	MIMAT0004683	21.60

9	hsa-miR-487b-3p	MIMAT0003180	17.90
10	hsa-miR-508-3p	MIMAT0002880	16.67
11	hsa-miR-31-3p	MIMAT0004504	15.43
12	hsa-miR-33a-5p	MIMAT0000091	8.02
13	hsa-miR-30a-5p	MIMAT0000087	6.79
14	hsa-miR-335-5p	MIMAT0000765	6.79
15	hsa-miR-514a-3p	MIMAT0002883	6.79
16	hsa-miR-432-5p	MIMAT0002814	5.56
17	hsa-miR-1307-3p	MIMAT0005951	5.56
18	hsa-miR-1262	MIMAT0005914	4.32
19	hsa-miR-101-5p	MIMAT0004513	3.09
20	hsa-miR-32-3p	MIMAT0004505	3.09
21	hsa-miR-195-3p	MIMAT0004615	0.62
22	hsa-miR-483-3p	MIMAT0002173	0.62

Supplementary Table S2.5. Contribution of individual miRNAs using MED analysis in HNSC

Rank	miRNA	MIMAT-ID	MED-Score
1	hsa-miR-93-3p	MIMAT0004509	27.14
2	hsa-miR-335-5p	MIMAT0000765	18.57
3	hsa-miR-219a-1-3p	MIMAT0004567	18.10
4	hsa-miR-361-3p	MIMAT0004682	16.19
5	hsa-miR-493-3p	MIMAT0003161	15.71
6	hsa-miR-188-3p	MIMAT0004613	14.76
7	hsa-miR-3690	MIMAT0018119	12.38
8	hsa-miR-103a-3p	MIMAT0000101	11.43
9	hsa-miR-101-5p	MIMAT0004513	10.00
10	hsa-miR-206	MIMAT0000462	9.52
11	hsa-miR-151a-5p	MIMAT0004697	9.52
12	hsa-miR-187-3p	MIMAT0000262	5.24
13	hsa-miR-7-5p	MIMAT0000252	4.29
14	hsa-miR-18a-5p	MIMAT0000072	3.81
15	hsa-miR-181a-2-3p	MIMAT0004558	3.81
16	hsa-miR-365a-5p	MIMAT0009199	3.81
17	hsa-miR-125a-3p	MIMAT0004602	3.33
18	hsa-miR-30e-5p	MIMAT0000692	1.43
19	hsa-miR-3614-3p	MIMAT0017993	1.43
20	hsa-miR-409-3p	MIMAT0001639	0.48

Supplementary Table S2.6. Contribution of individual miRNAs using MED analysis in KIRC

Rank	miRNA	MIMAT-ID	MED-Score
1	hsa-miR-144-5p	MIMAT0004600	89.06
2	hsa-miR-744-5p	MIMAT0004945	40.63
3	hsa-miR-550a-3p	MIMAT0003257	38.28

4	hsa-miR-1296-5p	MIMAT0005794	35.16
5	hsa-let-7i-3p	MIMAT0004585	28.91
6	hsa-miR-18a-5p	MIMAT0000072	26.56
7	hsa-miR-628-5p	MIMAT0004809	19.53
8	hsa-miR-197-3p	MIMAT0000227	17.97
9	hsa-miR-222-5p	MIMAT0004569	17.19
10	hsa-miR-126-3p	MIMAT0000445	14.06
11	hsa-miR-489-3p	MIMAT0002805	14.06
12	hsa-miR-27a-3p	MIMAT0000084	12.50
13	hsa-miR-3615	MIMAT0017994	11.72
14	hsa-miR-301a-3p	MIMAT0000688	5.47
15	hsa-miR-148a-3p	MIMAT0000243	4.69
16	hsa-miR-136-3p	MIMAT0004606	4.69
17	hsa-miR-675-3p	MIMAT0006790	1.56
18	hsa-miR-34a-5p	MIMAT0000255	0.78

Supplementary Table S2.7. Contribution of individual miRNAs using MED analysis in KIRP

Rank	miRNA	MIMAT-ID	MED-Score
1	hsa-miR-491-5p	MIMAT0002807	18.39
2	hsa-miR-769-5p	MIMAT0003886	16.09
3	hsa-miR-29c-5p	MIMAT0004673	11.49
4	hsa-miR-16-5p	MIMAT0000069	9.20
5	hsa-miR-200b-5p	MIMAT0004571	7.66
6	hsa-miR-485-3p	MIMAT0002176	7.66
7	hsa-miR-22-5p	MIMAT0004495	6.90
8	hsa-miR-629-3p	MIMAT0003298	5.36
9	hsa-miR-320b	MIMAT0005792	5.36
10	hsa-miR-217	MIMAT0000274	2.30
11	hsa-miR-224-5p	MIMAT0000281	1.53
12	hsa-miR-542-5p	MIMAT0003340	1.53

Supplementary Table S2.8. Contribution of individual miRNAs using MED analysis in LIHCC

Rank	miRNA	MIMAT-ID	MED-Score
1	hsa-miR-550a-2	MIMAT0004800	60.91269
2	hsa-miR-549	MIMAT0003333	54.72223
3	hsa-miR-518b	MIMAT0002844	51.15079
4	hsa-miR-512-2	MIMAT0002822	50.67461
5	hsa-miR-1179	MIMAT0005824	27.73809
6	hsa-miR-574-3p	MIMAT0003239	27.02382
7	hsa-miR-424-3p	MIMAT0004749	26.62697
8	hsa-miR-4286	MIMAT0016916	24.7222
9	hsa-let-7i-3p	MIMAT0004585	24.16667
10	hsa-miR-320a	MIMAT0037311	22.97617
11	hsa-miR-17-3p	MIMAT0000071	22.81745

12	hsa-miR-299	MIMAT0000687	22.02382
13	hsa-miR-3651	MIMAT0018071	17.02382
14	hsa-miR-2277-5p	MIMAT0017352	13.76985
15	hsa-miR-621	MIMAT0003290	13.61111
16	hsa-miR-181c-5p	MIMAT0000258	13.05555
17	hsa-miR-539	MIMAT0003163	12.9762
18	hsa-miR-106b	MIMAT0000680	10.83334
19	hsa-miR-1269	MIMAT0005923	8.531742
20	hsa-miR-139	MIMAT0000250	6.706364
21	hsa-miR-152-3p	MIMAT0000438	6.626987
22	hsa-miR-2355	MIMAT0016895	3.76984
23	hsa-miR-150	MIMAT0000451	2.103168

Supplementary Table S2.9. Contribution of individual miRNAs using MED analysis in LUAD

Rank	**miRNA**	**MIMAT-ID**	**MED-Score**
1	hsa-miR-671-5p	MIMAT0003880	29.65
2	hsa-miR-3651	MIMAT0018071	27.88
3	hsa-miR-1304-5p	MIMAT0005892	24.78
4	hsa-miR-342-3p	MIMAT0000753	24.34
5	hsa-miR-548v	MIMAT0015020	22.12
6	hsa-miR-296-3p	MIMAT0004679	22.12
7	hsa-miR-598-3p	MIMAT0003266	21.68
8	hsa-miR-190a-5p	MIMAT0000458	21.24
9	hsa-miR-144-5p	MIMAT0004600	16.37
10	hsa-miR-185-3p	MIMAT0004611	15.93
11	hsa-miR-181b-5p	MIMAT0000257	15.49
12	hsa-miR-3614-3p	MIMAT0017993	15.04
13	hsa-miR-126-3p	MIMAT0000445	14.16
14	hsa-miR-589-3p	MIMAT0003256	14.16
15	hsa-miR-26a-1-3p	MIMAT0004499	13.72
16	hsa-miR-148a-5p	MIMAT0004549	13.27
17	hsa-miR-3605-3p	MIMAT0017982	12.83
18	hsa-miR-627-5p	MIMAT0003296	12.83
19	hsa-miR-376c-3p	MIMAT0000720	12.39
20	hsa-miR-30b-3p	MIMAT0004589	11.50
21	hsa-miR-3200-3p	MIMAT0015085	10.18
22	hsa-miR-378a-3p	MIMAT0000732	9.29
23	hsa-miR-103a-3p	MIMAT0000101	7.96
24	hsa-miR-203a-3p	MIMAT0000264	7.96
25	hsa-miR-576-5p	MIMAT0003241	7.08
26	hsa-miR-939-5p	MIMAT0004982	2.21
27	hsa-miR-655-3p	MIMAT0003331	2.21
28	hsa-miR-582-5p	MIMAT0003247	1.77
29	hsa-miR-181a-3p	MIMAT0000270	0.44

Supplementary Table S2.10. Contribution of individual miRNAs using MED analysis in LUSC

Rank	miRNA	MIMAT-ID	MED-Score
1	hsa-miR-181a-2-3p	MIMAT0004558	28.02
2	hsa-miR-664a-3p	MIMAT0005949	20.35
3	hsa-miR-769-3p	MIMAT0003887	19.17
4	hsa-miR-29b-2-5p	MIMAT0004515	17.40
5	hsa-miR-3614-5p	MIMAT0017992	16.22
6	hsa-miR-214-3p	MIMAT0000271	13.86
7	hsa-miR-200c-5p	MIMAT0004657	12.68
8	hsa-miR-3613-5p	MIMAT0017990	12.09
9	hsa-miR-196a-5p	MIMAT0000226	10.32
10	hsa-miR-551b-3p	MIMAT0003233	9.73
11	hsa-miR-301a-3p	MIMAT0000688	9.14
12	hsa-miR-450a-5p	MIMAT0001545	9.14
13	hsa-let-7d-5p	MIMAT0000065	7.96
14	hsa-miR-187-3p	MIMAT0000262	7.96
15	hsa-miR-20b-3p	MIMAT0004752	7.96
16	hsa-miR-887-3p	MIMAT0004951	6.19
17	hsa-miR-625-3p	MIMAT0004808	0.88
18	hsa-miR-3615	MIMAT0017994	0.29

Supplementary Table S2.11. Contribution of individual miRNAs using MED analysis in READ

Rank	miRNA	MIMAT-ID	MED-Score
1	hsa-miR-10a-5p	MIMAT0000253	30.30
2	hsa-miR-9-5p	MIMAT0000441	30.30
3	hsa-miR-135b-3p	MIMAT0004698	27.27
4	hsa-miR-491-5p	MIMAT0002807	24.24
5	hsa-miR-31-3p	MIMAT0004504	18.18
6	hsa-miR-656-3p	MIMAT0003332	18.18
7	hsa-miR-140-5p	MIMAT0000431	15.15
8	hsa-miR-1269a	MIMAT0005923	15.15
9	hsa-miR-1468-5p	MIMAT0006789	9.09
10	hsa-miR-935	MIMAT0004978	9.09
11	hsa-miR-200b-3p	MIMAT0000318	3.03

Supplementary Table S2.12. Contribution of individual miRNAs using MED analysis in SKCM

Rank	miRNA	MIMAT-ID	MED-Score
1	hsa-miR-211-5p	MIMAT0000268	39.07
2	hsa-miR-194-5p	MIMAT0000460	31.36

3	hsa-miR-3614-5p	MIMAT0017992	30.33
4	hsa-miR-326	MIMAT0000756	29.31
5	hsa-miR-4326	MIMAT0016888	28.79
6	hsa-miR-1180-3p	MIMAT0005825	28.79
7	hsa-miR-664a-3p	MIMAT0005949	27.25
8	hsa-miR-26a-1-3p	MIMAT0004499	21.59
9	hsa-miR-132-5p	MIMAT0004594	19.02
10	hsa-miR-1538	MIMAT0007400	16.97
11	hsa-miR-10a-5p	MIMAT0000253	15.42
12	hsa-miR-423-3p	MIMAT0001340	13.37
13	hsa-miR-338-3p	MIMAT0000763	11.83
14	hsa-miR-30c-2-3p	MIMAT0004550	11.31
15	hsa-miR-769-3p	MIMAT0003887	11.31
16	hsa-miR-2277-5p	MIMAT0017352	9.25
17	hsa-miR-16-5p	MIMAT0000069	5.66
18	hsa-miR-181d-5p	MIMAT0002821	5.14
19	hsa-miR-3648	MIMAT0018068	4.63
20	hsa-miR-589-3p	MIMAT0003256	3.60
21	hsa-miR-16-2-3p	MIMAT0004518	2.57
22	hsa-miR-29a-3p	MIMAT0000086	2.06
23	hsa-miR-24-3p	MIMAT0000080	2.06
24	hsa-miR-486-5p	MIMAT0002177	2.06
25	hsa-miR-3682-3p	MIMAT0018110	1.54
26	hsa-miR-33a-3p	MIMAT0004506	1.03
27	hsa-miR-377-5p	MIMAT0004689	0.51

Supplementary Table S2.13. Contribution of individual miRNAs using MED analysis in STAD

Rank	**miRNA**	**MIMAT-ID**	**MED-Score**
1	hsa-miR-130a-3p	MIMAT0000425	34.38
2	hsa-miR-320b	MIMAT0005792	30.18
3	hsa-miR-141-5p	MIMAT0004598	29.13
4	hsa-miR-3065-5p	MIMAT0015066	25.46
5	hsa-miR-887-3p	MIMAT0004951	24.41
6	hsa-miR-362-3p	MIMAT0004683	20.73
7	hsa-miR-135a-5p	MIMAT0000428	19.69
8	hsa-miR-21-3p	MIMAT0004494	16.01
9	hsa-miR-148b-3p	MIMAT0000759	14.96
10	hsa-miR-580-3p	MIMAT0003245	12.86
11	hsa-miR-330-3p	MIMAT0000751	8.66
12	hsa-miR-143-3p	MIMAT0000435	6.56
13	hsa-miR-339-5p	MIMAT0000764	6.56
14	hsa-miR-30e-5p	MIMAT0000692	5.51
15	hsa-miR-3928-3p	MIMAT0018205	4.99
16	hsa-miR-935	MIMAT0004978	4.46
17	hsa-miR-127-5p	MIMAT0004604	3.94

18	hsa-miR-424-3p	MIMAT0004749	2.89
19	hsa-miR-221-3p	MIMAT0000278	1.84
20	hsa-miR-193a-3p	MIMAT0000459	0.26

Supplementary Table S2.14. Contribution of individual miRNAs using MED analysis in THCA

Rank	miRNA	MIMAT-ID	MED-Score
1	hsa-miR-940	MIMAT0004983	34.80
2	hsa-let-7i-5p	MIMAT0000415	25.60
3	hsa-miR-1249-3p	MIMAT0005901	23.60
4	hsa-miR-101-5p	MIMAT0004513	23.20
5	hsa-miR-874-3p	MIMAT0004911	23.20
6	hsa-miR-3605-3p	MIMAT0017982	19.60
7	hsa-miR-592	MIMAT0003260	18.80
8	hsa-miR-188-3p	MIMAT0004613	16.40
9	hsa-miR-30d-5p	MIMAT0000245	13.60
10	hsa-miR-218-1-3p	MIMAT0004565	13.20
11	hsa-miR-23a-5p	MIMAT0004496	12.00
12	hsa-miR-324-3p	MIMAT0000762	11.20
13	hsa-miR-10a-5p	MIMAT0000253	10.40
14	hsa-miR-431-3p	MIMAT0004757	10.00
15	hsa-miR-199b-5p	MIMAT0000263	9.20
16	hsa-miR-514a-3p	MIMAT0002883	7.20
17	hsa-miR-10b-5p	MIMAT0000254	6.40
18	hsa-let-7c-5p	MIMAT0000064	5.60
19	hsa-miR-27b-5p	MIMAT0004588	5.60
20	hsa-miR-192-5p	MIMAT0000222	4.80
21	hsa-miR-382-5p	MIMAT0000737	4.40
22	hsa-miR-625-3p	MIMAT0004808	3.20
23	hsa-miR-92b-3p	MIMAT0003218	3.20
24	hsa-miR-181a-2-3p	MIMAT0004558	0.80
25	hsa-miR-3615	MIMAT0017994	0.40
26	hsa-miR-582-5p	MIMAT0003247	0.40

Supplementary Table S2.15. Contribution of individual miRNAs using MED analysis in UVM

Rank	miRNA	MIMAT-ID	MED-Score
1	hsa-miR-335-5p	MIMAT0000765	50.63
2	hsa-miR-192-3p	MIMAT0004543	45.57
3	hsa-miR-3687	MIMAT0018115	45.57
4	hsa-miR-664a-5p	MIMAT0005948	35.44
5	hsa-miR-1247-5p	MIMAT0005899	35.44
6	hsa-miR-3613-3p	MIMAT0017991	20.25
7	hsa-let-7i-3p	MIMAT0004585	20.25
8	hsa-miR-224-5p	MIMAT0000281	20.25
9	hsa-miR-3917	MIMAT0018191	20.25

10	hsa-miR-20b-3p	MIMAT0004752	15.19
11	hsa-miR-362-3p	MIMAT0004683	10.13
12	hsa-miR-581	MIMAT0003246	10.13
13	hsa-miR-222-5p	MIMAT0004569	5.06

Supplementary Table S3. Comparison of expression difference of has-let-7i-3p, has-miR-362-3p, and has-miR-3651 in cancer vs normal samples

miRNA	Cancer type	Fold change	log2(Fold change)	Mean RPM* (tumor)	Mean RPM* (normal)	p-value	adjusted p-value
hsa-let-7i-3p	Breast invasive carcinoma	-2.05	-1.04	78.73	161.63	1.21e-26	5.6e-26
	Kidney renal clear cell carcinoma	1.55	0.63	80.23	51.77	3.35e-12	8.7e-12
	Liver hepatocellular carcinoma	-1.42	-0.5	36.06	51.08	8.39e-10	3.02e-9
	Prostate adenocarcinoma	-1.54	-0.62	16.8	25.87	1.06e-8	3.56e-8
	Pan-kidney cohort (KICH+KIRC+KIRP)	1.26	0.33	60.03	47.83	0.000107	0.000158
	Uterine Corpus Endometrial Carcinoma	-1.2	-0.26	76.76	92.02	0.0022	0.00334
	Lung adenocarcinoma	-1.17	-0.23	117.97	138.33	0.0124	0.019
	Cholangiocarcinoma	1.6	0.67	53.7	33.64	0.00849	0.0219
	Lung squamous cell carcinoma	1.21	0.27	125.65	104	0.0227	0.0308
	Stomach adenocarcinoma	-1.82	-0.86	75.82	137.73	0.026	0.0386
	Bladder Urothelial Carcinoma	-1.13	-0.18	65.7	74.31	0.0328	0.0487
	Kidney renal papillary cell carcinoma	-1.33	-0.41	33.11	43.95	0.0618	0.0772
	Thyroid carcinoma	-1.09	-0.12	467.46	508.8	0.0642	0.0911
	Stomach and Esophageal carcinoma	-1.72	-0.78	66.97	115.14	0.178	0.213
	Cervical squamous cell carcinoma and	1.58	0.66	82.23	52.11	0.255	0.377

	endocervical adenocarcinoma						
	Pheochromocytoma and Paraganglioma	1.39	0.47	27.92	20.13	0.264	0.387
	Esophageal carcinoma	1.15	0.2	45.82	40.02	0.294	0.42
	Kidney Chromophobe	-1.04	-0.05	42.21	43.8	0.386	0.451
	Skin Cutaneous Melanoma	-1.58	-0.66	85.33	134.57	0.103	0.543
	Head and Neck squamous cell carcinoma	-1.05	-0.07	112.93	118.22	0.597	0.638
	Thymoma	-1.11	-0.15	69.61	77.46	0.238	0.678
	Pancreatic adenocarcinoma	-1	-0.01	76.59	76.9	0.92	0.981
hsa-miR-362-3p	Pan-kidney cohort (KICH+KIRC+KIRP)	-1.81	-0.86	2.8	5.08	7.02E-16	1.76E-15
	Liver hepatocellular carcinoma	2.33	1.22	4.23	1.82	4.02E-16	3.93E-15
	Head and Neck squamous cell carcinoma	-1.92	-0.94	2.44	4.69	7.64E-13	4.47E-12
	Lung squamous cell carcinoma	-1.67	-0.74	2.36	3.95	9.72E-12	2.99E-11
	Breast invasive carcinoma	1.94	0.96	1.63	0.84	1.98E-11	4.40E-11
	Kidney renal clear cell carcinoma	-1.67	-0.74	2.17	3.62	4.73E-09	9.64E-09
	Kidney renal papillary cell carcinoma	-2.4	-1.26	2.96	7.12	1.21E-08	3.80E-08
	Stomach adenocarcinoma	1.72	0.78	3.91	2.28	0.0000132	0.0000379
	Bladder Urothelial Carcinoma	1.76	0.82	2.83	1.6	0.0013	0.00261
	Uterine Corpus Endometrial Carcinoma	-1.4	-0.48	4.73	6.6	0.00427	0.00633

	Stomach and Esophageal carcinoma	1.31	0.39	3.77	2.88	0.00446	0.00717
	Lung adenocarcinoma	-1.22	-0.29	2.53	3.09	0.0274	0.0395
	Esophageal carcinoma	-1.4	-0.49	3.41	4.78	0.0443	0.0938
	Thyroid carcinoma	-1.1	-0.14	2.3	2.54	0.0931	0.129
	Kidney Chromophobe	1	0	5.63	5.61	0.353	0.417
	Pancreatic adenocarcinoma	-1.47	-0.56	2.44	3.59	0.121	0.438
	Thymoma	2.7	1.43	4.93	1.83	0.0376	0.509
	Skin Cutaneous Melanoma	3.8	1.93	4.69	1.23	0.12	0.574
	Pheochromocytoma and Paraganglioma	-1	0	2.51	2.51	0.459	0.59
	Prostate adenocarcinoma	-1.06	-0.08	2.32	2.45	0.603	0.663
	Cervical squamous cell carcinoma and endocervical adenocarcinoma	-1.06	-0.08	3.5	3.71	0.6	0.689
hsa-miR-3651	Lung squamous cell carcinoma	3.8	1.93	2.05	0.54	1.49E-12	4.87E-12
	Uterine Corpus Endometrial Carcinoma	3.78	1.92	2.15	0.57	5.02E-09	1.39E-08
	Stomach and Esophageal carcinoma	3.29	1.72	2.11	0.64	8.20E-08	3.21E-07
	Head and Neck squamous cell carcinoma	2.98	1.58	1.87	0.62	1.15E-07	3.23E-07
	Breast invasive carcinoma	2.18	1.12	1.35	0.62	1.42E-06	0.00000236
	Stomach adenocarcinoma	3.15	1.65	1.57	0.5	9.66E-07	0.00000342
	Kidney Chromophobe	4.68	2.23	0.47	0.1	9.91E-06	0.0000255
	Thyroid carcinoma	-1.53	-0.61	1.02	1.57	0.0114	0.0186

	Esophageal carcinoma	3.11	1.64	3.38	1.09	0.0417	0.0903
	Pan-kidney cohort (KICH+KIRC+KIRP)	1.62	0.7	0.44	0.27	0.211	0.235
	Liver hepatocellular carcinoma	1.44	0.53	0.85	0.59	0.216	0.263
	Pancreatic adenocarcinoma	-1.24	-0.31	0.27	0.34	0.498	0.757
	Kidney renal papillary cell carcinoma	1.28	0.36	0.42	0.33	0.74	0.768
	Thymoma	1.95	0.97	0.75	0.38	0.838	0.964

Supplementary Table S4. Co-expression analysis of miRNA signatures across 15 cancers

Cancer	BLCA-Signature	Correlated miRNAs	R
BLCA	hsa.miR.136.5p	hsa.miR.127.5p	0.85083
	hsa.miR.337.3p	hsa.miR.493.5p	0.87111
		hsa.miR.431.3p	0.86363
		hsa.miR.432.5p	0.85247
		hsa.miR.487b.3p	0.84928
		hsa.miR.654.3p	0.84251
		hsa.miR.127.5p	0.83623
		hsa.miR.409.3p	0.82585
		hsa.miR.758.3p	0.82543
		hsa.miR.379.5p	0.81228
		hsa.miR.376c.3p	0.81211
		hsa.miR.370.3p	0.80815
	hsa.miR.512.3p	hsa.miR.526b.5p	0.87879
	hsa.miR.27a.3p	hsa.miR.23a.3p	0.86959
	hsa.miR.199a.5p	hsa.miR.214.5p	0.88195
	hsa.miR.526b.5p	hsa.miR.512.3p	0.87879
	hsa.miR.660.5p	hsa.miR.532.5p	0.82708
	hsa.miR.411.5p	hsa.miR.379.5p	0.90819
		hsa.miR.127.3p	0.88842
		hsa.miR.654.3p	0.84351
		hsa.miR.134.5p	0.83746
		hsa.miR.376c.3p	0.82878
		hsa.miR.381.3p	0.8251
		hsa.miR.889.3p	0.8228
		hsa.miR.369.5p	0.82235
		hsa.miR.382.5p	0.81615
		hsa.miR.410.3p	0.81458
		hsa.miR.493.3p	0.8135
		hsa.miR.758.3p	0.81267
BRCA	hsa.miR.379	hsa.miR.127	0.8525
		hsa.miR.758	0.83849
		hsa.miR.410	0.80367
	hsa.miR.500a	hsa.miR.501	0.84981
COAD	hsa.miR.450b.5p	hsa.miR.542.3p	0.86189
	hsa.miR.17.3p	hsa.miR.20a.5p	0.80638
	hsa.miR.500a.3p	hsa.miR.501.3p	0.90779
		hsa.miR.532.5p	0.86472
	hsa.miR.127.5p	hsa.miR.136.5p	0.82682
	hsa.miR.125b.2.3p	hsa.miR.99a.5p	0.8971
		hsa.let.7c.5p	0.86362
		hsa.miR.125b.5p	0.81756

	hsa.miR.191.5p	hsa.miR.425.5p	0.8532
ESCA	hsa.miR.199a.5p	hsa.miR.214.5p	0.88019
	hsa.miR.23a.3p	hsa.miR.27a.3p	0.86622
	hsa.miR.487b.3p	hsa.miR.127.3p	0.81253
		hsa.miR.889.3p	0.80128
	hsa.miR.508.3p	hsa.miR.509.3p	0.89842
		hsa.miR.514a.3p	0.8673
	hsa.miR.514a.3p	hsa.miR.508.3p	0.8673
		hsa.miR.509.3p	0.83004
	hsa.miR.432.5p	hsa.miR.431.3p	0.84021
		hsa.miR.382.5p	0.80104
HNSC	hsa.miR.493.3p	hsa.miR.409.3p	0.87754
		hsa.miR.382.5p	0.85962
		hsa.miR.889.3p	0.85175
		hsa.miR.758.3p	0.84649
		hsa.miR.127.3p	0.84367
		hsa.miR.493.5p	0.83876
		hsa.miR.432.5p	0.8339
		hsa.miR.379.5p	0.82919
		hsa.miR.410.3p	0.82704
		hsa.miR.370.3p	0.81859
		hsa.miR.134.5p	0.81074
		hsa.miR.431.3p	0.81054
		hsa.miR.654.3p	0.80543
	hsa.miR.206	hsa.miR.133b	0.95344
		hsa.miR.1.3p	0.94774
	hsa.miR.18a.5p	hsa.miR.17.5p	0.82446
		hsa.miR.19a.3p	0.82434
	hsa.miR.409.3p	hsa.miR.382.5p	0.93486
		hsa.miR.758.3p	0.89757
		hsa.miR.134.5p	0.88559
		hsa.miR.379.5p	0.8779
		hsa.miR.493.3p	0.87754
		hsa.miR.889.3p	0.87683
		hsa.miR.127.3p	0.87673
		hsa.miR.432.5p	0.87539
		hsa.miR.493.5p	0.86652
		hsa.miR.370.3p	0.85972
		hsa.miR.654.3p	0.85626
		hsa.miR.431.3p	0.84675
		hsa.miR.410.3p	0.82573
		hsa.miR.337.3p	0.81909
		hsa.miR.485.3p	0.80923
		hsa.miR.487b.3p	0.8017

		hsa.miR.127.5p	0.80004
KIRC	hsa.miR.144.5p	hsa.miR.451a	0.94915
		hsa.miR.486.5p	0.92824
	hsa.miR.489.3p	hsa.miR.653.5p	0.81512
KIRP	hsa.miR.224.5p	hsa.miR.452.5p	0.8625
	hsa.miR.542.5p	hsa.miR.450b.5p	0.82058
LIHCC	hsa-miR-518b	hsa-miR-512	0.88368
		hsa-miR-525	0.88135
		hsa-miR-517	0.88
		hsa-miR-520a	0.87077
		hsa-miR-526b	0.86433
		hsa-miR-519a	0.85918
		hsa-miR-516a	0.84481
		hsa-miR-522	0.84263
		hsa-miR-1323	0.80711
	hsa-miR-512	hsa-miR-518b	0.87175
		hsa-miR-525	0.86591
		hsa-miR-520b	0.85993
		hsa-miR-519a	0.85658
		hsa-miR-522	0.85275
		hsa-miR-516a	0.8434
		hsa-miR-526b	0.84138
		hsa-miR-517a	0.83647
		hsa-miR-1323	0.82907
LUAD	hsa.miR.144.5p	hsa.miR.451a	0.8937
	hsa.miR.376c.3p	hsa.miR.495.3p	0.8324
		hsa.miR.487b.3p	0.82167
		hsa.miR.381.3p	0.82055
		hsa.miR.382.5p	0.81617
		hsa.miR.654.3p	0.81027
		hsa.miR.889.3p	0.80956
		hsa.miR.493.5p	0.80489
		hsa.miR.134.5p	0.80376
		hsa.miR.379.5p	0.80133
		hsa.miR.369.3p	0.8001
LUSC	NA	NA	NA
READ	hsa.miR.140.5p	hsa.miR.126.3p	0.82597
	hsa.miR.200b.3p	hsa.miR.429	0.85611
SKCM	hsa.miR.194.5p	hsa.miR.192.5p	0.83789
	hsa.miR.486.5p	hsa.miR.451a	0.92664
		hsa.miR.144.5p	0.80551
STAD	hsa.miR.141.5p	hsa.miR.200c.3p	0.8094
	hsa.miR.127.5p	hsa.miR.134.5p	0.89068
		hsa.miR.136.5p	0.86676

		hsa.miR.409.5p	0.83392
		hsa.miR.337.3p	0.82606
	hsa.miR.221.3p	hsa.miR.222.3p	0.89969
THCA	hsa.miR.199b.5p	hsa.miR.214.5p	0.86736
		hsa.miR.136.5p	0.84914
		hsa.miR.127.5p	0.81443
	hsa.miR.514a.3p	hsa.miR.509.3p	0.86009
		hsa.miR.508.3p	0.83453
	hsa.miR.192.5p	hsa.miR.194.5p	0.8509
		hsa.miR.409.3p	0.87451
		hsa.miR.337.3p	0.8741
		hsa.miR.134.5p	0.87061
		hsa.miR.889.3p	0.86136
		hsa.miR.381.3p	0.86114
		hsa.miR.127.5p	0.85932
		hsa.miR.127.3p	0.85734
		hsa.miR.379.5p	0.84578
		hsa.miR.136.5p	0.83969
		hsa.miR.758.3p	0.83922
		hsa.miR.136.3p	0.83552
		hsa.miR.654.3p	0.83144
		hsa.miR.409.5p	0.82336
		hsa.miR.493.5p	0.82297
		hsa.miR.410.3p	0.80161
UVM	hsa.miR.224.5p	hsa.miR.452.5p	0.83224

Abbreviations: NA- Not Available.

Supplementary Table S5. Top-10 ranked miRNAs involvement in BLCA

Rank	BLCA	Literature
Rank-1	hsa-miR-31-3p	1
Rank-2	hsa-miR-29b-2-5p	2, 3
Rank-3	hsa-miR-193b-3p	4, 5
Rank-4	hsa-miR-10b-5p	6
Rank-5	hsa-miR-125a-3p	7, 8
Rank-6	hsa-miR-136-5p	-
Rank-7	hsa-miR-3912-3p	-
Rank-8	hsa-miR-205-5p	9, 10
Rank-9	hsa-miR-337-3p	11
Rank-10	hsa-miR-29a-5p	12

Supplementary Table S6. Top-10 ranked miRNAs involvement in BRCA

Rank	BRCA	Literature
1	hsa-miR-200c-5p	13, 14
2	hsa-miR-503	15
3	hsa-miR-1307-3p	16
4	hsa-miR-361-3p	17
5	hsa-miR-212	18
6	hsa-miR-592	19
7	hsa-miR-1185-1	-
8	hsa-miR-146b	20
9	hsa-miR-1468-5p	-
10	hsa-miR-769-3p	21

Supplementary Table S7. Top-10 ranked miRNAs involvement in COAD

Rank	COAD	Literature
1	hsa-miR-188-3p	22
2	hsa-miR-1976	-
3	hsa-miR-320a	23
4	hsa-miR-450b-5p	24
5	hsa-miR-140-3p	25
6	hsa-miR-17-3p	26
7	hsa-miR-301a-3p	27
8	hsa-miR-582-5p	-
9	hsa-miR-491-3p	28
10	hsa-miR-501-5p	-

Supplementary Table S8. Top-10 ranked miRNAs involvement in ESCA

Rank	ESCA	Literature
1	hsa-miR-708-5p	29, 30
2	hsa-miR-199a-5p	31, 32
3	hsa-miR-33b-5p	33, 34
4	hsa-miR-23a-3p	35
5	hsa-miR-423-5p	36
6	hsa-miR-193b-5p	37
7	hsa-miR-3677-3p	38
8	hsa-miR-362-3p	39
9	hsa-miR-487b-3p	-
10	hsa-miR-508-3p	40

Supplementary Table S9. Top-10 ranked miRNAs involvement in HNSC

Rank	HNSC	Literature
1	hsa-miR-93-3p	41, 42
2	hsa-miR-335-5p	43
3	hsa-miR-219a-1-3p	-
4	hsa-miR-361-3p	-
5	hsa-miR-493-3p	44
6	hsa-miR-188-3p	-
7	hsa-miR-3690	45
8	hsa-miR-103a-3p	46
9	hsa-miR-101-5p	47
10	hsa-miR-206	48, 49

Supplementary Table S10. Top-10 ranked miRNAs involvement in KIRC

Rank	KIRC	Literature
1	hsa-miR-144-5p	50
2	hsa-miR-744-5p	-
3	hsa-miR-550a-3p	-
4	hsa-miR-1296-5p	-
5	hsa-let-7i-3p	51
6	hsa-miR-18a-5p	52

7	hsa-miR-628-5p	-
8	hsa-miR-197-3p	51
9	hsa-miR-222-5p	53
10	hsa-miR-126-3p	54, 55

Supplementary Table S11. Top-10 ranked miRNAs involvement in KIRP

Rank	**KIRP**	**Literature**
1	hsa-miR-491-5p	-
2	hsa-miR-769-5p	56
3	hsa-miR-29c-5p	-
4	hsa-miR-16-5p	57
5	hsa-miR-200b-5p	58
6	hsa-miR-485-3p	59
7	hsa-miR-22-5p	58
8	hsa-miR-629-3p	-
9	hsa-miR-320b	57
10	hsa-miR-217	60

Supplementary Table S12. Top-10 ranked miRNAs involvement in LIHCC

Rank	**LIHCC**	**Literature**
1	hsa-miR-550a-2	61
2	hsa-miR-549	-
3	hsa-miR-518b	62
4	hsa-miR-512-2	63
5	hsa-miR-1179	64
6	hsa-miR-574-3p	65
7	hsa-miR-424-3p	66
8	hsa-miR-4286	67
9	hsa-let-7i-3p	68
10	hsa-miR-320a	69

Supplementary Table S13. Top-10 ranked miRNAs involvement in LUAD

Rank	**LUAD**	**Literature**

1	hsa-miR-671-5p	70
2	hsa-miR-3651	71
3	hsa-miR-1304-5p	72
4	hsa-miR-342-3p	73
5	hsa-miR-548v	74
6	hsa-miR-296-3p	71
7	hsa-miR-598-3p	75
8	hsa-miR-190a-5p	-
9	hsa-miR-144-5p	76
10	hsa-miR-185-3p	76

Supplementary Table S14. Top-10 ranked miRNAs involvement in LUSC

Rank	**LUSC**	**Literature**
1	hsa-miR-181a-2-3p	77
2	hsa-miR-664a-3p	-
3	hsa-miR-769-3p	78
4	hsa-miR-29b-2-5p	79
5	hsa-miR-3614-5p	80
6	hsa-miR-214-3p	81
7	hsa-miR-200c-5p	82, 83
8	hsa-miR-3613-5p	84
9	hsa-miR-196a-5p	85
10	hsa-miR-551b-3p	86

Supplementary Table S15. Top-10 ranked miRNAs involvement in SKCM

Rank	**SKCM**	**Literature**
1	hsa-miR-211-5p	87
2	hsa-miR-194-5p	88
3	hsa-miR-3614-5p	-
4	hsa-miR-326	-
5	hsa-miR-4326	-
6	hsa-miR-1180-3p	89
7	hsa-miR-664a-3p	90
8	hsa-miR-26a-1-3p	91
9	hsa-miR-132-5p	92

10	hsa-miR-1538	93

Supplementary Table S16. Top-10 ranked miRNAs involvement in STAD

Rank	STAD	Literature
1	hsa-miR-130a-3p	94
2	hsa-miR-320b	95, 96
3	hsa-miR-141-5p	97
4	hsa-miR-3065-5p	98
5	hsa-miR-887-3p	-
6	hsa-miR-362-3p	99
7	hsa-miR-135a-5p	100
8	hsa-miR-21-3p	101, 102
9	hsa-miR-148b-3p	103
10	hsa-miR-580-3p	-

Supplementary Table S17. Top-10 ranked miRNAs involvement in THCA

Rank	THCA	Literature
1	hsa-miR-940	104
2	hsa-let-7i-5p	105
3	hsa-miR-1249-3p	106
4	hsa-miR-101-5p	107
5	hsa-miR-874-3p	108
6	hsa-miR-3605-3p	-
7	hsa-miR-592	-
8	hsa-miR-188-3p	109
9	hsa-miR-30d-5p	110
10	hsa-miR-218-1-3p	111

Supplementary Table S18. Top-10 ranked miRNAs involvement in READ

Rank	READ	Literature
1	hsa-miR-10a-5p	112
2	hsa-miR-9-5p	113
3	hsa-miR-135b-3p	114
4	hsa-miR-491-5p	115

5	hsa-miR-31-3p	116
6	hsa-miR-656-3p	117
7	hsa-miR-140-5p	118
8	hsa-miR-1269a	119
9	hsa-miR-1468-5p	120
10	hsa-miR-935	-

Supplementary Table S19. Top-10 ranked miRNAs involvement in UVM

Rank	**UVM**	**Literature**
1	hsa-miR-335-5p	121
2	hsa-miR-192-3p	122
3	hsa-miR-3687	-
4	hsa-miR-664a-5p	121
5	hsa-miR-1247-5p	123
6	hsa-miR-3613-3p	-
7	hsa-let-7i-3p	-
8	hsa-miR-224-5p	124
9	hsa-miR-3917	-
10	hsa-miR-20b-3p	-

Supplementary Table S20. MiRNAs that were not previously reported in cancers

Cancer type	**miRNA previously not reported**	**Rank of the miRNA in the signature**
BLCA	hsa-miR-136-5p	6
	hsa-miR-3912-3p	7
BRCA	hsa-miR-1185-1	7
	hsa-miR-1468-5p	9
COAD	hsa-miR-1976	2
	hsa-miR-582-5p	8
	hsa-miR-501-5p	10
ESCA	hsa-miR-487b-3p	9
HNSC	hsa-miR-219a-1-3p	3
	hsa-miR-361-3p	4
	hsa-miR-188-3p	6
KIRC	hsa-miR-744-5p	3
	hsa-miR-550a-3p	4
	hsa-miR-1296-5p	5
	hsa-miR-628-5p	7
KIRP	hsa-miR-491-5p	1

	hsa-miR-29c-5p	3
	hsa-miR-629-3p	8
LIHCC	hsa-miR-549	2
LUAD	hsa-miR-190a-5p	8
LUSC	hsa-miR-664a-3p	2
SKCM	hsa-miR-3614-5p	3
	hsa-miR-326	4
	hsa-miR-4326	5
STAD	hsa-miR-887-3p	5
	hsa-miR-580-3p	10
THCA	hsa-miR-3605-3p	6
	hsa-miR-592	7
READ	hsa-miR-935	10
UVM	hsa-miR-3687	3
	hsa-miR-3613-3p	6
	hsa-let-7i-3p	7
	hsa-miR-3917	9
	hsa-miR-20b-3p	10

Supplementary Table S21. KEGG pathway analysis of miRNA signatures across 15 cancers

Cancer	**KEGG pathway**	**p-value**
BLCA	Proteoglycans in cancer	5.55E-11
	Glioma	1.08E-06
	ECM-receptor interaction	1.66E-06
	ErbB signaling pathway	2.95E-06
	Axon guidance	8.06E-06
	Signaling pathways regulating pluripotency of stem cells	8.53E-06
	Phosphatidylinositol signaling system	1.6E-05
	Renal cell carcinoma	6.8E-05
	Prion diseases	0.00011
	Neurotrophin signaling pathway	0.00015
	Acute myeloid leukemia	0.00057
	mTOR signaling pathway	0.00084
	TGF-beta signaling pathway	0.00084
	Pathways in cancer	0.00084
	Ras signaling pathway	0.00093
	Hippo signaling pathway	0.00093
	Focal adhesion	0.00093
	Colorectal cancer	0.00123
	Endometrial cancer	0.00134
	Rap1 signaling pathway	0.00178

	Choline metabolism in cancer	0.00246
	Prolactin signaling pathway	0.00248
	Circadian rhythm	0.00307
	Gap junction	0.00324
	Prostate cancer	0.00324
	Wnt signaling pathway	0.00324
	T cell receptor signaling pathway	0.004
	Melanoma	0.00468
	AMPK signaling pathway	0.00468
BRCA	KEGG pathway	p-value
	Mucin type O-Glycan biosynthesis	3.02E-15
	Proteoglycans in cancer	6.30E-13
	Hippo signaling pathway	2.01E-09
	ECM-receptor interaction	4.29E-09
	Signaling pathways regulating pluripotency of stem cells	6.02E-07
	FoxO signaling pathway	1.03E-05
	TGF-beta signaling pathway	1.25E-05
	Renal cell carcinoma	1.34E-05
	Focal adhesion	1.51E-05
	Axon guidance	1.88E-05
	Adherens junction	7.60E-05
	Wnt signaling pathway	7.60E-05
	Rap1 signaling pathway	8.12E-05
	Prion diseases	9.47E-05
	Glioma	0.00012
	Ras signaling pathway	0.00032
	MAPK signaling pathway	0.00037
	Thyroid hormone signaling pathway	0.00107
	Endocytosis	0.00144
	Pathways in cancer	0.00161
	Circadian rhythm	0.00212
	Choline metabolism in cancer	0.00212
	ErbB signaling pathway	0.00212
	Melanoma	0.0032
	Bacterial invasion of epithelial cells	0.00377
COAD	Morphine addiction	2.04E-07
	Signaling pathways regulating pluripotency of stem cells	5.03E-07
	Prion diseases	2.95E-06
	Proteoglycans in cancer	2.95E-06

	Glutamatergic synapse	6E-06
	Axon guidance	6E-06
	Transcriptional misregulation in cancer	1.8E-05
	Adrenergic signaling in cardiomyocytes	2.9E-05
	Hippo signaling pathway	0.00017
	Wnt signaling pathway	0.00027
	Long-term depression	0.00034
	Glioma	0.00034
	FoxO signaling pathway	0.00044
	Amphetamine addiction	0.00054
	Circadian rhythm	0.00063
	Estrogen signaling pathway	0.00064
	cAMP signaling pathway	0.00075
	Oxytocin signaling pathway	0.00075
	Focal adhesion	0.00085
	TGF-beta signaling pathway	0.00089
	Retrograde endocannabinoid signaling	0.00106
	Regulation of actin cytoskeleton	0.00167
	Renal cell carcinoma	0.00257
	Colorectal cancer	0.00305
	Dopaminergic synapse	0.00399
ESCA	Axon guidance	3.30E-05
	FoxO signaling pathway	3.30E-05
	Glioma	3.30E-05
	Long-term depression	5.83E-05
	GABAergic synapse	8.00E-05
	Glutamatergic synapse	0.00021
	Non-small cell lung cancer	0.00035
	Renal cell carcinoma	0.00035
	Phosphatidylinositol signaling system	0.00056
	Gap junction	0.00056
	Aldosterone-regulated sodium reabsorption	0.0007
	Morphine addiction	0.00112
	TGF-beta signaling pathway	0.0013
	Retrograde endocannabinoid signaling	0.0013
	Prolactin signaling pathway	0.00138
	ErbB signaling pathway	0.00138
	Circadian rhythm	0.00154
	Thyroid hormone signaling pathway	0.00154
	Signaling pathways regulating pluripotency of stem cells	0.00154

	Proteoglycans in cancer	0.00195
	Oxytocin signaling pathway	0.00251
	Adrenergic signaling in cardiomyocytes	0.00295
	Estrogen signaling pathway	0.00295
	Platelet activation	0.00342
	MAPK signaling pathway	0.00387
	Melanoma	0.00405
	Ras signaling pathway	0.0041
	Long-term potentiation	0.00435
HNSC	Prion diseases	9.28E-08
	Proteoglycans in cancer	9.28E-08
	Fatty acid biosynthesis	1.22E-06
	cGMP-PKG signaling pathway	0.00022
	Adherens junction	0.00038
	Adrenergic signaling in cardiomyocytes	0.00042
	Gap junction	0.00068
	AMPK signaling pathway	0.00068
	Rap1 signaling pathway	0.00068
	Signaling pathways regulating pluripotency of stem cells	0.00072
	GABAergic synapse	0.00186
	Hippo signaling pathway	0.00212
	Morphine addiction	0.00237
	Circadian entrainment	0.00237
	Oxytocin signaling pathway	0.00237
	Vascular smooth muscle contraction	0.00266
	Ubiquitin mediated proteolysis	0.00312
	Lysine degradation	0.00312
	Ras signaling pathway	0.00312
	Axon guidance	0.00392
	Pancreatic cancer	0.00467
KIRC	Prion diseases	1.98E-10
	Proteoglycans in cancer	7.53E-07
	Glioma	2.30E-06
	ErbB signaling pathway	5.38E-06
	Ras signaling pathway	6.23E-05
	ECM-receptor interaction	0.00123
	Amphetamine addiction	0.00129
	Focal adhesion	0.00129
	TGF-beta signaling pathway	0.00159
	Renal cell carcinoma	0.00159

	Rap1 signaling pathway	0.00159
	Gap junction	0.00214
	Estrogen signaling pathway	0.00214
	Long-term potentiation	0.00214
	PI3K-Akt signaling pathway	0.00214
	Axon guidance	0.00236
	Lysine degradation	0.00248
	Phosphatidylinositol signaling system	0.0027
	Dorso-ventral axis formation	0.00276
	Choline metabolism in cancer	0.00336
	Mucin type O-Glycan biosynthesis	0.00381
	Signaling pathways regulating pluripotency of stem cells	0.00442
KIRP	Fatty acid biosynthesis	1.27E-17
	Signaling pathways regulating pluripotency of stem cells	1.67E-09
	Proteoglycans in cancer	1.21E-08
	Prolactin signaling pathway	1.73E-06
	Hippo signaling pathway	1.81E-06
	Prostate cancer	0.00011
	FoxO signaling pathway	0.00013
	Rap1 signaling pathway	0.00017
	Melanoma	0.00026
	Pathways in cancer	0.0003
	Long-term depression	0.00035
	PI3K-Akt signaling pathway	0.00056
	Endometrial cancer	0.00066
	Glioma	0.00066
	Thyroid cancer	0.00084
	Colorectal cancer	0.00092
	Estrogen signaling pathway	0.00114
	TGF-beta signaling pathway	0.00208
	Non-small cell lung cancer	0.00227
	AMPK signaling pathway	0.00463
LIHCC	Fatty acid biosynthesis	2.61E-12
	ECM-receptor interaction	1.63E-11
	Fatty acid metabolism	2.79E-11
	Hepatitis B	3.58E-09
	Glioma	2.90E-08
	Proteoglycans in cancer	1.11E-07
	Lysine degradation	3.32E-07

	Hippo signaling pathway	1.95E-06
	Pathways in cancer	4.2E-06
	Viral carcinogenesis	5.37E-06
	TGF-beta signaling pathway	9.14E-06
	Estrogen signaling pathway	1.7E-05
	Chronic myeloid leukemia	3.9E-05
	Prostate cancer	0.00011
	Renal cell carcinoma	0.00015
	Adherens junction	0.00076
	Fatty acid elongation	0.00081
	Prion diseases	0.00139
	Endocytosis	0.00141
LUAD	Fatty acid biosynthesis	7.47E-10
	Axon guidance	9.10E-08
	Signaling pathways regulating pluripotency of stem cells	6.07E-06
	TGF-beta signaling pathway	9.26E-06
	Proteoglycans in cancer	9.26E-06
	Amphetamine addiction	4.99E-05
	Pathways in cancer	4.99E-05
	Hippo signaling pathway	9.75E-05
	Transcriptional misregulation in cancer	9.75E-05
	Thyroid hormone signaling pathway	0.00046
	Ubiquitin mediated proteolysis	0.00053
	N-Glycan biosynthesis	0.00209
	Glycosphingolipid biosynthesis - ganglio series	0.00221
	Adherens junction	0.00221
	Circadian rhythm	0.0023
	Rap1 signaling pathway	0.0027
	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	0.00389
LUSC	Glycosphingolipid biosynthesis - lacto and neolacto series	7.01E-13
	Prion diseases	1.70E-06
	Proteoglycans in cancer	2.28E-06
	TGF-beta signaling pathway	2.92E-06
	Mucin type O-Glycan biosynthesis	1.35E-05
	Signaling pathways regulating pluripotency of stem cells	1.35E-05
	ErbB signaling pathway	2.03E-05
	mTOR signaling pathway	6.97E-05

	FoxO signaling pathway	0.0009
READ	GABAergic synapse	1.25E-06
	Thyroid hormone signaling pathway	1.25E-06
	Estrogen signaling pathway	1.25E-06
	Axon guidance	5.97E-05
	Proteoglycans in cancer	5.97E-05
	ErbB signaling pathway	0.00033
	Prolactin signaling pathway	0.00033
	Renal cell carcinoma	0.00033
	Adrenergic signaling in cardiomyocytes	0.00037
	Morphine addiction	0.0012
	Ras signaling pathway	0.00208
	Phosphatidylinositol signaling system	0.0021
	Cocaine addiction	0.00238
	Pancreatic cancer	0.00238
	Signaling pathways regulating pluripotency of stem cells	0.00238
	Mucin type O-Glycan biosynthesis	0.0027
	Rap1 signaling pathway	0.00374
	Biotin metabolism	0.00421
	Long-term depression	0.00421
	Focal adhesion	0.00421
	Pathways in cancer	0.00421
	Neurotrophin signaling pathway	0.00483
	Oxytocin signaling pathway	0.00483
SKCM	Fatty acid biosynthesis	6.12E-11
	Fatty acid metabolism	6.12E-11
	ECM-receptor interaction	6.12E-11
	Proteoglycans in cancer	1.53E-07
	Signaling pathways regulating pluripotency of stem cells	1.3E-05
	FoxO signaling pathway	8.6E-05
	Glioma	0.0001
	ErbB signaling pathway	0.00014
	Endometrial cancer	0.00014
	Hippo signaling pathway	0.00037
	Pathways in cancer	0.00041
	Focal adhesion	0.00052
	Thyroid hormone signaling pathway	0.00075
	PI3K-Akt signaling pathway	0.00075
	mTOR signaling pathway	0.00084

	Colorectal cancer	0.00086
	Long-term depression	0.00086
	Wnt signaling pathway	0.00086
	Melanoma	0.00086
	Choline metabolism in cancer	0.00123
	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	0.00178
	Adrenergic signaling in cardiomyocytes	0.00266
	TGF-beta signaling pathway	0.0029
	Prostate cancer	0.00298
	Thyroid cancer	0.00373
	Neurotrophin signaling pathway	0.00475
	Oxytocin signaling pathway	0.00475
STAD	ECM-receptor interaction	5.52E-10
	Renal cell carcinoma	6.37E-07
	Ras signaling pathway	7.78E-07
	Axon guidance	7.78E-07
	Pathways in cancer	8.76E-07
	Proteoglycans in cancer	3.33E-06
	Prion diseases	7.68E-06
	Adherens junction	7.68E-06
	Long-term depression	9.64E-06
	ErbB signaling pathway	9.64E-06
	Hippo signaling pathway	1.21E-05
	FoxO signaling pathway	1.67E-05
	TGF-beta signaling pathway	1.76E-05
	Focal adhesion	1.76E-05
	Glioma	5.42E-05
	Choline metabolism in cancer	0.00019
	Chronic myeloid leukemia	0.00023
	Signaling pathways regulating pluripotency of stem cells	0.00023
	Prolactin signaling pathway	0.00023
	Colorectal cancer	0.00028
	Mucin type O-Glycan biosynthesis	0.00046
	Pancreatic cancer	0.00046
	Endocrine and other factor-regulated calcium reabsorption	0.00049
	Melanoma	0.00053
	PI3K-Akt signaling pathway	0.0006
	Rap1 signaling pathway	0.00118

	Circadian rhythm	0.00174
	Thyroid hormone signaling pathway	0.0022
	Regulation of actin cytoskeleton	0.00398
	Prostate cancer	0.00398
	cGMP-PKG signaling pathway	0.00497
THCA	Prion diseases	1.49E-07
	Proteoglycans in cancer	1.48E-06
	Axon guidance	6.31E-06
	Glutamatergic synapse	6.63E-05
	Signaling pathways regulating pluripotency of stem cells	0.00016
	Long-term depression	0.0002
	Morphine addiction	0.0002
	ErbB signaling pathway	0.0002
	FoxO signaling pathway	0.00025
	TGF-beta signaling pathway	0.00033
	Transcriptional misregulation in cancer	0.00038
	Chronic myeloid leukemia	0.00099
	Ubiquitin mediated proteolysis	0.00218
	Retrograde endocannabinoid signaling	0.00242
	Renal cell carcinoma	0.0026
	cGMP-PKG signaling pathway	0.00265
	Regulation of actin cytoskeleton	0.00265
	Glioma	0.00273
	Glycosaminoglycan biosynthesis - keratan sulfate	0.00433
UVM	Hippo signaling pathway	5.37E-12
	Signaling pathways regulating pluripotency of stem cells	9.55E-11
	Pathways in cancer	2.24E-07
	Ubiquitin mediated proteolysis	3.48E-06
	Thyroid hormone signaling pathway	3.48E-06
	Transcriptional misregulation in cancer	3.48E-06
	Proteoglycans in cancer	3.48E-06
	Renal cell carcinoma	4.88E-06
	Wnt signaling pathway	1.03E-05
	Axon guidance	1.47E-05
	FoxO signaling pathway	1.58E-05
	Phosphatidylinositol signaling system	4.56E-05
	Adherens junction	0.00012
	Endocrine and other factor-regulated calcium reabsorption	0.00014

Circadian rhythm	0.00015
TGF-beta signaling pathway	0.0004
Rap1 signaling pathway	0.0004
AMPK signaling pathway	0.00071
Long-term depression	0.00103
Ras signaling pathway	0.00165
Colorectal cancer	0.00188
mRNA surveillance pathway	0.002
Morphine addiction	0.00202
MAPK signaling pathway	0.00304
Sphingolipid signaling pathway	0.00331
Cholinergic synapse	0.00485
Protein processing in endoplasmic reticulum	0.00591

Supplementary Table S22. GO category analysis of miRNA signatures across 15 cancers

Cancer	GO Category	genes	miRNAs	p-value
BLCA	cellular_component	3963	9	7.55E-19
	protein binding transcription factor activity	173	10	8.66E-18
	protein complex	1074	10	3.84E-17
	epidermal growth factor receptor signaling pathway	95	12	4.88E-17
	enzyme binding	457	12	5.25E-17
	molecular_function	5054	14	7.98E-17
	gene expression	217	14	2.00E-16
	Fc-epsilon receptor signaling pathway	91	15	2.60E-16
	nucleic acid binding transcription factor activity	379	16	5.40E-16
	neurotrophin TRK receptor signaling pathway	127	16	6.64E-16
	cellular protein modification process	927	19	8.01E-16
	biosynthetic process	1518	23	8.67E-16
	cellular nitrogen compound metabolic process	1839	23	9.21E-16
	ion binding	2413	23	9.50E-16
	organelle	3878	28	1.06E-15
	cytosol	790	11	1.67E-15
	nucleoplasm	336	9	1.37E-12
	transcription, DNA-templated	458	7	1.07E-11
	cellular component assembly	349	7	1.16E-09
	fibroblast growth factor receptor signaling pathway	71	9	1.02E-08
	symbiosis, encompassing mutualism through parasitism	130	5	3.18E-08
	small molecule metabolic process	541	8	9.61E-08
	biological_process	3279	7	9.70E-08

	viral process	119	5	1.29E-07
	catabolic process	335	4	2.13E-07
	cytoskeletal protein binding	200	7	2.00E-06
	cell death	237	6	5.99E-06
	blood coagulation	118	5	7.45E-06
	phosphatidylinositol-mediated signaling	51	8	7.85E-06
	response to stress	433	6	3.51E-05
	mitotic cell cycle	69	3	7.20E-05
	macromolecular complex assembly	217	6	0.00022
	synaptic transmission	93	4	0.004
	toll-like receptor 10 signaling pathway	26	4	0.00438
	nucleobase-containing compound catabolic process	150	3	0.00486
BRCA	mitotic cell cycle	87	5	<1E-325
	cellular protein modification process	329	5	<1E-325
	biological_process	1365	5	<1E-325
	viral process	108	5	<1E-325
	small molecule metabolic process	287	5	<1E-325
	symbiosis, encompassing mutualism through parasitism	119	5	<1E-325
	membrane organization	113	5	<1E-325
	biosynthetic process	528	6	<1E-325
	gene expression	157	6	<1E-325
	cellular nitrogen compound metabolic process	684	8	<1E-326
	catabolic process	225	3	8.33E-15
	cellular component assembly	190	7	5.48E-14
	response to stress	242	3	6.43E-14
	macromolecular complex assembly	133	6	4.60E-12
	nucleobase-containing compound catabolic process	131	5	1.16E-11
	mRNA metabolic process	52	4	1.37E-11
	RNA metabolic process	54	4	5.92E-11
	neurotrophin TRK receptor signaling pathway	43	3	1.04E-10
	cellular protein metabolic process	73	5	4.98E-09
	cellular lipid metabolic process	30	3	3.64E-07
	Fc-epsilon receptor signaling pathway	29	4	4.47E-07
	protein complex assembly	101	5	5.38E-07
	DNA metabolic process	93	3	1.52E-05
	cell death	123	4	2.56E-05
	viral life cycle	24	4	5.19E-05
	transcription, DNA-templated	119	2	0.00113
	epidermal growth factor receptor signaling pathway	25	2	0.00223

	transcription initiation from RNA polymerase II promoter	21	2	0.00406
	G2/M transition of mitotic cell cycle	23	2	0.00438
COAD	biological_process	3548	7	6.51E-22
	nucleoplasm	316	8	8.67E-22
	neurotrophin TRK receptor signaling pathway	83	8	3.40E-20
	nucleic acid binding transcription factor activity	317	9	8.46E-20
	cellular_component	3941	9	9.60E-20
	transcription, DNA-templated	611	9	5.71E-18
	enzyme binding	401	9	9.21E-18
	protein binding transcription factor activity	180	10	2.57E-17
	molecular_function	4155	11	5.57E-17
	protein complex	1102	11	2.99E-16
	gene expression	219	12	4.78E-16
	cellular protein modification process	766	13	5.09E-16
	biosynthetic process	1364	15	6.27E-16
	ion binding	1982	16	6.84E-16
	cellular nitrogen compound metabolic process	1696	18	8.43E-15
	organelle	3396	19	6.10E-14
	mitotic cell cycle	104	7	8.20E-14
	cellular component assembly	244	5	3.71E-13
	cytosol	538	5	2.85E-12
	Fc-epsilon receptor signaling pathway	52	7	3.27E-12
	cytoskeletal protein binding	218	8	5.12E-12
	catabolic process	492	9	6.00E-12
	macromolecular complex assembly	196	7	2.70E-10
	blood coagulation	103	4	4.08E-09
	nucleobase-containing compound catabolic process	198	6	6.11E-09
	epidermal growth factor receptor signaling pathway	66	6	1.15E-08
	RNA binding	399	7	3.38E-08
	small molecule metabolic process	430	6	3.94E-07
	symbiosis, encompassing mutualism through parasitism	130	5	2.19E-06
	viral process	113	5	4.88E-06
	protein complex assembly	133	5	3.17E-05
	synaptic transmission	89	4	0.0001
	fibroblast growth factor receptor signaling pathway	53	6	0.00025
	enzyme regulator activity	169	4	0.00033
	cell death	174	4	0.00068
	regulation of transcription, DNA-templated	62	1	0.00069
	microtubule organizing center	90	4	0.00104

	response to stress	357	4	0.00317
	nucleic acid binding	54	1	0.0032
	cell-cell signaling	103	3	0.00486
ESCA	cellular_component	3045	7	2.89E-23
	molecular_function	3396	8	6.40E-22
	nucleic acid binding transcription factor activity	291	9	1.99E-20
	gene expression	159	9	4.53E-18
	neurotrophin TRK receptor signaling pathway	96	10	6.16E-18
	cellular protein modification process	676	11	9.60E-18
	biosynthetic process	1067	12	5.57E-17
	ion binding	1681	12	5.69E-17
	cellular nitrogen compound metabolic process	1430	16	2.65E-16
	organelle	2841	16	3.32E-16
	transcription, DNA-templated	375	5	5.55E-16
	enzyme binding	328	7	1.48E-14
	Fc-epsilon receptor signaling pathway	50	4	6.93E-12
	protein binding transcription factor activity	131	7	3.20E-08
	protein complex	600	4	3.97E-08
	epidermal growth factor receptor signaling pathway	65	4	5.19E-08
	biological_process	2825	6	4.89E-07
	nucleoplasm	270	6	4.94E-07
	catabolic process	275	4	1.30E-06
	blood coagulation	120	7	1.60E-06
	synaptic transmission	107	6	1.65E-06
	cellular component assembly	248	4	2.02E-05
	small molecule metabolic process	299	4	3.66E-05
	cytosol	370	3	0.00036
	fibroblast growth factor receptor signaling pathway	54	5	0.00097
	enzyme regulator activity	120	2	0.00131
	post-translational protein modification	36	2	0.00211
	cell death	151	3	0.00271
	cytoskeletal protein binding	156	4	0.00433
HNSC	nucleic acid binding transcription factor activity	240	7	2.62E-23
	Fc-epsilon receptor signaling pathway	63	7	5.22E-23
	neurotrophin TRK receptor signaling pathway	91	8	5.36E-21
	gene expression	169	9	3.11E-18
	molecular_function	3534	10	4.07E-18
	cellular protein modification process	647	11	9.45E-19
	biosynthetic process	983	11	3.62E-17
	ion binding	1559	12	1.93E-17

	organelle	2495	12	2.51E-16
	cellular nitrogen compound metabolic process	1231	13	1.80E-16
	cellular_component	3144	8	1.11E-16
	enzyme binding	322	8	1.11E-16
	protein complex	760	6	8.88E-16
	epidermal growth factor receptor signaling pathway	72	8	5.02E-14
	blood coagulation	134	8	2.18E-13
	cytosol	509	6	3.68E-12
	transcription, DNA-templated	117	2	1.53E-11
	protein binding transcription factor activity	140	7	3.05E-11
	catabolic process	321	4	5.96E-09
	nucleoplasm	174	3	2.63E-08
	fibroblast growth factor receptor signaling pathway	59	6	1.02E-07
	symbiosis, encompassing mutualism through parasitism	118	5	2.09E-07
	nucleobase-containing compound catabolic process	144	3	1.59E-06
	small molecule metabolic process	264	4	2.91E-06
	viral process	106	5	3.21E-06
	cellular component assembly	186	3	2.09E-05
	biological_process	1946	3	2.22E-05
	synaptic transmission	87	5	2.38E-05
	platelet activation	50	4	0.00014
	phosphatidylinositol-mediated signaling	34	4	0.00045
	regulation of transcription, DNA-templated	62	1	0.00051
	cytoskeletal protein binding	93	2	0.00122
	cellular protein metabolic process	69	3	0.00323
	macromolecular complex assembly	97	2	0.00348
	response to stress	180	3	0.00437
	nucleic acid binding	54	1	0.00449
KIRC	molecular_function	2909	7	1.56E-24
	cellular_component	2662	7	2.69E-23
	nucleic acid binding transcription factor activity	231	8	1.48E-20
	cellular protein modification process	538	8	4.75E-20
	biosynthetic process	837	10	3.86E-19
	cellular nitrogen compound metabolic process	1028	11	2.96E-18
	ion binding	1328	11	4.00E-17
	organelle	2049	13	6.27E-18
	Fc-epsilon receptor signaling pathway	55	5	2.22E-16
	neurotrophin TRK receptor signaling pathway	68	5	4.44E-16
	epidermal growth factor receptor signaling pathway	65	5	2.44E-15
	gene expression	131	6	1.20E-12

	protein binding transcription factor activity	115	6	2.74E-10
	protein complex	500	4	1.12E-08
	enzyme binding	212	5	1.59E-07
	catabolic process	179	3	2.16E-07
	synaptic transmission	80	4	4.43E-07
	nervous system development	23	2	5.09E-07
	transcription, DNA-templated	337	5	9.21E-07
	biological_process	2416	5	1.53E-06
	fibroblast growth factor receptor signaling pathway	53	5	3.33E-06
	cytosol	380	4	4.32E-06
	homophilic cell adhesion via plasma membrane adhesion molecules	19	2	3.18E-05
	cellular component assembly	163	3	8.19E-05
	axon guidance	90	3	0.00013
	cell-cell signaling	115	4	0.00014
	blood coagulation	77	4	0.00026
	symbiosis, encompassing mutualism through parasitism	77	3	0.00032
	small molecule metabolic process	303	4	0.00085
	nucleoplasm	165	3	0.00129
	macromolecular complex assembly	129	4	0.00132
	viral process	66	3	0.00178
	phosphatidylinositol-mediated signaling	31	4	0.00209
	response to stress	235	2	0.00241
	cell death	95	2	0.00849
	cell adhesion	32	2	0.02661
	nucleobase-containing compound catabolic process	63	2	0.03911
	protein complex assembly	65	1	0.04679
	enzyme regulator activity	69	2	0.04702
KIRP	molecular_function	2322	5	1.27E-20
	neurotrophin TRK receptor signaling pathway	76	6	3.07E-20
	cellular protein modification process	515	8	2.36E-19
	gene expression	160	9	1.97E-18
	ion binding	1357	9	3.88E-17
	biosynthetic process	934	10	4.81E-18
	cellular nitrogen compound metabolic process	1137	10	4.44E-17
	organelle	2205	10	1.52E-16
	nucleic acid binding transcription factor activity	189	5	2.66E-15
	protein complex	634	5	1.09E-14
	cellular_component	2227	4	1.39E-14
	Fc-epsilon receptor signaling pathway	45	5	5.80E-14

	cytosol	370	3	3.87E-12
	biological_process	1506	2	2.76E-11
	epidermal growth factor receptor signaling pathway	62	5	9.95E-11
	nucleoplasm	189	4	4.63E-10
	enzyme binding	192	3	1.16E-09
	symbiosis, encompassing mutualism through parasitism	86	3	2.12E-07
	catabolic process	306	5	3.35E-07
	blood coagulation	95	5	5.69E-07
	fibroblast growth factor receptor signaling pathway	51	4	2.18E-06
	RNA binding	273	4	6.25E-06
	viral process	75	3	7.37E-06
	cellular component assembly	180	3	8.81E-06
	small molecule metabolic process	379	5	1.28E-05
	protein binding transcription factor activity	75	3	1.48E-05
	macromolecular complex assembly	144	4	2.13E-05
	transcription, DNA-templated	191	2	2.34E-05
	mitotic cell cycle	68	4	0.00024
	membrane organization	92	4	0.00027
	response to stress	261	4	0.00029
	phosphatidylinositol-mediated signaling	33	3	0.00034
	cytoskeletal protein binding	98	3	0.0004
	protein complex assembly	97	3	0.00112
	nervous system development	41	2	0.00189
	cell death	106	2	0.0022
LIHCC	transcription, DNA-templated	790	6	3.80E-25
	transcription initiation from RNA polymerase II promoter	90	6	8.84E-25
	protein complex assembly	250	6	1.11E-24
	cytoskeletal protein binding	249	6	1.36E-24
	enzyme regulator activity	280	6	3.16E-24
	epidermal growth factor receptor signaling pathway	95	7	4.55E-24
	blood coagulation	178	7	1.55E-23
	fibroblast growth factor receptor signaling pathway	79	7	2.61E-23
	immune system process	463	8	4.94E-22
	DNA metabolic process	271	8	1.08E-21
	mRNA metabolic process	104	8	4.73E-21
	Fc-epsilon receptor signaling pathway	79	8	7.67E-21
	mitotic cell cycle	214	9	8.60E-21
	nucleic acid binding transcription factor activity	373	9	2.00E-20
	cell death	374	9	2.64E-20

RNA metabolic process	113	9	4.37E-20
membrane organization	256	9	7.83E-20
protein binding transcription factor activity	229	10	9.93E-20
cellular component assembly	462	10	1.09E-19
cellular protein metabolic process	214	10	1.43E-19
neurotrophin TRK receptor signaling pathway	136	10	2.49E-19
response to stress	780	11	3.92E-19
nucleobase-containing compound catabolic process	368	11	7.90E-19
small molecule metabolic process	842	11	1.49E-18
macromolecular complex assembly	335	11	1.84E-18
catabolic process	755	12	2.38E-18
ion binding	2071	12	2.77E-18
biological_process	4973	13	4.40E-18
molecular_function	5196	14	5.51E-18
cellular_component	5145	14	1.01E-17
nucleoplasm	565	14	1.41E-17
cellular protein modification process	970	14	2.17E-17
protein complex	1429	14	3.83E-17
cytosol	1124	15	3.92E-17
biosynthetic process	1584	15	5.95E-17
viral process	284	15	6.04E-17
enzyme binding	572	15	1.98E-16
poly(A) RNA binding	634	15	2.17E-16
RNA binding	778	16	2.67E-16
gene expression	354	16	2.86E-16
symbiosis, encompassing mutualism through parasitism	317	16	3.13E-16
cellular nitrogen compound metabolic process	1942	17	3.53E-16
organelle	3811	19	7.66E-16
transforming growth factor beta receptor signaling pathway	82	5	1.25E-15
platelet activation	74	6	3.14E-13
TRIF-dependent toll-like receptor signaling pathway	40	6	6.62E-13
post-translational protein modification	74	6	2.35E-12
microtubule organizing center	174	6	6.78E-12
mRNA processing	185	7	2.16E-11
MyD88-independent toll-like receptor signaling pathway	41	6	4.87E-11
phosphatidylinositol-mediated signaling	51	5	8.88E-11
toll-like receptor 10 signaling pathway	33	6	1.94E-10
platelet degranulation	34	5	2.97E-10

innate immune response	202	5	3.21E-10
Fc-gamma receptor signaling pathway involved in phagocytosis	38	5	3.80E-10
small conjugating protein binding	42	4	4.73E-10
toll-like receptor TLR1:TLR2 signaling pathway	33	5	5.38E-10
toll-like receptor TLR6:TLR2 signaling pathway	33	5	5.38E-10
intrinsic apoptotic signaling pathway	34	6	6.79E-10
toll-like receptor 3 signaling pathway	43	6	8.38E-10
transcription from RNA polymerase II promoter	211	7	3.45E-09
mitotic nuclear envelope disassembly	26	5	7.33E-09
RNA splicing	116	6	9.93E-09
transcription factor binding	169	4	1.03E-08
G2/M transition of mitotic cell cycle	69	6	1.05E-08
toll-like receptor 5 signaling pathway	32	5	1.70E-08
toll-like receptor 9 signaling pathway	34	5	2.39E-08
cellular component disassembly involved in execution phase of apoptosis	28	6	7.29E-08
ribonucleoprotein complex assembly	53	4	1.10E-07
nucleocytoplasmic transport	109	5	1.15E-07
cell cycle	233	5	2.55E-07
toll-like receptor 4 signaling pathway	45	6	2.68E-07
hexose transport	24	6	2.82E-07
activation of signaling protein activity involved in unfolded protein response	39	5	4.60E-07
stress-activated MAPK cascade	25	4	6.84E-07
toll-like receptor signaling pathway	45	5	6.86E-07
protein N-linked glycosylation via asparagine	45	6	7.95E-07
viral life cycle	46	5	2.30E-06
nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay	25	6	2.45E-06
insulin receptor signaling pathway	56	3	3.18E-06
toll-like receptor 2 signaling pathway	34	5	4.63E-06
regulation of transcription from RNA polymerase II promoter in response to hypoxia	18	6	4.83E-06
positive regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway	18	6	7.79E-06
cellular lipid metabolic process	54	4	1.01E-05
cellular component movement	44	4	1.34E-05
regulation of glucose transport	21	5	2.61E-05
cell junction organization	47	4	3.38E-05
G1/S transition of mitotic cell cycle	66	6	4.33E-05

	vesicle-mediated transport	269	4	4.58E-05
	in utero embryonic development	124	6	7.73E-05
	mRNA splicing, via spliceosome	55	2	0.00011
	protein targeting	51	1	0.00016
	focal adhesion	144	4	0.00019
	cell cycle arrest	59	4	0.00029
	chromatin organization	55	5	0.00037
	cellular response to hypoxia	45	3	0.0005
	cytoskeleton organization	144	2	0.00071
	termination of RNA polymerase II transcription	24	3	0.0015
	apoptotic signaling pathway	40	2	0.00176
	transcription coactivator activity	104	4	0.00231
	axon guidance	96	2	0.00238
	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest	30	4	0.00253
	extracellular matrix disassembly	31	4	0.00287
	positive regulation of apoptotic process	102	3	0.00463
LUAD	cellular_component	3483	8	1.37E-22
	protein binding transcription factor activity	155	9	2.35E-20
	molecular_function	3472	9	6.03E-19
	nucleic acid binding transcription factor activity	282	10	7.41E-19
	gene expression	207	13	7.44E-19
	cellular protein modification process	843	18	7.91E-19
	cellular nitrogen compound metabolic process	1610	21	2.76E-18
	biosynthetic process	1384	22	3.02E-18
	ion binding	2139	22	5.44E-18
	organelle	3447	24	1.25E-17
	blood coagulation	139	8	7.77E-16
	neurotrophin TRK receptor signaling pathway	87	8	1.11E-15
	protein complex	759	6	1.33E-15
	enzyme binding	327	8	4.05E-13
	Fc-epsilon receptor signaling pathway	59	8	7.57E-11
	transcription, DNA-templated	444	6	8.43E-11
	cellular component assembly	260	5	4.16E-10
	nucleoplasm	252	7	3.74E-09
	cytosol	494	5	4.75E-08
	symbiosis, encompassing mutualism through parasitism	143	7	5.81E-08
	viral process	130	7	6.02E-07
	cytoskeletal protein binding	154	5	1.04E-06
	small molecule metabolic process	456	6	1.42E-05

	biological_process	2374	5	6.28E-05
	catabolic process	339	5	0.00012
	macromolecular complex assembly	153	4	0.00015
	epidermal growth factor receptor signaling pathway	48	4	0.00251
	nucleobase-containing compound catabolic process	122	3	0.00352
LUSC	molecular_function	3331	9	2.69E-19
	cellular protein modification process	600	9	9.83E-19
	biosynthetic process	949	11	2.34E-18
	cellular nitrogen compound metabolic process	1159	12	4.31E-16
	organelle	2294	12	5.61E-16
	ion binding	1451	13	6.67E-16
	cellular_component	2483	5	2.77E-13
	gene expression	138	8	3.51E-12
	nucleic acid binding transcription factor activity	185	6	1.42E-11
	neurotrophin TRK receptor signaling pathway	67	6	1.51E-11
	small molecule metabolic process	431	5	1.19E-10
	protein binding transcription factor activity	67	4	9.02E-10
	protein complex	664	5	1.90E-09
	cytosol	392	5	1.61E-08
	Fc-epsilon receptor signaling pathway	44	6	2.15E-08
	catabolic process	309	4	1.15E-06
	biological_process	2448	4	1.69E-06
	epidermal growth factor receptor signaling pathway	50	5	5.67E-06
	enzyme binding	267	6	1.84E-05
	nucleoplasm	98	4	2.65E-05
	cytoskeletal protein binding	145	3	8.45E-05
	response to stress	191	4	9.22E-05
	blood coagulation	68	3	0.00034
	transcription, DNA-templated	325	4	0.00058
	phosphatidylinositol-mediated signaling	45	6	0.00064
	cellular component assembly	184	3	0.00147
	fibroblast growth factor receptor signaling pathway	43	4	0.00249
	synaptic transmission	67	3	0.00924
READ	molecular_function	2659	4	1.34E-19
	nucleic acid binding transcription factor activity	235	6	8.73E-19
	cellular protein modification process	558	6	2.26E-18
	biosynthetic process	796	6	3.06E-18
	ion binding	1332	8	2.05E-16
	cellular nitrogen compound metabolic process	1039	9	2.28E-16
	organelle	2166	10	2.55E-16

	cellular_component	2658	4	2.20E-14
	neurotrophin TRK receptor signaling pathway	61	3	1.18E-13
	Fc-epsilon receptor signaling pathway	44	3	1.11E-12
	gene expression	120	5	4.28E-12
	protein binding transcription factor activity	98	4	7.91E-12
	cytoskeletal protein binding	163	3	3.50E-11
	enzyme binding	252	4	7.67E-11
	transcription, DNA-templated	216	3	1.17E-10
	blood coagulation	93	3	4.57E-10
	protein complex	592	3	1.68E-09
	nucleoplasm	181	4	8.03E-09
	cellular component assembly	235	3	1.23E-08
	biological_process	2416	3	1.07E-07
	cytosol	440	3	2.70E-07
	enzyme regulator activity	124	2	3.35E-07
	epidermal growth factor receptor signaling pathway	48	3	3.44E-06
	macromolecular complex assembly	74	1	2.32E-05
	transcription initiation from RNA polymerase II promoter	45	3	5.12E-05
	cell-cell signaling	79	2	0.00017
	synaptic transmission	47	1	0.00018
	protein complex assembly	66	1	0.00028
	cell death	130	3	0.00061
	symbiosis, encompassing mutualism through parasitism	61	2	0.00069
	viral process	54	2	0.00094
	platelet activation	38	3	0.00416
SKCM	cellular_component	4014	9	1.04E-20
	neurotrophin TRK receptor signaling pathway	101	9	3.68E-19
	nucleic acid binding transcription factor activity	337	10	4.66E-19
	gene expression	182	10	4.82E-19
	Fc-epsilon receptor signaling pathway	85	10	9.75E-19
	molecular_function	4772	13	2.00E-18
	cellular protein modification process	833	14	3.73E-18
	biosynthetic process	1384	15	5.97E-18
	ion binding	2201	18	1.48E-16
	organelle	3503	18	2.01E-16
	cellular nitrogen compound metabolic process	1762	19	2.34E-16
	protein complex	985	8	5.55E-16
	enzyme binding	399	11	1.12E-12
	small molecule metabolic process	527	6	1.19E-10

	protein binding transcription factor activity	152	8	3.48E-10
	catabolic process	427	6	1.65E-09
	biological_process	3565	8	1.07E-08
	nucleoplasm	252	7	1.41E-08
	cytosol	420	4	3.16E-08
	cellular component assembly	334	7	3.17E-08
	cytoskeletal protein binding	221	8	1.84E-07
	symbiosis, encompassing mutualism through parasitism	108	5	8.55E-07
	epidermal growth factor receptor signaling pathway	71	7	8.67E-07
	transcription, DNA-templated	461	5	2.06E-06
	extracellular matrix disassembly	26	1	2.39E-06
	phosphatidylinositol-mediated signaling	51	6	2.37E-05
	viral process	84	4	2.55E-05
	fibroblast growth factor receptor signaling pathway	61	5	3.16E-05
	extracellular matrix organization	44	1	6.51E-05
	endoplasmic reticulum lumen	33	1	7.25E-05
	collagen catabolic process	23	1	0.00026
	membrane organization	147	6	0.00095
	synaptic transmission	90	4	0.0011
STAD	cytosol	676	8	2.11E-26
	enzyme binding	385	9	2.80E-23
	cellular_component	4268	10	4.13E-23
	nucleoplasm	368	10	4.41E-21
	epidermal growth factor receptor signaling pathway	89	10	1.02E-19
	protein binding transcription factor activity	171	11	1.11E-19
	neurotrophin TRK receptor signaling pathway	122	11	1.19E-19
	gene expression	217	12	1.33E-19
	Fc-epsilon receptor signaling pathway	85	12	3.10E-19
	nucleic acid binding transcription factor activity	393	13	7.03E-19
	protein complex	1112	13	9.97E-19
	molecular_function	4963	14	1.16E-18
	biosynthetic process	1375	16	3.33E-18
	ion binding	2170	17	1.27E-17
	cellular protein modification process	893	18	1.02E-16
	cellular nitrogen compound metabolic process	1760	19	1.18E-16
	organelle	3520	19	1.29E-16
	blood coagulation	162	10	2.22E-16
	biological_process	3373	7	1.28E-14
	cellular component assembly	360	8	1.52E-14
	transcription, DNA-templated	514	6	5.91E-12

	catabolic process	423	6	2.01E-11
	mitotic cell cycle	85	4	6.28E-10
	cell death	210	5	1.79E-09
	symbiosis, encompassing mutualism through parasitism	138	6	4.82E-09
	RNA binding	257	4	1.94E-08
	fibroblast growth factor receptor signaling pathway	67	7	4.43E-08
	macromolecular complex assembly	210	6	8.05E-08
	viral process	124	6	1.06E-07
	response to stress	323	3	2.91E-06
	small molecule metabolic process	477	6	8.06E-06
	nervous system development	58	4	2.37E-05
	cytoskeletal protein binding	114	3	2.99E-05
	phosphatidylinositol-mediated signaling	42	6	3.37E-05
	synaptic transmission	72	3	5.96E-05
	transcription initiation from RNA polymerase II promoter	68	7	6.46E-05
	nucleobase-containing compound catabolic process	177	4	9.00E-05
	cell-cell signaling	123	4	0.00011
	protein complex assembly	183	6	0.00018
	enzyme regulator activity	178	5	0.00032
	post-translational protein modification	28	2	0.00085
	axon guidance	83	3	0.00425
	Fc-gamma receptor signaling pathway involved in phagocytosis	22	3	0.00997
THCA	transcription, DNA-templated	305	6	5.65E-27
	enzyme binding	317	6	2.95E-24
	nucleic acid binding transcription factor activity	266	8	3.09E-24
	protein binding transcription factor activity	153	9	1.51E-23
	cellular_component	3623	11	2.11E-22
	molecular_function	3655	12	4.36E-21
	cellular protein modification process	651	12	1.75E-20
	gene expression	163	13	8.06E-20
	cellular nitrogen compound metabolic process	1380	18	5.87E-19
	biosynthetic process	1188	19	6.24E-19
	ion binding	1767	19	7.03E-19
	organelle	2787	19	2.12E-18
	Fc-epsilon receptor signaling pathway	61	6	1.11E-16
	neurotrophin TRK receptor signaling pathway	80	7	2.22E-16
	protein complex	658	4	4.14E-10
	blood coagulation	115	5	2.73E-09

	cytosol	470	5	4.08E-09
	nucleoplasm	175	5	1.42E-08
	epidermal growth factor receptor signaling pathway	71	8	2.18E-08
	biological_process	2523	5	2.78E-08
	cellular component assembly	278	6	1.54E-06
	catabolic process	375	5	3.80E-05
	transcription initiation from RNA polymerase II promoter	43	4	0.00029
	phosphatidylinositol-mediated signaling	41	5	0.00042
	regulation of transcription, DNA-templated	86	2	0.00044
	response to stress	315	4	0.00047
	viral process	86	3	0.00057
	post-translational protein modification	41	4	0.00064
	cytoskeletal protein binding	140	3	0.00113
	small molecule metabolic process	318	4	0.00155
	symbiosis, encompassing mutualism through parasitism	91	3	0.00236
	macromolecular complex assembly	163	5	0.0028
UVM	molecular_function	3842	3	4.49E-24
	cellular_component	3650	3	3.88E-21
	enzyme binding	364	3	1.34E-20
	protein binding transcription factor activity	175	4	1.94E-20
	nucleic acid binding transcription factor activity	338	4	5.56E-20
	nucleoplasm	390	4	1.20E-19
	Fc-epsilon receptor signaling pathway	67	4	5.73E-19
	protein complex	957	4	5.90E-19
	neurotrophin TRK receptor signaling pathway	100	4	8.05E-19
	transcription, DNA-templated	686	5	9.47E-19
	biosynthetic process	1236	6	3.20E-17
	gene expression	217	6	4.06E-17
	cellular protein modification process	766	7	7.19E-17
	ion binding	1750	7	1.60E-16
	cellular nitrogen compound metabolic process	1533	8	1.63E-15
	organelle	2867	8	1.65E-15
	epidermal growth factor receptor signaling pathway	79	3	1.96E-13
	biological_process	3261	1	1.61E-12
	cellular component assembly	324	2	2.10E-11
	small molecule metabolic process	537	3	6.44E-11
	viral process	118	1	7.00E-11
	symbiosis, encompassing mutualism through parasitism	130	1	7.84E-11

response to stress	526	3	1.23E-10
RNA binding	441	2	4.39E-10
catabolic process	446	3	1.04E-09
blood coagulation	133	4	6.46E-08
cytosol	557	1	8.22E-08
TRIF-dependent toll-like receptor signaling pathway	30	4	3.70E-07
phosphatidylinositol-mediated signaling	53	3	4.40E-07
MyD88-independent toll-like receptor signaling pathway	31	4	2.33E-06
mitotic cell cycle	92	1	2.71E-06
nervous system development	121	3	1.36E-05
post-translational protein modification	51	1	1.79E-05
cell death	211	2	2.14E-05
fibroblast growth factor receptor signaling pathway	58	2	2.45E-05
cytoskeletal protein binding	197	3	3.89E-05
macromolecular complex assembly	198	2	4.27E-05
nucleobase-containing compound catabolic process	186	1	0.00011
transcription initiation from RNA polymerase II promoter	67	2	0.00013
toll-like receptor 3 signaling pathway	30	4	0.00015
toll-like receptor 10 signaling pathway	25	3	0.00019
toll-like receptor 4 signaling pathway	34	3	0.00034
cellular protein metabolic process	100	1	0.00034
positive regulation of transcription, DNA-templated	243	2	0.00055
toll-like receptor TLR1:TLR2 signaling pathway	25	3	0.00059
toll-like receptor TLR6:TLR2 signaling pathway	25	3	0.00059
transcription from RNA polymerase II promoter	172	2	0.001
toll-like receptor 9 signaling pathway	27	3	0.00183
toll-like receptor 5 signaling pathway	25	3	0.00186
DNA metabolic process	167	1	0.00282
membrane organization	127	1	0.005

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