

Supplementary Information

Method

CLEAR-CLIP. Mouse keratinocytes of the designated genotype were maintained in E-low calcium medium. Inducible cells were treated with 3 ug/ml final concentration doxycycline for 24 hours before performing CLEAR-CLIP. One 15cm dish of confluent cells was used per sample. Cells were washed once with cold PBS. 10mls of cold PBS was then added and cells were irradiated with 300mJ/cm² UVC (254nm wavelength). Cells were then scraped from the plates in cold PBS and pelleted by centrifugation at 1,000g for 2 minutes. Pellets were frozen at -80°C until needed. Cells were then lysed on ice with occasional vortexing in 1ml of lysis buffer (50mM Tris-HCl pH 7.4, 100mM NaCl, 1mM MgCl₂, 0.1 mM CaCl₂, 1% NP-40, 0.5% Sodium Deoxycholate, 0.1% SDS) containing 1X protease inhibitors (Roche #88665) and RNaseOUT (Invitrogen #10777019) at 4ul/ml final concentration. Next, TurboDNase (Invitrogen #AM2238, 10U), RNase A (0.13ug) and RNase T1 (0.13U) were added and samples were incubated at 37°C for 5 minutes with occasional mixing. Samples were immediately placed on ice and then centrifuged at 16,160g at 4°C for 20 minutes to clear lysate. 25ul of Protein-G Dynabeads (Invitrogen #10004D) were used per IP. Dynabeads were pre-washed with lysis buffer and pre-incubated with 3ul of Wako Anti-Mouse-Ago2 (2D4) antibody. The dynabead/antibody mixture was added to the lysate and rocked for 2 hours at 4°C. All steps after the IP were done on bead until samples were loaded into the polyacrylamide gel. Beads were captured on a magnetic stand and the supernatant removed, then washed 3 times with cold High Salt Clip Wash Buffer (50mM Tris-HCl pH 7.4, 1M NaCl, 1mM EDTA, 1% NP-40, 0.5% sodium deoxycholate, 0.1% SDS) for 3 minutes with rocking. Samples were then washed 2 times with PNK wash buffer (20mM Tris-HCl pH 7.4, 10mM MgCl₂, 0.2% Tween-20). Samples were then phosphorylated at 37°C for 20 minutes in 50ul of PNK mixture: 41.8ul H₂O, 5 ul 10X PNK buffer (NEB), 1 ul RNaseOUT, 1.67 ul ATP (30 mM), 0.5 ul T4 PNK - 3' phosphatase minus (NEB M0236L). Samples were then washed 3 times on a magnetic rack with PNK wash buffer. miRNA-mRNA

ligation was then carried out overnight at room temperature in 100ul of mixture: 49.25 ul H₂O, 30 ul 50% PEG-8000 (NEB #B1004) 10 ul 10X T4 RNA ligation buffer (NEB), 2.5 ul RNaseOUT, 1 ul ATP (100mM), 1 ul BSA (10 mg/ml), 6.25 ul T4 RNA ligase 1 (10U/ul – NEB M0204). Next morning, an additional 2.5 ul T4 RNA ligase 1 (10U/ul) and 1 ul ATP (100mM) were added and ligation was continued for another 5 hours. Samples were then washed 2 times with lysis buffer, once with PNK/EDTA/EGTA (50 mM Tris pH 7.4, 10 mM EDTA, 10 mM EGTA, 0.5% Igepal) and twice more with PNK wash buffer. Next, samples were treated with phosphatase at 37°C for 20 minutes with 50ul of mix: 41ul H₂O, 5ul 10X FastAP buffer, 3ul FastAP enzyme (Thermo Fisher #EF0651) and 1ul RNaseOUT. Samples were then washed two times with PNK wash buffer. Next, 3' adapter ligation was performed on beads overnight in 40 ul of mixture: 17ul H₂O, 4ul 10X T4 RNA ligation buffer (NEB), 1ul of 3'linker (5'-Adenylated & 3' blocked - custom ordered from IDT), 16ul 50% PEG-8000, 1 ul RNaseOUT and 1ul T4 RNA ligase 2 truncated K227Q (NEB M0351). Samples were then washed twice with PNK buffer. Next, samples were then radiolabeled on bead with 50ul of the following mix: 5 ul 10X PNK buffer (NEB), 1 ul RNaseOUT, 1.5 ul γ -p³²-ATP (15 μ Ci), 1 ul PNK enzyme (NEB M0201) and 41.5 ul H₂O. Radiolabeling was carried out for 5 minutes at 37°C, after which another 2 ul of cold ATP (10mM) was added and the samples were then incubated for another 5 minutes at 37°C. Samples were then washed three times with PNK buffer, and then re-suspended in 25 ul of 1.2X LDS NuPAGE Loading buffer (Thermo Fisher #NP0007) with 60 mM DTT added. Samples were then heated to 70°C for 10 minutes with occasional agitation and supernatant was separated from beads on a magnetic stand. Samples were loaded on an 8% Bis-Tris gel and run at 200V for 2 hours on ice. Protein-RNA complexes were then transferred to a nitrocellulose membrane at 90V for 90min. The membrane was washed with PBS and exposed to a phosphoscreen for 1 hour at -20°C. Fragments corresponding to the Argonaute complex with the miRNA & mRNA (~110 kDa to 160 kDa) were then excised and RNA was isolated by following the protocol published for irClip (Zarnegar et al. 2016): 15 ul of Proteinase K (Thermo

scientific EO0491) at 20 mg/ml was added to 285 ul of Proteinase K/SDS buffer (100 mM Tris-HCl pH 7.5, 50 mM NaCl, 1 mM EDTA, 0.2% SDS). This solution was heated to 37°C for 20 minutes to inactivate any RNases, added to nitrocellulose membrane fragments and incubated at 50°C for 1 hour. Samples were briefly centrifuged and then 375 ul of saturated phenol/choloform/isoamyl alcohol (25:24:1) was added and incubated for 10 minutes at 37°C. Samples were then centrifuged at 16,000g at room temperature for 3 minutes, the aqueous layer was removed to a new tube and precipitated overnight at -20°C with 2 ul Glycoblue (ThermoFisher #AM9516) and 900 ul of 100% ethanol. RNA was pelleted by centrifugation at 16,160g at 4°C for 20 minutes and the supernatant removed. Pellet was washed with 70% ethanol and left to air dry at room temperature for 5 minutes. Next, 5' adapters were ligated by adding 8ul of the following mix to the pellet and thoroughly resuspending: 2 ul 50% PEG-8000, 1ul 10X NEB RNA ligation buffer, 1 ul 10mM ATP, 4 ul H₂O. Samples were then heated briefly to 95°C, placed on ice and additional components were added: 0.5 ul RNaseOUT, 1 ul T4 RNA ligase 1 (10U/ul – NEB M0204), 0.5 ul 100 uM 5' RNA linker (Blocked at 5' end & NNNN at 3' end for bias reduction and barcoding). Ligation was carried out at 37°C for 4 hours with rocking. RT-PCR was then carried out in ligation buffer by adding 8.5 ul of the following mix to the sample: 4 ul 5X first-strand buffer (Invitrogen), 1.5 ul 100mM DTT, 2ul 1 uM RT primer, 1 ul 10mM dNTPs. Samples were heated to 65°C for 5 minutes, transferred to a PCR tube and then enzymes were added: 1 ul Superscript III (Thermo Fisher #18080093) and 0.5 ul RNaseOUT. RT reaction was then performed in a thermocycler: 50°C for 1 hour, 85°C for 5 minutes, and then hold at 4°C. Libraries were then amplified from the cDNA by PCR taking aliquots after cycles 12, 17 and 22. PCR mix: 18.8 ul H₂O, 8 ul 5X HF buffer (NEB), 1 ul 25 uM library 1st round forward primer, 1 ul 25 uM RT primer, 0.8 ul 10 mM dNTPs, 0.4 ul Phusion polymerase (NEB M0530) and 10 ul cDNA. Cycling parameters: Initial denaturation at 98°C for 30 seconds and then amplification cycles at 98°C for 15 seconds, 56°C for 30 seconds and then 72°C for 20 seconds. PCR products were run on a 9% acrylamide gel and then stained with SYBR gold

(ThermoFisher #211494) at 1:10,000 for 10 minutes. The area corresponding to approximately 73 to 150 base pairs was excised from the lowest cycles condition that showed a product. Gel pieces were then frozen at -80°C for one hour and centrifuged through a hole in the tube made with a 20G needle to break up the gel. 350 ul HSCB buffer (25 mM Tris-HCl pH 7.5, 400 mM NaCl, 0.1% SDS) was added and samples were then rocked overnight at 4°C. The next day the gel slurry was transferred to a 0.22 um filter tube and spun at 16,000g for 20 minutes at room temperature. Samples were then precipitated overnight at -20°C in the presence of 1 ml 100% ethanol and 2ul Glycoblue. The next day samples were centrifuged at 16,160g at 4°C for 20 minutes. The pellet was washed with 70% ethanol and then air dried for 5 minutes. The pellet was then resuspended in 20 ul of H₂O. Next, high throughput sequencing barcodes were added by PCR using the following mix: 10 ul previous PCR product, 3.84 ul H₂O, 4 ul 5X HF buffer, 0.66 ul 10mM dNTPs, 0.5 ul 25 uM Illumina Index Primer, 0.5 ul 25 uM Illumina RP1 primer and 0.5 ul Phusion. Cycling conditions: Initial Denaturation at 98°C for 30 seconds, 2 cycles of: 98°C for 15 seconds, 50°C for 20 seconds, 72°C for 45 seconds and then 4 cycles of: 98°C for 15 seconds and 72°C for 50 seconds and then a final extension at 72°C for 3 minutes. PCR products were then run on a 9% acrylamide gel and stained with SYBR gold as above. Products corresponding to sizes approximately 144-200 base pairs were excised and isolated from the gel as above. Libraries were mixed in equal amounts and sequenced on an Illumina HiSeq 4000 by the Microarray and Genomics Core at the University of Colorado Anschutz Medical Campus. Primers and adapters used for CLEAR-CLIP were published previously(17).

Supplemental Figure Legend

Figure S1. Characterization of CLEAR-CLIP results. A, Sequence diagram of murine members of the miR-200 family showing the two related seed sequences and conservation in the 3' end. B, qPCR validation of RNA used for RNA-seq showing miRNA levels after miR-200b

cluster induction. Shown as the average of biological triplicates +/- the standard deviation. C, qPCR validation of RNA used for RNA-seq showing miR-205 level after miR-205 induction. Shown as the average of biological triplicates +/- the standard deviation. D, Log2 fold change in gene expression following miR-200b cluster induction of genes found only in CLEAR-CLIP, only in HITS-CLIP or found in both. Only CLEAR-CLIP genes with a seed (6mer or better) were used since HITS-CLIP requires a seed for determining targets. E, Log2 fold change in gene expression upon miR-205 induction of genes found only in CLEAR-CLIP (with a seed), only in HITS-CLIP or found in both. F, Log2 fold change in gene expression following miR-200b cluster induction of genes that had a CLEAR-CLIP area in only one gene area (3'UTR, 5'UTR, CDS or Intron). Panels D, E & F: Number of genes are shown in parenthesis for each group and p-values were calculated using the Kolmogorov–Smirnov test. G, miR-200 high confidence areas were annotated to the genome and searched for motifs (6mer, 7merA1, 7merM8 and 8mer). The percent of motifs observed is shown for each annotation category as a stacked bar graph. H, Overlap of miR-200 members within individual areas is shown and whether the overlap was within or across seed type families. I, High confidence areas calculated for each miR-200 member individually (as in figure 1H) were searched for their cognate motif (6mer, 7merA1, 7merM8 and 8mer). The percentage of areas with each motif is shown for each miR-200 member (non-motif areas were excluded). J, Full table of miR-200 GO term clustering is shown, including GO categories that were only observed for one miR-200 family member.

Figure S2. Characterization of CLEAR-CLIP by gene expression level and highly targeted genes without motifs.

A, miR-200 high confidence areas that were found only in control samples, only in inducible samples or in both were searched for motifs - 6mers, 7mers (7merM8 or 7merA1) and 8mers. The percent of areas with each motif is shown as a stacked bar graph for each category. B, The

basemean from our RNA-seq is shown as a violin plot for genes with miR-200 high confidence areas found only in control samples, only in inducible samples or in both samples. P-values were calculated using the Kolmogorov–Smirnov test. C, Log₂ gene expression levels are shown for genes with CLEAR-CLIP reads from miRNAs other than miR-200s that were found to be derepressed or not upon induction of the miR-200b cluster. D, The log₂ number of CLEAR-CLIP reads is shown for genes with CLEAR-CLIP reads from miRNAs other than miR-200s that were found to be derepressed or not upon induction of the miR-200b cluster. P-values for panels C & D were calculated using an unpaired two-sided t-test. E, 3'UTR areas are shown as examples of genes highly targeted by miR-200s that do not have a miR-200 motif within CLEAR-CLIP areas and that are not repressed upon induction of miR-200s. All CLEAR-CLIP reads are shown for each gene on the top row. miR-200 specific CLEAR-CLIP reads are then shown in descending order: Control, miR-200 DKO and miR-200 induced libraries. Scales for each track are shown in the upper left of each box. miR-200 motifs (if present) are shown on the bottom with an arrow.

Figure S3. Characterization of the miR-205 motif and targeted ncRNAs. A, The top motif found by HOMER is shown for miR-205 CLEAR-CLIP areas that did not have a 6mer or better canonical motif. The reverse complement of miR-205 is shown below the motif with the seed underlined. B, Examples of non-coding RNAs that were found to be targeted by miR-200s are shown for control, miR-200 DKO and miR-200 Tg samples. Fold change data upon induction of the miR-200b cluster is also shown below for important non-coding RNAs. C, The distance from each miR-200 CLEAR-CLIP site to the 3' end of non-coding RNAs was calculated and shown here as a histogram for non-coding RNAs that were found to be repressed (>0.1 Log₂ fold change) upon miR-200b cluster induction (effective) or not (ineffective). The x axis has been clipped at 20,000 for clarity.

Figure S4. Gene repression by the number of CLEAR-CLIP areas per gene and gene expression of areas found by CLEAR-CLIP or TargetScan. A, Log2 fold change in gene expression levels upon induction of the miR-200b cluster are shown for genes with 1, 2, 3 or 4+ miR-200 CLEAR-CLIP areas. B, Log2 fold change in gene expression levels upon induction of the miR-200b cluster are shown for genes with 1, 2 or 3+ miR-200 CLEAR-CLIP areas with a miR-200 seed. C, Log2 fold change in gene expression levels upon induction of miR-205 are shown for genes with 1, 2 or 3+ miR-205 CLEAR-CLIP areas. Panels A, B & C: The number of genes in each group are shown in parenthesis and p-values were calculated using the Kolmogorov–Smirnov test. D, Log2 gene expression levels as measured by RNA-seq are shown for miR-200 and miR-205 targets that were found only in CLEAR-CLIP, only by TargetScan or found in both.

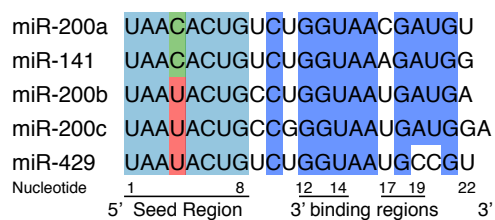
Figure S5. Global miRNA targeting analysis. Hierarchical clustering of top is shown for miRNAs based on their CLEAR-CLIP gene targets. Blue indicates that a gene was targeted by a miRNA and white indicates no targeting.

Table S1. List of samples used for CLEAR-CLIP. Table contains the sample type, experiment, the number of sequencing reads and number of CLEAR-CLIP reads.

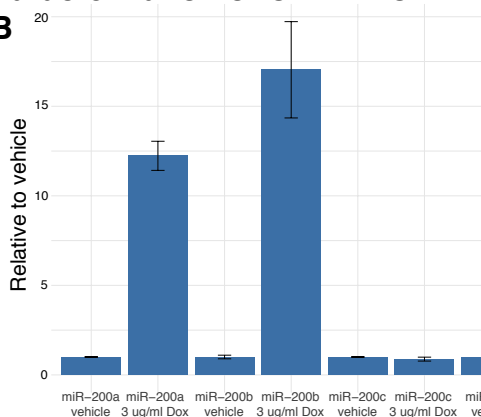
Table S2. Full table showing GO term results for miRNAs that are heavily targeted. The table shows the GO term, the overlap, significance and the genes within the GO term.

Supplemental figure 1. Further characterization of CLEAR-CLIP results

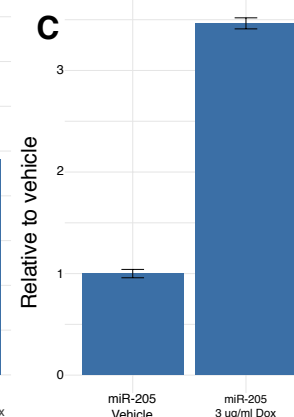
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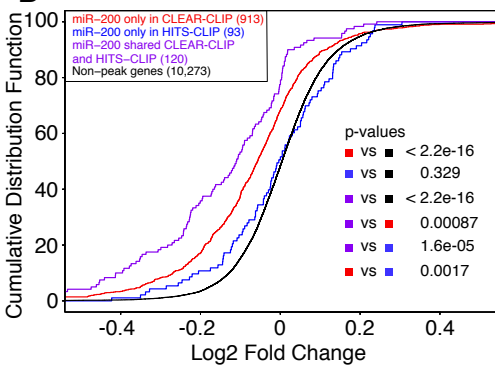
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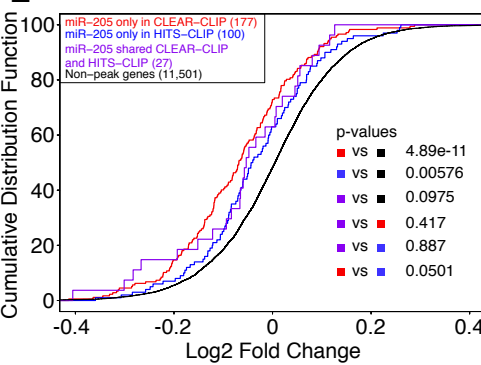
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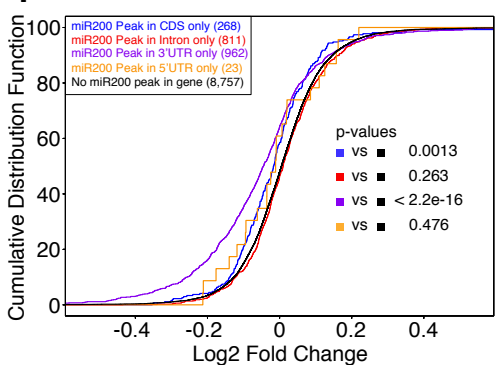
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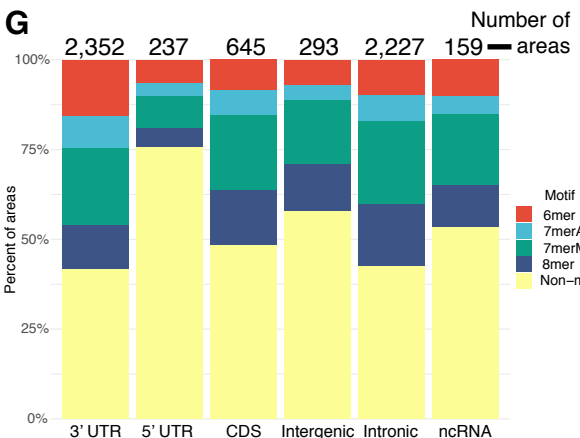
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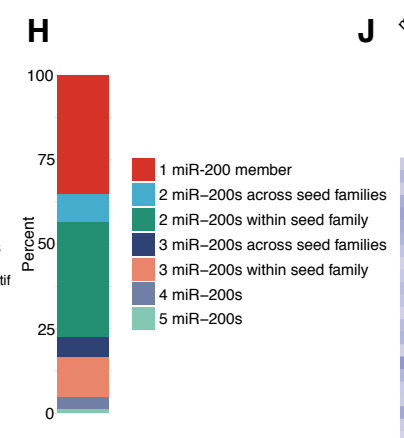
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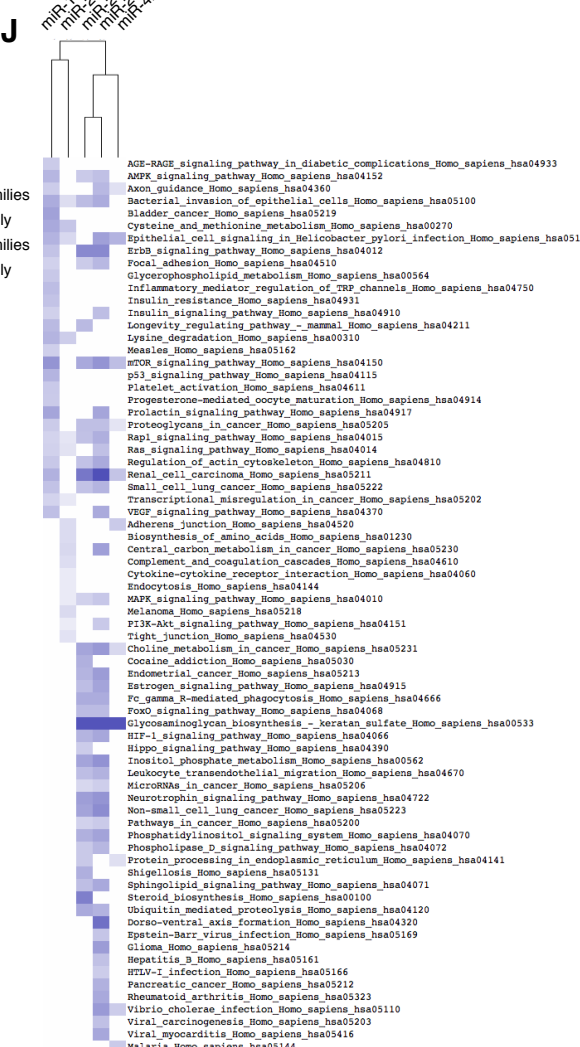
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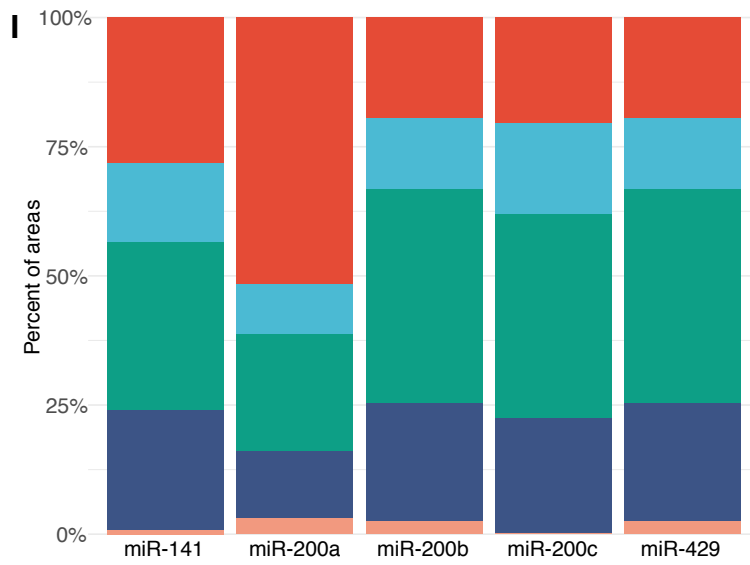
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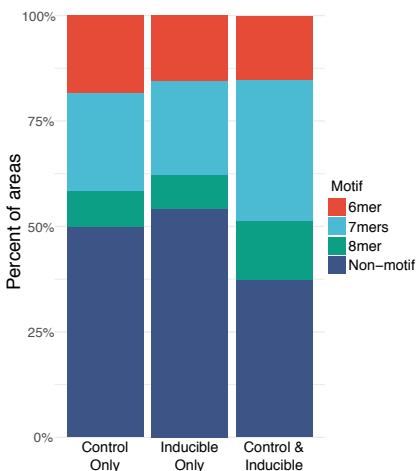
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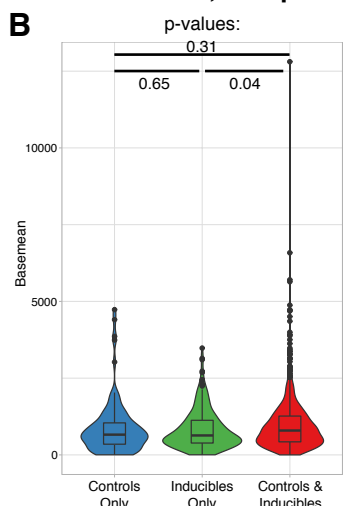
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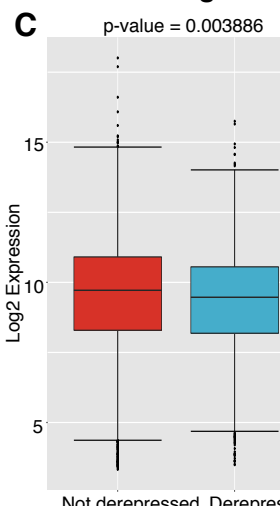
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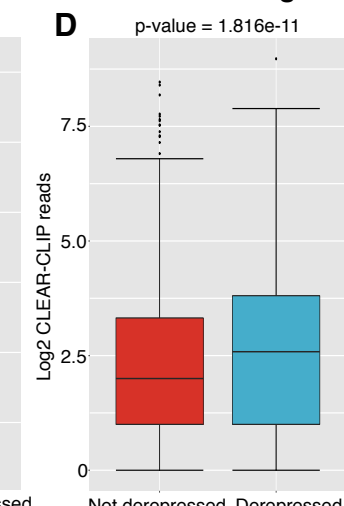
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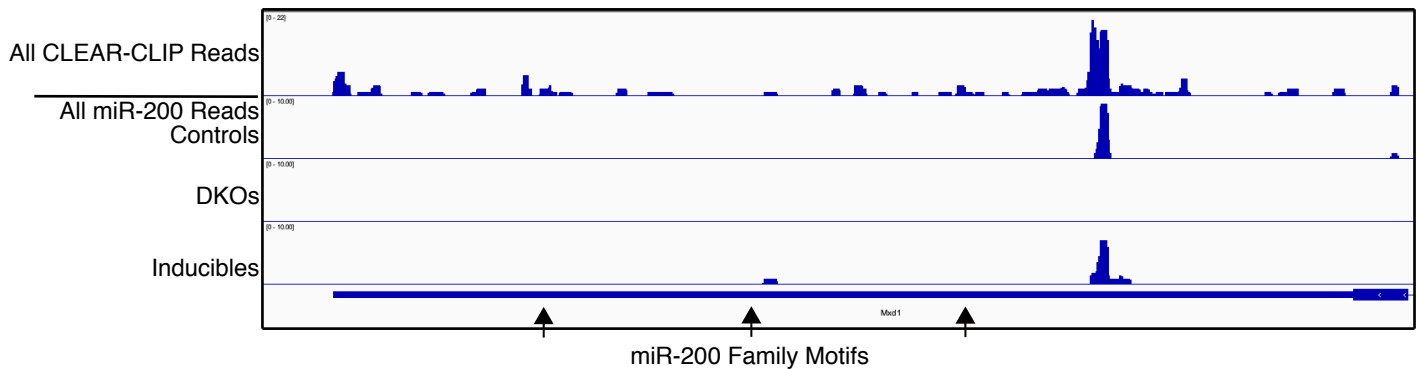
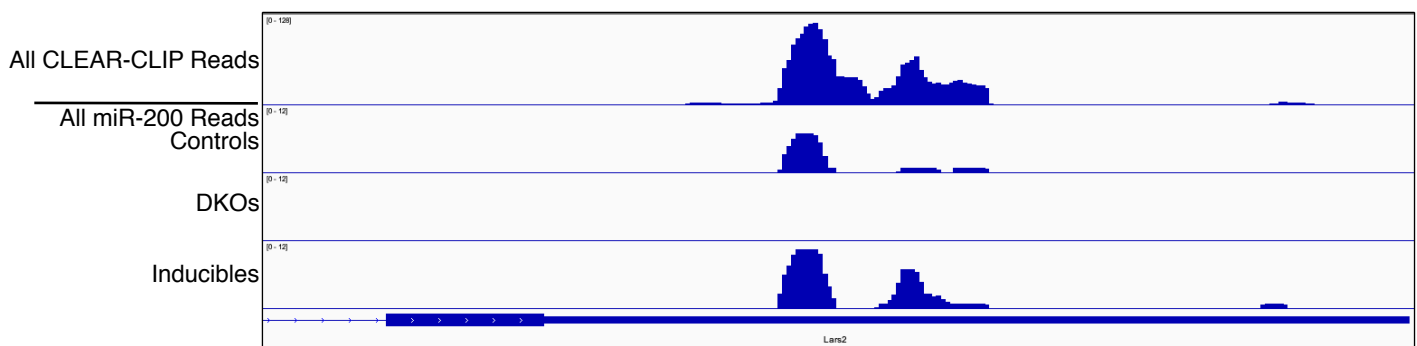
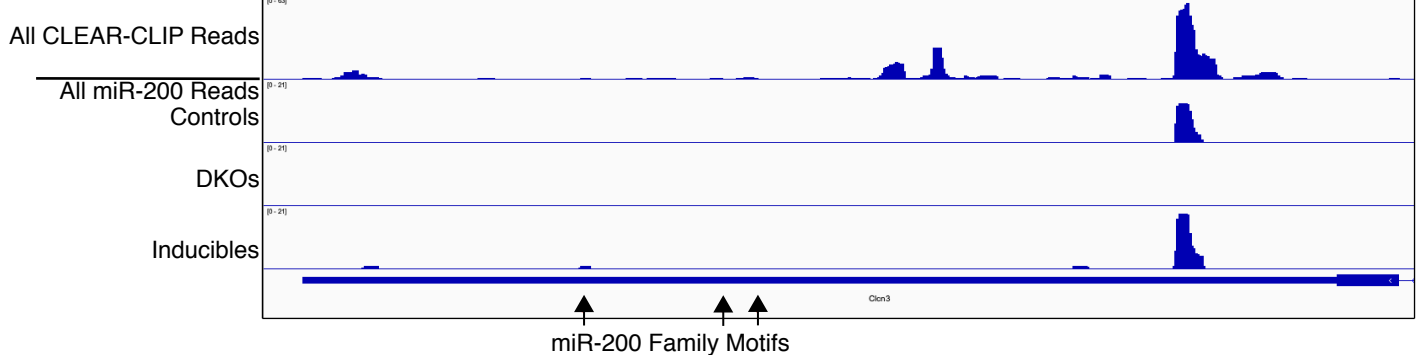
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D




E



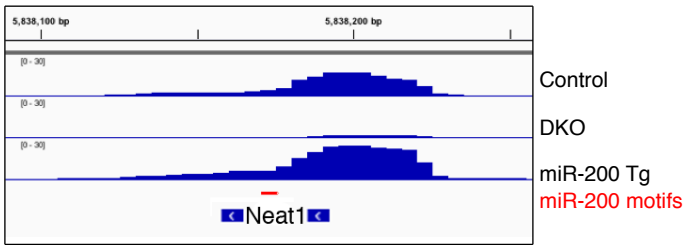
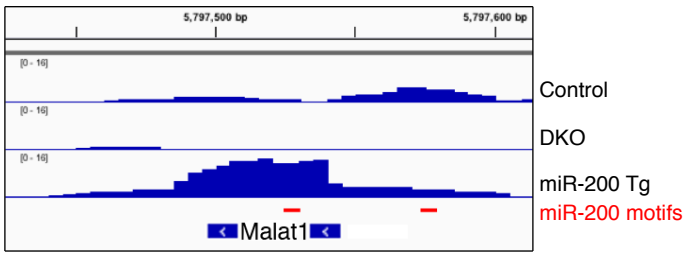
Supplemental figure 3. Further miR-205 motif characterization and examples of targeted ncRNAs

A

Motif	P-value	log P-value	% of Targets	% of Background
	1e-415	-9.557e+02	21.79%	3.45%

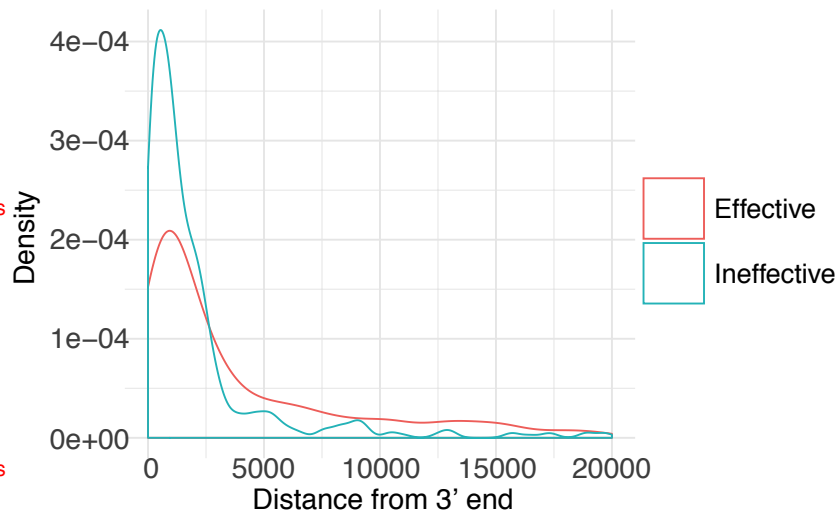
CAGACUCCGGUGGAAUGAAGGA miR-205 Reverse Complement

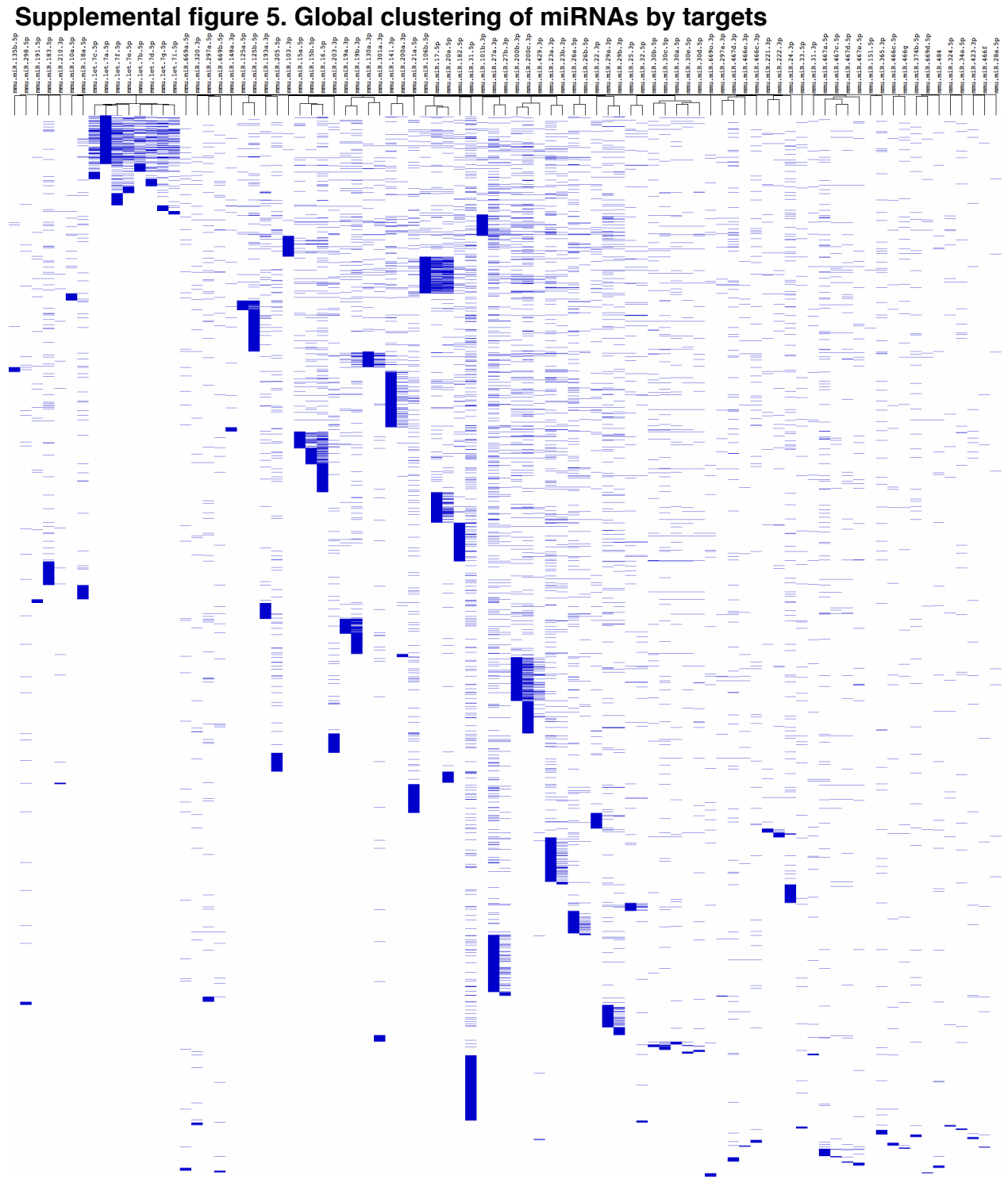
B



Log2 Fold Change	
Malat1	-0.24
Neat1	-0.12
Tug1	-0.04
Gas5	-0.05
Firre	-0.03

C





Supplementary Table 1. Samples used for CLEAR-CLIP

Sample	Type	Experiment	Total sequencing reads	Number of unique CLEAR-CLIP reads
K14-Cre keratinocytes (Control)	Control 1	Group 1	28,951,235	22,394
K14-Cre keratinocytes (Control)	Control 2	Group 1	69,562,643	19,308
K14-Cre keratinocytes (Control)	Control 3	Group 1	58,490,875	36,400
K14-Cre keratinocytes (Control)	Control 4	Group 1	36,321,840	37,567
K14-Cre keratinocytes (Control)	Control 5	Group 1	32,850,327	33,594
K14-Cre keratinocytes (Control)	Control 6	Group 1	47,737,230	33,483
miR-200 DKO keratinocytes	miR-200 DKO 1	Group 1	36,217,636	23,204
miR-200 DKO keratinocytes	miR-200 DKO 2	Group 1	19,825,464	16,620
miR-200 DKO keratinocytes	miR-200 DKO 3	Group 1	26,394,791	11,596
miR-200b cluster inducible keratinocytes (Un-induced)	Control 1	Group 2	39,414,925	57,279
miR-200b cluster inducible keratinocytes (Un-induced)	Control 2	Group 2	41,967,583	143,874
miR-200b cluster inducible keratinocytes (Un-induced)	Control 3	Group 2	35,724,788	127,034
miR-200b cluster inducible keratinocytes	Inducible 1	Group 2	41,895,809	147,001
miR-200b cluster inducible keratinocytes	Inducible 2	Group 2	69,418,670	150,488
miR-200b cluster inducible keratinocytes	Inducible 3	Group 2	24,074,912	152,936
miR-200 DKO keratinocytes	miR-200 DKO 1	Group 2	51,932,214	79,810
miR-200 DKO keratinocytes	miR-200 DKO 2	Group 2	27,092,199	103,480
miR-200 DKO keratinocytes	miR-200 DKO 3	Group 2	30,629,688	33,951
		Total	718,502,829	1,230,019

Supplementary Table 2. GO terms associated with miRNA targets

Term	Overlap	P-value	Adjusted P-value	Old P-value	Old Adjusted P-value	Z-score	Combined Score	Genes
Proteoglycans in cancer_Homo sapiens_hsa05205	54/203	2.234E-17	5.51799E-15	5.16123E-11	1.27482E-08	-2.013336866	77.19163974	ITGB1;CDKN1A;CBLB;PIK3CB;ACTB;IGF1R;PPP1CB;CCND1;CTSL;PLAU;MYC;ITGAV;ARHGFE12;PPP1R12A;PDPK1;GAB1;PLAUR;RRAS2;FRS2;HSPG2;TIAM1;CTNNB1;PIK3CA;ITGA5;EZR;MET;CD44;HBEFG;DDX5;SDCA4;ROCK2;SRC;PIK3R1;IQGAP1;HIF1A;THBS1;EGFR;CDC42;NRAS;MAPK1;PLCG1;SMAD2;CAV2;CAV1;FZD6;RDX;WNT7A;MSN;BRAF;VEGFA;RPS6KB1;MDM2;SDC1;CTNNB1
Focal adhesion_Homo sapiens_hsa04510	47/202	5.89789E-13	4.86156E-11	3.62364E-08	2.98346E-06	-1.896682124	53.41376404	ITGB1;GSK3B;ROCK2;SRC;LAMA3;PTEN;XIAP;LAMC2;PIK3R1;PIK3CB;LAMC1;THBS1;ACTB;EGFR;CRKL;IGF1R;RAP1B;PPP1CB;CDC42;CCND3;MAPK8;CCND2;CCND1;CAPN2;PAK6;MAPK1;ITGAV;ITGB6;PAK2;JUN;PPP1R12A;CAV2;ITGA3;PDPK1;ACTN1;CAV1;BRAF;VEGFA;COL4A2;PIK3CA;COL4A1;CTNNB1;ITGA6;ITGA5;CRK;MET;VCL
Adherens junction_Homo sapiens_hsa04520	27/74	5.90472E-13	4.86156E-11	2.10495E-08	2.59962E-06	-1.80359470	50.78535563	SRC;CTNNND1;PTPRJ;IQGAP1;WASL;NLK;MLLT4;PTPRF;EGFR;ACTB;IGF1R;CDC42;CDH1;MAPK1;SMAD2;ACTN1;INSR;TGFBFR1;TGFBFR2;TJP1;SNAI2;CTNNB1;PVRL4;PVRL2;MET;PVRL1;VCL
FoxO signaling pathway_Homo sapiens_hsa04068	36/133	2.71921E-11	1.34329E-10	6.57695E-08	3.57372E-06	-1.724599199	45.92724875	CDKN1A;CDKN1B;FOXG1;SETD7;PTEN;PIK3R1;PIK3CB;FOXO3;NLK;STK4;EGFR;IGF1R;NRAS;MAPK8;BCL2L1;CCND2;CCND1;MAPK1;SMAD2;PLK3;HOMER1;CHUK;PDPK1;INSR;PLK2;BRAF;FBXO32;TGFBFR1;TGFBFR2;PIK3CA;BCL6;CCNG2;CDK2;MDM2;ATM;SGK3
Hippo signaling pathway_Homo sapiens_hsa04390	39/153	2.6664E-12	1.34329E-10	7.23425E-08	3.57372E-06	-1.664311085	44.3543769	YAP1;YWHAE;GSK3B;BMPR2;YWHAB;SERPINE1;PPP2R2A;ACTB;CTGF;PPP1CB;PPP2CB;PARD6B;CCND3;CCND2;CCND1;CDH1;MYC;TEAD1;YWHAG;SMAD2;TEAD4;YWTR1;PRKCI;FBXW11;FZD6;WNT7A;CSNK1D;YWHAZ;TGFBFR1;SMAD7;TGFBFR2;MOB1B;LATS1;DLG1;LATS2;SNAI2;CTNNB1;AJUBA;BMPR1A
Regulation of actin cytoskeleton_Homo sapiens_hsa04810	46/214	1.97943E-11	6.98455E-10	3.74286E-07	1.15561E-05	-1.772519354	43.68485414	ITGB1;NCKAP1;ROCK2;SRC;ARPC1A;PIK3R1;IQGAP1;WASL;PIK3CB;ACTB;EGFR;CRKL;PPP1CB;CDC42;NRAS;FLN2;PAK6;MAPK1;PIP4K2B;ITGAV;ITGB6;PAK2;ARHGFE12;PPP1R12A;ITGA3;ACTN1;LIMK1;NRAS;RRAS2;MSN;BRAF;GNG12;SH2;ENAH;TIAM1;DIAPH2;PIKFYVE;PIK3CA;MYH9;ITGA6;ITGA5;PFN1;EZR;CRK;VCL;FGFR2
Protein processing in endoplasmic reticulum_Homo sapiens_hsa04141	40/169	1.75587E-11	6.98455E-10	2.65583E-07	9.37173E-06	-1.694934096	41.97583829	TRAM1;SEC23A;RPN2;PRKCSH;SEL1L;CUL1;DERL1;HSP90B1;UBE2J1;ERO1L;SEC61A2;ATXN3;MAPK8;GANAB;HSPH1;MAN1A2;LMAN2;CAPN2;SSR1;SEC63;PDIA3;EDEM3;HSPA8;SEC24A;HSPA5;EDEM1;SSR2;SSR3;SYVN1;MOGS;YOD1;UBE2G1;MARCKB;PDIAB;CKAP4;DNAJC5;CANX;ERP29;YHOU1;NFE2L2
p53 signaling pathway_Homo sapiens_hsa04115	24/69	3.69495E-11	1.14082E-09	2.65595E-07	9.37173E-06	-1.529528901	36.74153062	CDKN1A;RRM2;APAF1;E2F4;IGFBP3;SERPINE1;PTEN;TNFRSF10B;PPM1D;THBS1;SERPINB5;CCND3;CDD6;CCND2;CCND1;ZMAT3;CCNG2;PERP;CCNG1;CDK2;MDM2;PMAIP1;ATM;MDM4
Pathways in cancer_Homo sapiens_hsa05200	67/397	7.07619E-11	1.94202E-09	2.28425E-06	4.86568E-05	-1.896231922	44.31816407	ITGB1;GSK3B;CDKN1A;CDKN1B;PTEN;SLC2A1;CBLB;LAMC2;PIK3CB;LAMC1;CRKL;IGF1R;CCND1;CDH1;MYC;ITGAV;ARHGFE12;CHUK;ITGA3;FOS;TGFBFR1;RUNX1;TGFBFR2;COL4A2;PIK3CA;COL4A1;TRAF6;IKK;CRK;MET;ROCK2;LAMA3;GNAI3;PAR2;TGFA;XIAP;PIK3R1;PTGS2;STK4;HIF1A;ADCY6;EGFR;HSP90B1;CDC42;NRAS;MAPK8;E2F2;MAPK1;E2F3;PLCG1;SMAD2;JUN;EGLN3;JUP;FZD6;WNT7A;BRAF;GNG12;VEGFA;CDK6;LPA6;CDK2;CCDC6;MDM2;GNA3;CTNNB1;FGFR2
Bacterial invasion of epithelial cells_Homo sapiens_hsa05100	25/78	1.10566E-10	2.73098E-09	5.33366E-07	1.46371E-05	-1.510833424	34.63647268	ITGB1;SRC;ARPC1A;CLTC;CBLB;PIK3CB;PIK3R1;WASL;LACTB;CRKL;CDC42;CDH1;SEPT11;CAV2;CAV1;GAB1;SEPT2;CD2AP;PIK3CA;CTTN;CTNNB1;ITGA5;CRK;MET;VCL
ErbB signaling pathway_Homo sapiens_hsa04012	26/87	2.68955E-10	6.03927E-09	9.62207E-07	2.37665E-05	-1.60286839	35.32157063	GSK3B;CDKN1A;CDKN1B;SRC;TGFA;CBLB;PIK3CB;PIK3R1;EGFR;HSP90B1;IGF1R;NRAS;MAPK8;MYC;PAK6;ABL2;MAPK1;PLCG1;PAK2;JUN;GAB1;BRAF;EREG;PIK3CA;RPS6KB1;CRK;HBEFG
PI3K-Akt signaling pathway_Homo sapiens_hsa04151	59/341	3.59601E-10	7.40178E-09	4.87208E-06	8.0227E-05	-1.781845463	38.74806006	YWHAE;ITGB1;ATF2;GSK3B;CDKN1A;CDKN1B;YWHAB;PTEN;LAMC2;PPP2R2A;PIK3CB;LAMC1;IGF1R;CCND3;CCND2;CCND1;MYC;CREB3L2;ITGAV;ITGB6;YWHAG;CHUK;ITGA3;PDPK1;YWHAZ;CREB1;COL4A2;PIK3CA;COL4A1;DDIT4;SGK3;ITGA6;ITGA5;MET;EPHA2;JFNAR1;PHLPP2;LAMA3;LPA2;PIK3R1;EFNA5;FOXO3;THBS1;EGFR;HSP90B1;PPP2CB;NRAS;BCL2L1;MAPK1;MCL1;INSR;GNG12;VEGFA;CDK6;RPS6KB1;LPA6;CDK2;MDM2;FGFR2
Small cell lung cancer_Homo sapiens_hsa05222	25/86	1.12994E-09	2.14689E-08	2.36389E-06	4.86568E-05	-1.51033928	31.11465026	ITGB1;CDKN1B;LAMA3;PTEN;XIAP;LAMC2;PIK3CB;LAMC1;PIK3R1;PTGS2;CCND1;MYC;E2F2;E2F3;ITGAV;APAF1;CHUK;ITGA3;CDK6;PIK3CA;COL4A2;COL4A1;TRAF6;CDK2;ITGA6
Prostate cancer_Homo sapiens_hsa05215	25/89	2.49022E-09	4.28831E-08	3.95279E-06	7.5103E-05	-1.590800867	31.51519173	GSK3B;CDKN1A;CDKN1B;PTEN;TGFA;PIK3CB;PIK3R1;EGFR;HSP90B1;IGF1R;NRAS;CCND1;CREB3L2;E2F2;MAPK1;E2F3;CHUK;PDPK1;BRAF;CREB1;PIK3CA;CDK2;MDM2;CTNNB1;FGFR2
MicrRNAs in cancer_Homo sapiens_hsa05206	52/297	2.60423E-09	4.28831E-08	1.36979E-05	0.000211461	-1.570451519	31.0417446	CDKN1A;CDKN1B;BMPR2;PTEN;GLS;CRKL;CCND2;CCND1;PLAU;MYC;PIM1;TPM1;DNMT3A;KIF23;DICER1;SERPINB5;CDC25A;CDC25B;FOXO1;PIK3CA;DDIT4;FSCN1;ITGA5;EZR;CRK;MET;CD44;NOTCH2;NOTCH1;PTGS2;SLC7A1;THBS1;EGFR;NRAS;BCL2L1;IGFBP1;E2F2;HMBOX1;MAPK1;E2F3;PLCG1;MCL1;RDX;HMGA2;VEGFA;MARCKS;CDK6;CCNG1;MDM2;SPRY2;ATM;MDM4
Renal cell carcinoma_Homo sapiens_hsa05211	21/66	3.94345E-09	6.0877E-08	4.756E-06	8.0227E-05	-1.382324	26.74964095	JUN;EGLN3;GAB1;SLC2A1;TGFA;BRAF;PIK3CB;PIK3R1;HIF1A;VEGFA;CRKL;RAP1B;CDC42;FLCN;NRAS;PIK3CA;PAK6;MAPK1;PAK2;CRK;MET
Endocytosis_Homo sapiens_hsa04144	46/259	1.35428E-08	1.96769E-07	3.19314E-05	0.000415109	-1.568879463	28.42403297	RAB3C;TRFC;SRC;ARPC1A;CLTC;CBLB;ADRB2;WASL;RAB22A;EGFR;IGF1R;EEA1;CDC42;CYTH3;PARD6B;RAB11FIP1;KIF5B;EP515;LDLR;SNX5;SMAD2;ARFGEF1;HSPA8;PRKCI;PDCD6IP;STI1;CAV2;CAV1;ARAP2;VPS37A;VPS37B;IGF2R;TGFBFR1;TGFBFR2;EHDL;RAB10;ZFYVE16;NEED4;TRAF6;CAPZA2;CHMP4C;MDM2;MET;FGFR2;ARF6;SPG20
MAPK signaling pathway_Homo sapiens_hsa04010	45/255	2.37278E-08	3.25598E-07	4.46397E-05	0.000501182	-1.564972331	27.47562316	ATF2;ZAK;NLK;STK4;DUSP16;EGFR;CRKL;ELK4;RAP1B;CDC42;PPP3CA;RPS6KA3;NRAS;MAPK8;MYC;MNK2;MAPK1;PAK2;MAP3K2;MAP2K3;HSPA8;JUN;MAPK31;CHUK;DUSP1;RRAS2;BRAF;FOS;GNG12;DUSP8;TGFBFR1;DUSP7;CDC25B;TGFBFR2;IL1A;TAOK1;TRAF6;RASA1;MAPKAPK2;RASA2;NF1;RAPGEF2;TAB2;CRK;FGFR2
Chronic myeloid leukemia_Homo sapiens_hsa05220	21/73	2.93371E-08	3.81383E-07	1.72682E-05	0.000250896	-1.348210794	23.38392388	CDKN1A;CDKN1B;CHUK;BRAF;CBLB;PIK3CB;PIK3R1;TGFBFR1;RUNX1;TGFBFR2;CRKL;NRAS;CDK6;PIK3CA;CCND1;MYC;MDM2;E2F2;MAPK1;E2F3;CRK
TNF signaling pathway_Homo sapiens_hsa04668	26/110	6.08046E-08	7.50937E-07	3.42556E-05	0.000422984	-1.40386524	23.31312479	ATF2;TNFAIP3;CXCL1;NOD2;PIK3R1;PIK3CB;CXCL3;PTGS2;CXCL5;MAPK8;CREB3L2;MAPK1;JUNB;MAP2K3;EDN1;JUN;JAG1;CHUK;LIF;DAB2IP;CLAR;FOS;CREB1;PIK3CA;TAB3;TAB2
Bladder cancer_Homo sapiens_hsa05219	15/41	8.04703E-08	9.46484E-07	2.91535E-05	0.00040005	-0.891028564	14.55528805	CDKN1A;SRC;BRAF;THBS1;EGFR;VEGFA;NRAS;CCND1;CDH1;MYC;MDM2;E2F2;MAPK1;E2F3;HBEFG;ITGB1;CHUK;FBXW11;ROCK2;SRC;ARPC1A;NOD2;WASL;ACTB;CRKL;CDC42;MAPK8;CTTN;MAPK1;ITGA5;PFN1;CRK;VCL;CD44
Shigellosis_Homo sapiens_hsa05131	19/65	1.0021E-07	1.12508E-06	3.59622E-05	0.000422984	-0.984198069	15.86133438	ITGB1;SRC;CTNNND1;GNAI3;LPA2;PIK3R1;PIK3CB;EFNA5;MLLT4;THBS1;ADCY6;ACTB;EGFR;CRKL;IGF1R;RAP1B;CDC42;PARD6B;NRAS;CDH1;MAPK1;PLCG1;MAP2K3;PRKCI;INSR;BRAF;VEGFA;TIAM1;PIK3CA;ADORA2B;GNA3;RAPGEF2;CTNNB1;PFN1;CRK;MET;FGFR2;EPHA2
Rap1 signaling pathway_Homo sapiens_hsa04015	38/211	1.66939E-07	1.79278E-06	0.000121014	0.001153385	-1.408555998	21.98141249	ATF2;CDKN1A;DDX3X;CDKN1B;YWHAB;SRC;PTEN;PIK3R1;PIK3CB;NRAS;MAPK8;CCND1;MYC;CREB3L2;E2F2;MAPK1;E2F3;JUN;MAP3K1;APAF1;CHUK;FOS;HSPG2;YWHAZ;TGFBFR1;CREB1;CDK6;PIK3CA;CDK2;JFNAR1
Hepatitis B_Homo sapiens_hsa05161	30/146	1.74367E-07	1.79453E-06	8.45482E-05	0.000907974	-1.350119213	21.01069258	XIAP;PIK3R1;PIK3CB;ACTB;LMNB1;NRAS;MAPK8;BCL2L1;CTSL;CAPN2;PMAIP1;CASP2;MAPK1;CTSD;SPTAN1;CTSC;CTSB;MCL1;JUN;APAF1;CHUK;PDPK1;DAB2IP;TNFRSF10B;CLAR;FOS;PTPN13;PIK3CA;ATM
AGE-RAGE signaling pathway in diabetic complications_Homo sapiens_hsa04933	23/101	7.04872E-07	6.44827E-06	0.000155094	0.00141882	-1.31837144	18.67506123	SMAD2;EDN1;JUN;CDKN1B;SERPINE1;PIK3R1;PIK3CB;F3;TGFBFR1;TGFBFR2;VEGFA;CDC42;IL1A;THBD;NRAS;MAPK8;CCND1;PIK3CA;COL4A2;COL4A1;PIM1;MAPK1;PLCG1
Pancreatic cancer_Homo sapiens_hsa05212	18/66	6.80538E-07	6.44827E-06	0.000121409	0.001153385	-1.087114109	15.43743639	SMAD2;CHUK;TGFA;BRAF;PIK3CB;PIK3R1;TGFBFR1;EGFR;TGFBFR2;VEGFA;CDC42;MAPK8;CDK6;PIK3CA;CCND1;E2F2;MAPK1;E2F3
Axon guidance_Homo sapiens_hsa04360	26/127	1.21888E-06	1.07522E-05	0.000260526	0.002115869	-1.082876274	14.74615607	ITGB1;GSK3B;NRP1;SEMA3C;ROCK2;GNAI3;EFNA5;CDC42;PPP3CA;NRAS;ABLUM1;CFL2;PAK6;PLXNA1;MAPK1;PAK2;EPHA4;ARHGFE12;SEMA4D;SEMA4B;LIMK2;SEMA4C;RASA1;EPHA1;MET;EPHA2;PDPK1;TGFA;BRAF;PIK3CB;PIK3R1;FOXO3;STK4;EGFR;NRAS;CDK6;PIK3CA;CCND1;E2F2;MAPK1;E2F3;PLCG1
Non-small cell lung cancer_Homo sapiens_hsa05223	16/56	1.4266E-06	1.21507E-05	0.000183281	0.001616797	-0.911760645	12.27249335	ACVR1;SMAD2;TGIF1;BMPR2;FST;CUL1;ACVR1B;THBS1;TGFBFR1;ACVR2A;TGFBFR2;SMAD7;PPP2CB;ZFYVE16;RPS6KB1;SP1;MYC;MAPK1;E2F5;BMPR1A
TGF-beta signaling pathway_Homo sapiens_hsa04350	20/84	1.75931E-06	1.4485E-05	0.000249208	0.002115869	-0.995769726	13.19453293	DDX5;CDKN1A;CCNT2;CDKN1B;KMT2A;DOT1L;JMJD1C;IGF1R;ELK4;H0XA9;CCND2;PLAU;MYC;NFKBIZ;WHS1;JUP;H3F3B;FUS;IGFBP3;HMGA2;KLF3;PBX1;RUNX1;TGFBFR2;GOLPH3;SPINT1;BCL6;SP1;BMP2K;MDM2;ATM;MET
Transcriptional misregulation in cancer_Homo sapiens_hsa05202	32/180	2.05816E-06	1.63989E-05	0.000500675	0.003637259	-1.043074923	13.65771029	CDKN1A;PTEN;TGFA;BRAF;PIK3CB;PIK3R1;EGFR;IGF1R;NRAS;CDK6;PIK3CA;CCND1;MDM2;E2F2;MAPK1;E2F3;PLCG1
Glioma_Homo sapiens_hsa05214	17/65	2.61056E-06	1.98705E-05	0.000283674	0.002189605	-0.929807675	11.95355757	GSK3B;PDPK1;PTEN;BRAF;PIK3CB;PIK3R1;FOXO3;EGFR;NRAS;PIK3CA;CCND1;CDH1;MYC;CTNNB1;MAPK1
Endometrial cancer_Homo sapiens_hsa05213	15/52	2.65476E-06	1.98705E-05	0.000265554	0.002115869	-0.632105033	8.1156985849	GSK3B;BMPR2;RIF1;PIK3R1;PIK3CB;ACVR1B;IGF1R;NRAS;MYC;SMARCAD1;MAPK1;SKL1;ACVR1;SMAD2;ZFXH3;PCGF3;FZD6;LIF;WNT7A;KLF4;ACVR2A;REST;PIK3CA;CTNNB1;JL6ST;FGFR2;BMPR1A
Signaling pathways regulating pluripotency of stem cells_Homo sapiens_hsa04550	27/142	3.42522E-06	2.46384E-05	0.000553718	0.003907667	-1.005649004	12.65543484	GSK3B;BMPR2;RIF1;PIK3R1;PIK3CB;ACVR1B;IGF1R;NRAS;MYC;SMARCAD1;MAPK1;SKL1;ACVR1;SMAD2;ZFXH3;PCGF3;FZD6;LIF;WNT7A;KLF4;ACVR2A;REST;PIK3CA;CTNNB1;JL6ST;FGFR2;BMPR1A

Thyroid hormone signaling pathway_Homo sapiens_hsa04919	24/118	3.49127E-06	2.46384E-05	0.000482611	0.003612273	-0.949245146	11.9274983	PFKFB2;NOTCH2;MED1;GSK3B;NOTCH1;PDPK1;SRC;SLC2A1;ATP1B3;PIK3R1;PIK3CB;HIF1A;ACTB;ME D13;NRAS;MED13;CCND1;PIK3CA;MYC;MDM2;CTNNB1;MAPK1;ITGAV;PLCG1
HTLV-1 infection_Homo sapiens_hsa05166	40/258	4.27833E-06	2.93541E-05	0.001191918	0.007355539	-1.068700316	13.2112168	ATF2;NRP1;GSK3B;CDKN1A;SLC2A1;XIAP;PIK3R1;PIK3CB;ADCY6;ETS2;ELK4;PPP3CA;NRAS;CCND3;ZF P36;MAPK8;CCND2;CCND1;MYC;CDK27;E2F2;E2F3;MYBL1;SMAD2;JUN;MAP3K1;CHUK;FZD6;RRAS2; WNT7A;FOS;TGFBF1;TGFBF2;DLG1;CREB1;PIK3CA;CANX;TBP1;CTNNB1;ATM
Cell cycle_Homo sapiens_hsa04110	24/124	8.57441E-06	5.724E-05	0.000890643	0.005945647	-0.823124878	9.603174245	SMAD2;YWHAE;GSK3B;CDKN1A;CDKN1B;YWHAH;CUL1;YWHAZ;CDC25A;CDC25B;CCND3;WEE1;CCN D2;CDK6;CCND1;MYC;CDK27;CDK2;MDM2;E2F2;E2F3;ATM;E2F5;YWHAH
Melanoma_Homo sapiens_hsa05218	17/71	9.54266E-06	6.20273E-05	0.000675097	0.004631913	-0.698982624	8.080056076	CDKN1A;PTEN;BRAF;PIK3CB;PIK3R1;EGFR;IGF1R;NRAS;CDK6;PIK3CA;CCND1;CDH1;MDM2;E2F2;MA PK1;E2F3;MET
Viral carcinogenesis_Homo sapiens_hsa05203	33/205	1.29978E-05	8.23195E-05	0.001831958	0.010283946	-1.015692047	11.4272763	YWHAH;ATF2;CDKN1A;CDKN1B;DDX3X;YWHAH;SRC;UBE3A;CHD4;PIK3R1;PIK3CB;CDC42;NRAS;CCND 3;CCND2;CCND1;CREB3L2;PMAIP1;MAPK1;YWHAH;JUN;ACTN1;YWHAZ;DLG1;CREB1;CDK6;PIK3CA; MAPKAPK2;RASA2;CDK2;MDM2;TBP1;IL6ST
Neurotrophin signaling pathway_Homo sapiens_hsa04722	23/120	1.54871E-05	9.56329E-05	0.001267687	0.007455209	-0.849623447	9.410006902	YWHAH;GSK3B;JUN;MAP3K1;PDPK1;GAB1;FRS2;BRAF;PIK3R1;PIK3CB;FOXO3;CRKL;RAP1B;CDC42;R PS6KA3;NRAS;MAPK8;PIK3CA;TRAF6;MAPKAPK2;MAPK1;PLCG1;CRK
mTOR signaling pathway_Homo sapiens_hsa04150	15/60	1.81443E-05	0.000109309	0.00094126	0.006156317	-0.455271233	4.970264956	CAB39;PDPK1;PTEN;BRAF;PIK3CB;PIK3R1;HIF1A;VEGFA;RPS6KA3;PIK3CA;RPS6KB1;DDIT4;MAPK1;UL K1;RICTOR
ECM-receptor interaction_Homo sapiens_hsa04512	18/82	1.90777E-05	0.000112195	0.001133166	0.007176717	-0.466859551	5.073357179	ITGB1;SDC4;ITGA3;LAMA3;LAMC2;LAMC1;HSPG2;THBS1;COL4A2;COL4A1;DAG1;SDC1;ITGA6;ITGAV; ITGA5;ITGB6;AGRN;CD44
Tight junction_Homo sapiens_hsa04530	25/139	2.12046E-05	0.000121803	0.001737595	0.00998107	-0.697128336	7.50200094	ZAK;SRC;PTEN;GNAI3;PPP2R2A;F11R;CLDN1;MLLT4;ACTB;CDC42;PPP2CB;NRAS;PAR6B;SPTAN1;PR KC1;ACTN1;SHROOM2;RRAS2;ASH1;TJP1;CLDN4;CTTN;MYH9;CTNNB1;AMOTL1
Colorectal cancer_Homo sapiens_hsa05210	15/62	2.76556E-05	0.000155249	0.001257245	0.007455209	-0.310903293	3.263141886	SMAD2;GSK3B;JUN;BRAF;PIK3CB;FOS;PIK3R1;TGFBF1;TGFBF2;MAPK8;PIK3CA;CCND1;MYC;CTNNB 1;MAPK1
Ras signaling pathway_Homo sapiens_hsa04014	34/227	4.50103E-05	0.000241686	0.004412316	0.021796843	-0.844630491	8.453584851	RAB5C;PIK3R1;RASAL2;PIK3CB;EFNA5;STK4;MLLT4;EGFR;ETS2;JGFR1;RAP1B;CDC42;NRAS;MAPK8;P AK6;ABL2;MAPK1;PLCG1;PAK2;CHUK;INSR;GAB1;RRAS2;GNG12;VEGFA;TIAM1;PIK3CA;RASA1;RASA 2;NF1;MET;FGFR2;EPHA2;ARF6
HIF-1 signaling pathway_Homo sapiens_hsa04066	20/103	4.48285E-05	0.000241686	0.002248832	0.012343588	-0.659635777	6.604713046	EDN1;EGLN3;CDKN1A;CDKN1B;TFR3;INSR;SERPINE1;SLC2A1;PIK3R1;PIK3CB;HIF1A;EGFR;IGF1R;VE GFA;PIK3CA;RPS6KB1;MKNK2;HMOX1;MAPK1;PLCG1
Estrogen signaling pathway_Homo sapiens_hsa04915	19/99	8.12813E-05	0.000427159	0.003209835	0.016868709	-0.628222941	5.916348659	ATF2;HSP89A;JUN;SRC;GNAI3;PIK3R1;PIK3CB;FOS;EGFR;ADCY6;HSP90B1;NRAS;CREB1;PIK3CA;SP1;C REB3L2;GNAS;MAPK1;HBEFG
Epithelial cell signaling in Helicobacter pylori infection_Homo sapiens_hsa05120	15/68	8.7276E-05	0.000449108	0.002739822	0.014711654	-0.215159169	2.010971242	JUN;CHUK;SRC;ADAM10;CXCL1;F11R;EGFR;CDC42;TJP1;ADAM17;MAPK8;ATP6B1B2;PLCG1;MET;HB EGF
Salmonella infection_Homo sapiens_hsa05132	17/86	0.000129813	0.000654364	0.00398761	0.02028925	-0.295727655	2.646589389	JUN;ROCK2;ARPC1A;CXCL1;FOS;WASL;CXCL3;KLC1;ACTB;CDC42;TJP1;IL1A;DYNC1L1;MAPK8;MYH9; MAPK1;PFN1
Acute myeloid leukemia_Homo sapiens_hsa05221	13/57	0.000178223	0.000880423	0.004024993	0.02028925	-0.021571785	0.186217864	JUP;CHUK;BRAF;PIK3CB;PIK3R1;RUNX1;NRAS;PIK3CA;CCND1;RPS6KB1;MYC;PIM1;MAPK1
Lysosome_Homo sapiens_hsa04142	21/123	0.00020166	0.000976669	0.006620916	0.029733934	-0.518521977	4.412064675	CD164;ASAHI1;DUAA;CLTC;MGPR;GNS;JITAF;JGFR2;LAPTM4B;LAPTM4A;LAMP1;NPLC1;CTSL;AP1G1;LA MP2;PSAP;AP1S2;TPP1;CTSD;CTSC;CTSB
Arrhythmogenic right ventricular cardiomyopathy (ARVC)_Homo sapiens_hsa05412	15/74	0.000237755	0.001129336	0.005438866	0.02534717	-0.058784627	0.490514791	DSP;ITGB1;JUP;ITGA3;ACTN1;ACTB;GJA1;DAG1;CTNNB1;DSG2;ITGA6;ITGAV;ITGA5;ITGB6;DS2
Central carbon metabolism in cancer_Homo sapiens_hsa05230	14/67	0.000272531	0.001270099	0.005666994	0.025921249	-0.096084779	0.788640488	SLC2A1;PTEN;PIK3CB;PIK3R1;HIF1A;EGFR;GLS;SLC7A5;NRAS;PIK3CA;MYC;MAPK1;MET;FGFR2
Lysine degradation_Homo sapiens_hsa00310	12/52	0.000278771	0.001275118	0.005189081	0.024648136	0.410892387	-3.363203724	KMT2D;KMT2A;NSD1;KMT2C;DOT1L;SETD7;PLOC2;ASH1L;WHS1;COLGALT1;WHS1L1;SUVA420H1
Toxoplasmosis_Homo sapiens_hsa05145	20/118	0.000312631	0.001378926	0.008498571	0.035578764	-0.399308865	3.222617007	MAP2K3;ITGB1;HSP89A;CHUK;PDPK1;LAMA3;GNAI3;XIAP;LAMC2;PIK3R1;PIK3CB;LAMC1;MAPK8;PIK3 CA;TRAF6;PIF1;MAPK1;TAB2;ITGA6;LDLR
Leukocyte transendothelial migration_Homo sapiens_hsa04670	20/118	0.000312631	0.001378926	0.008498571	0.035578764	-0.341718889	2.757837861	ITGB1;ROCK2;ACTN1;CTNND1;GNAI3;MSN;PIK3R1;PIK3CB;F11R;CLDN1;MLLT4;ACTB;RAP1B;CDC42; CLDN4;PIK3CA;CTNNB1;PLCG1;EZR;VIL1
Choline metabolism in cancer_Homo sapiens_hsa05231	18/101	0.000326078	0.001413004	0.007903554	0.034248736	-0.356354411	2.860946693	JUN;CHKA;SLC44A1;SLC44A2;PDPK1;PIK3R1;PIK3CB;FOS;WASL;HIF1A;EGFR;NRAS;MAPK8;PIK3CA;R PS6KB1;SP1;MAPK1;PLCG1
Steroid biosynthesis_Homo sapiens_hsa00100	6/20	0.000351231	0.001495761	0.004999134	0.02421149	3.634906049	-28.91228017	SQLE;SOAT1;SC5D;DHCR24;MSMO1;HSD17B7;LSS
Chagas disease (American trypanosomiasis)_Homo sapiens_hsa05142	18/104	0.000471661	0.001974582	0.010181674	0.040562476	-0.255905891	1.96004701	SMAD2;JUN;CHUK;SERPINE1;GNAI3;PPP2R2A;PIK3R1;CFAR;PIK3CB;FOS;TGFBF1;TGFBF2;PPP2CB; MAPK8;PIK3CA;TRAF6;GNAS;MAPK1
Pathogenic Escherichia coli infection_Homo sapiens_hsa05130	12/55	0.00048398	0.001992384	0.007565169	0.033367799	0.617894868	-4.716680114	CDC42;ITGB1;CTTN;ROCK2;CDH1;ARPC1A;CTNNB1;WASL;EZR;CLDN1;YWHAZ;ACTB
Prolactin signaling pathway_Homo sapiens_hsa04917	14/72	0.000591906	0.002396733	0.009660795	0.039118301	0.055957736	-0.415887037	GSK3B;SRC;PIK3CB;FOS;PIK3R1;FOXO3;NRAS;MAPK8;CCND2;PIK3CA;CCND1;MAPK1;S0C56;S0C55
Thyroid cancer_Homo sapiens_hsa05216	8/29	0.000821581	0.003273073	0.008921976	0.0367288	1.896541791	-13.47356358	NRAS;CCND1;CDH1;MYC;CCDC6;CTNNB1;MAPK1;BRAF
Insulin resistance_Homo sapiens_hsa04931	18/109	0.00083937	0.003290863	0.015114145	0.058331152	-0.218042742	1.544366031	MGEA5;GSK3B;PDPK1;INSR;GFPT1;SLC2A1;PTEN;PIK3R1;PIK3CB;PTPRF;PPP1CB;RPS6KA3;MAPK8;C REB1;PIK3CA;RPS6KB1;CREB3L2;OGT
Sphingolipid signaling pathway_Homo sapiens_hsa04071	19/120	0.001033158	0.003926001	0.018296747	0.067747903	-0.132865011	0.913464867	CERS3;ASAHI1;ASAH2;CERS5;SGMS1;ROCK2;PDPK1;PTEN;GNAI3;PPP2R2A;PIK3R1;PIK3CB;PPP2CB;N RAS;SGPL1;MAPK8;PIK3CA;MAPK1;CTSD
Fc gamma R-mediated phagocytosis_Homo sapiens_hsa04666	16/93	0.00101804	0.003926001	0.015592226	0.059250459	-0.07238376	0.498715135	MYO10;LIMK2;ARPC1A;PIK3CB;PIK3R1;WASL;CRKL;CDC42;MARCKS;PIK3CA;RPS6KB1;CFI2;MAPK1;PL CG1;CRK;ARF6
T cell receptor signaling pathway_Homo sapiens_hsa04660	17/104	0.001297847	0.004784598	0.01938008	0.070395291	-0.055072504	0.366069628	GSK3B;JUN;CHUK;PDPK1;CLB;PIK3R1;PIK3CB;FOS;CDC42;PPP3CA;NRAS;DLG1;PIK3CA;PAK6;MAPK1; PLCG1;PAK2
VEGF signaling pathway_Homo sapiens_hsa04370	12/61	0.001283157	0.004784598	0.014808902	0.058060298	0.480669237	-3.200534227	CDC42;PPP3CA;NRAS;PIK3CA;SRC;MAPKAPK2;MAPK1;PIK3CB;PIK3R1;PLCG1;PTGS2;VEGFA
Osteoclast differentiation_Homo sapiens_hsa04380	20/132	0.00135099	0.004907274	0.023024077	0.081414528	-0.130051061	0.859236607	JUN;CHUK;PIK3R1;PIK3CB;FOS;TGFBF1;FOSL2;TGFBF2;IL1A;CYLD;PPP3CA;MAPK8;CREB1;PIK3CA;TR AF6;MAPK1;TAB2;SQSTM1;JUNB;IFNAR1
Hepatitis C_Homo sapiens_hsa05160	20/133	0.001483934	0.005312053	0.024534224	0.084166017	-0.093154981	0.606723867	GSK3B;CDKN1A;CHUK;CD81;PDPK1;BRAF;PPP2R2A;PIK3R1;PIK3CB;CLDN1;EGFR;PPP2CB;NRAS;CLDN 4;MAPK8;PIK3CA;TRAF6;MAPK1;LDLR;IFNAR1
Epstein-Barr virus infection_Homo sapiens_hsa05169	27/202	0.001558921	0.005423287	0.034247317	0.114311991	-0.218988687	1.415490661	YWHAH;ATF2;GSK3B;CDKN1A;CDKN1B;YWHAH;TNFAIP3;PIK3R1;PIK3CB;MAPK8;MYC;PLCG1;YWHA G;MAP2K3;HSP89A;JUN;CHUK;YWHAZ;PIK3CA;NEDD4;TRAF6;CDK2;MDM2;TBP1;POLR3G;TAB2;CD4 4
AMPK signaling pathway_Homo sapiens_hsa04152	19/124	0.001538745	0.005423287	0.02399309	0.083468917	-0.026398908	0.170980134	PFKFB2;CAB39;PDPK1;INSR;PPP2R2A;PIK3R1;PIK3CB;HMGR;FOXO3;IGF1R;RAP1B;PPP2CB;CREB1;C CND1;PIK3CA;RPS6KB1;RAB14;CREB3L2;ULK1
Progesterone-mediated oocyte maturation_Homo sapiens_hsa04914	16/98	0.001800252	0.006175864	0.023072943	0.081414528	0.04619024	-0.291914403	GNAI3;BRAF;PIK3R1;PIK3CB;CDC25A;ADCY6;CDC25B;IGF1R;RPS6KA3;MAPK8;PIK3CA;CDC27;CDK2;M APK1;CPEB2;CPEB4
Measles_Homo sapiens_hsa05162	20/136	0.001951458	0.006602878	0.029520067	0.099882965	-0.041893382	0.261380289	HSPA8;GSK3B;CDKN1B;CHUK;TNFRSF10B;MSN;TNFAIP3;CLB;PIK3R1;PIK3CB;JIL1;CCND3;CCND2;C DK6;CCND1;PIK3CA;TRAF6;CDK2;TAB2;IFNAR1
Dorso-ventral axis formation_Homo sapiens_hsa04320	7/27	0.002567854	0.008571079	0.018376961	0.067747903	2.822802699	-16.83712848	NOTCH2;NOTCH1;MAPK1;CPEB2;EGFR;ETS2;CPEB4
Wnt signaling pathway_Homo sapiens_hsa04310	20/142	0.003265917	0.010755574	0.041726875	0.133851145	-0.000322469	0.00184588	GSK3B;JUN;FBXW11;ROCK2;CSNK1A1;FZD6;CUL1;WNT7A;NLK;LRP6;VANGL1;PPP3CA;CCND3;MAPK 8;CCND2;CCND1;DAAM1;TLX1R1;MYC;CTNNB1
Oocyte meiosis_Homo sapiens_hsa04114	18/123	0.003373823	0.010964923	0.038994164	0.126731032	0.103271055	-0.58778878	YWHAH;FBXW11;YWHAH;CUL1;YWHAZ;ADCY6;IGF1R;PPP1CB;PPP3CA;PPP2CB;RPS6KA3;SLK;CDC27; CDK2;MAPK1;CPEB2;YWHAH;CPEB4
Chemokine signaling pathway_Homo sapiens_hsa04062	24/187	0.004659459	0.014946575	0.062124819	0.187132076	0.043148137	-0.231656136	GSK3B;CHUK;ROCK2;SRC;GNAI3;BRAF;CXCL1;PPBP;PIK3R1;PIK3CB;WASL;FOXO3;GNG12;CXCL3;ADC Y6;CXCL5;CRKL;RAP1B;CDC42;TIAM1;NRAS;PIK3CA;MAPK1;CRK
Ubiquitin mediated proteolysis_Homo sapiens_hsa04120	19/137	0.004836647	0.015122174	0.051957067	0.160417443	0.209970001	-1.119462125	UBE2H;MAP3K1;FBXW7;FBXW11;UBA6;HUWE1;CUL1;SYVN1;XIAP;UBE3A;CBLB;UBE2G1;UBE2Z;U BE2J1;TRAF6;NEDD4;CDC27;MDM2;UBE2K
Inositol phosphate metabolism_Homo sapiens_hsa00562	12/71	0.004827325	0.015122174	0.037125343	0.122266131	0.737953492	-3.935847496	PIKFYVE;MTMR3;PIK3CA;SYN1;IMPAD1;JPMK;PTEN;PI4K2B;PIK3CB;PLCG1;MTMR4;PIK3C2A
Insulin signaling pathway_Homo sapiens_hsa04910	19/139	0.005664591	0.017489424	0.057741371	0.176075538	0.17046095	-0.881883242	GSK3B;PRKCI;PDPK1;INSR;CLB;BRAF;PIK3R1;PIK3CB;PTPRF;CRKL;PPP1CB;NRAS;MAPK8;PIK3CA;RPS 6KB1;PRKAR1A;MKNK2;MAPK1;CRK
NOD-like receptor signaling pathway_Homo sapiens_hsa04621	10/57	0.007425736	0.02264391	0.045040862	0.14082396	1.370991519	-6.721702045	MAPK8;CHUK;TRAF6;TNFAIP3;TAB3;MAPK1;CXCL1;TAB2;NOD2;HSP90B1

N-Glycan biosynthesis_Homo sapiens_hsa00510	9/49	0.008017263	0.024149561	0.044989965	0.14082396	1.982903092	-9.569803956	GANAB;B4GALT1;RPN2;MAN1A2;MAN2A1;ALG2;MOGS;ALG11;MGAT2
Oxytocin signaling pathway_Homo sapiens_hsa04921	20/158	0.010684994	0.031797513	0.09141489	0.243656351	0.172097532	-0.78113606	JUN;CDKN1A;PPP1R12A;ROCK2;SRC;GNAI3;PIK3R1;PIK3CB;FOS;PTGS2;EGFR;ADCY6;ACTB;PPP1CB;PPP3CA;NRAS;CCND1;PIK3CA;GNAS;MAPK1
Phosphatidylinositol signaling system_Homo sapiens_hsa04070	14/98	0.011153753	0.032797345	0.073040314	0.214773304	0.500781397	-2.251502762	MTMR3;IPMK;PTEN;PIK3R1;PIK3CB;MTMR4;PIK3C2A;PIKFYVE;SYNJ1;PIK3CA;IMPAD1;PIP4K2B;PLCG1;CD52
GnRH signaling pathway_Homo sapiens_hsa04912	13/91	0.01414366	0.041099813	0.082001867	0.222576495	0.532211169	-2.266415295	MAP3K2;MAP2K3;JUN;MAP3K1;SRC;EGFR;ADCY6;CDC42;NRAS;MAPK8;GNAS;MAPK1;HBEGF
Platelet activation_Homo sapiens_hsa04611	16/122	0.015337686	0.04405126	0.098888852	0.257111016	0.326723739	-1.36486959	ITGB1;PRKCJ;ARHGEF12;PPP1R12A;ROCK2;SRC;GNAI3;PIK3R1;PIK3CB;ADCY6;ACTB;PPP1CB;RAP1B;PIK3CA;GNAS;MAPK1
B cell receptor signaling pathway_Homo sapiens_hsa04662	11/73	0.015845859	0.04498767	0.080513993	0.222576495	0.898462064	-3.723987838	GSK3B;PPP3CA;JUN;NRAS;PIK3CA;CHUK;CD81;MAPK1;PIK3CB;FOS;PIK3R1
Phagosome_Homo sapiens_hsa04145	19/154	0.016246236	0.045600232	0.115603057	0.294370672	0.381930088	-1.573511481	ITGB1;RAB5C;TRFC;M6PR;THBS1;ACTB;EEA1;SEC61A2;DYNC1L1;PIKFYVE;LAMP1;CTSL;LAMP2;CANX;ATP6V1B2;OLR1;ITGAV;ITGA5;VAMP3
Longevity regulating pathway - multiple species_Homo sapiens_hsa04213	10/64	0.016481814	0.045741665	0.078652417	0.221095035	1.321294289	-5.424570618	HSPA8;NRAS;PIK3CA;RPS6KB1;INSR;PIK3CB;PIK3R1;FOXO3;ADCY6;IGF1R
cAMP signaling pathway_Homo sapiens_hsa04024	23/199	0.018307779	0.049216248	0.143389634	0.350665738	0.381743898	-1.527139448	JUN;PPP1R12A;ROCK2;GNAI3;RRAS2;BRAF;ATP1B3;PIK3R1;ADRB2;FOS;PIK3CB;ATP2B1;MLLT4;ADCY6;RAP1B;PPP1CB;TIAM1;MAPK8;CREB1;PIK3CA;CREB3L2;GNAS;MAPK1
cGMP-PKG signaling pathway_Homo sapiens_hsa04022	20/167	0.018775269	0.049216248	0.131604825	0.328347393	0.423302444	-1.682718114	MEF2A;ATF2;PPP1R12A;ROCK2;INSR;GNAI3;ATP1B3;PIK3R1;PIK3CB;ADRB2;ATP2B1;ADCY6;PPP1CB;PPP3CA;CREB1;PIK3CA;CREB3L2;PIF;MAPK1;MEF2D
Longevity regulating pathway - mammal_Homo sapiens_hsa04211	13/94	0.018201484	0.049216248	0.097428494	0.256008915	0.664505737	-2.662177548	ATF2;INSR;PIK3CB;PIK3R1;FOXO3;ADCY6;IGF1R;NRAS;CREB1;PIK3CA;RPS6KB1;CREB3L2;JLKI1
Pertussis_Homo sapiens_hsa05133	11/75	0.019128582	0.049216248	0.091741055	0.243656351	1.320935809	-5.226377134	ITGB1;JL1A;JUN;MAPK8;CFL2;TRAF6;GNAI3;MAPK1;ITGA5;FOS;CXCL5
Regulation of lipolysis in adipocytes_Homo sapiens_hsa04923	9/56	0.018794875	0.049216248	0.081828727	0.222576495	1.65820651	-6.589996284	PIK3CA;INSR;GNAS;GNAI3;PIK3CB;ADRB2;PIK3R1;PTGS2;ADCY6
Sphingolipid metabolism_Homo sapiens_hsa00600	8/47	0.018870542	0.049216248	0.077736163	0.221095035	2.828823498	-11.23086264	CERS3;UGCC;ASAHI;SGPL1;CERS6;ASAH2;SGMS1;KDSR
Circadian rhythm_Homo sapiens_hsa04710	6/30	0.019098123	0.049216248	0.070020506	0.208374277	5.423005362	-21.46515113	CREB1;FBXW11;CUL1;FBXL3;CSNK1D;CLOCK