(54) Title: ULTRACONSERVED REGIONS ENCODING NCRNAS

(57) **Abstract:** Described herein are methods for differentiate human cancers comprising using one or more transcribed ultraconserved regions(T-UCR) expression profiles where the association between the genomic location of UCRs and the analyzed cancer-related genomic elements is highly statistically significant and comparable to that reported for miRNAs.

ULTRACONSERVED REGIONS ENCODING ncRNAs

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CROSS-REFERENCE TO RELATED APPLICATIONS

[0001]   This application claims the benefit of United States Provisional Application No. 60/963,329 filed August 3, 2007, and PCT/US2008/xxxxx filed xxxxx, 2008, the entire disclosure of which is expressly incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002]   This invention was not made with any Government support and the Government has no rights in this invention.

BACKGROUND

[0003] Taken as a whole, cancers are a significant source of mortality and morbidity in the U.S. and throughout the world. However, cancers are a large and varied class of diseases with diverse etiologies. Researchers therefore have been unable to develop treatments or diagnostic tests which cover more than a few types of cancer.

[0004] For example, cancers are associated with many different classes of chromosomal features. One such class of chromosomal features are perturbations in the genomic structure of certain genes, such as the deletion or mutation of tumor suppressor genes. The activation of proto-oncogenes by gene amplification or promoter activation (e.g., by viral integration), epigenetic modifications (e.g., a change in DNA methylation) and chromosomal translocations can also cause cancerigenesis. Such perturbations in the genomic structure which are involved in the etiology of cancers are called "cancer-associated genomic regions" or "CAGRs."

[0005] Chromosomal fragile sites are another class of chromosomal feature implicated in the etiology of cancers. Chromosomal fragile sites are regions of genomic DNA which show an abnormally high occurrence of gaps or breaks when DNA synthesis is perturbed during metaphase. These fragile sites are categorized as "rare" or "common." As their name suggests, rare fragile sites are uncommon. Such sites are associated with di- or tri-nucleotide repeats, can be induced in metaphase chromosomes by folic acid deficiency, and segregate in a Mendelian manner. An exemplary rare fragile site is the Fragile X site.

[0006]   Common fragile sites are revealed when cells are grown in the presence of aphidocolin or 5-azacytidine, which inhibit DNA polymerase. At least eighty-nine common fragile sites have been identified, and at least one such site is found on every human chromosome. Thus, while their function is poorly understood, common fragile sites represent a basic component of the human chromosome structure.

[0007]   Induction of fragile sites in vitro leads to increased sister-chromatid exchange and a high rate of chromosomal deletions, amplifications and translocations, while fragile sites have been colocalized with chromosome breakpoints in vivo. Also, most common fragile sites studied in tumor cells contain large, intra-locus deletions or translocations, and a number of tumors have been identified with deletions in multiple fragile sites. Chromosomal fragile sites are therefore mechanistically involved in producing many of the chromosomal lesions commonly seen in cancer cells.

[0008]   All malignant cells have specific alterations at DNA loci that encode genes for oncoproteins or tumor suppressors (Balmain et al., 2003; Wooster and Weber, 2003). This common feature has recently been expanded to include a large class of non-coding RNAs (ncRNAs) called microRNAs (miRNAs) (Ambros, 2004) that are also involved in cancer initiation and progression (Calin et al., 2002; Croce and Calin, 2005; Berezikov and Plasterk, 2005a; Esquela-Kerscher and Slack, 2006; Calin and Croce, 2006a). MiRNAs affect the regulation of gene expression at both the transcriptional and post-transcriptional levels (Ambros, 2003; Ambros, 2004).

[0009]   The extent of involvement of miRNAs and the involvement of other classes of ncRNAs in human tumorigenesis is unknown. Therefore, there is a need for further research into the molecular mechanisms and signal transduction pathways altered in cancer.

[00010]   There is a further need for the identification of new molecular markers and potential therapeutic agents.

[00011]   The ultraconserved regions (UCRs) of the human genome (Bejerano et al., 2004b) are also miRNAs that are almost completely conserved among various species (Berezikov et al., 2005b). For example, the active molecules of the *miR-16-1/miR-15a* cluster, has been shown to be an essential player in the initiation of chronic lymphocytic leukemia (CLL) (Calin et al., 2005a), and are completely conserved in human, mouse and rat and highly conserved in nine out of the ten sequenced primate species (Berezikov et al., 2005b). Comparative sequence analysis has identified a number of highly conserved genomic sequences. Some of these regions do not produce a transcript that is translated into protein and are therefore considered

to be non-genic. Various names have been applied to this class of sequences: conserved non-genic sequences (CNGs) (Dermitzakis et al., 2005), conserved non-coding sequences (CNSs/CNCs) (Meisler, 2001), multiple species conserved sequences (MCSs) (Thomas et al., 2003) or highly conserved regions (HCRs) (Duret et al., 1993).

[00012] UCRs are a subset of conserved sequences that are located in both intra- and inter-genic regions. They are absolutely conserved (100%) between orthologous regions of the human, rat, and mouse genomes (Bejerano et al., 2004b). In contrast to other regions of conserved sequence, 53% of the UCRs have been classified as non-exonic ('N', 256/481 without evidence of encoding protein), while the other 47% have been designated either exonic ('E', 111/481, that overlap mRNA of known protein-coding genes), or possibly exonic ('P', 114/481, with inconclusive evidence of overlap with protein coding genes).

[00013] A large portion of transcription products of the non-coding functional genomic regions have significant RNA secondary structures and are components of clusters containing other sequences with functional non-coding significance (Bejerano et al., 2004a). The UCRs represent a small fraction of the human genome that are likely to be functional but not encoding proteins, and have been called the "dark matter" of the human genome (Bejerano et al., 2004a). Because of the high degree of conservation, the UCRs may have fundamental functional importance for the ontogeny and phylogeny of mammals and other vertebrates. This was illustrated by the recent finding of a distal enhancer and an ultraconserved exon derived from a novel retroposon active in lobe-finned fishes and terrestrial vertebrates more than 400 million years ago and maintained as active in a "living fossil' coelacanth (Bejerano et al., 2006).

[00014] Further experimental proof of the functional importance of UCRs is based on analysis of mice with targeted mutations. Megabase deletions of gene deserts that lack ultraconserved elements or highly conserved sequences resulted in viable mice that developed apparently without detectable phenotypes (Nobrega et al., 2004). By contrast, gene deserts containing several UCRs (such as the two gene deserts surrounding the DA CHI gene on human chromosome 13g21.33) were shown to contain long-range enhancers, some of them composed of UCR sequences (Nobrega et al., 2003).

[00015] In spite of considerable research into therapies for cancer-related diseases, these diseases remain difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for diagnosing and/or treating cancer. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF INVENTION

[00016] Described herein is a thorough genomic interrogation of the status of UCRs in a large panel of human leukemias and carcinomas.

[00017] We investigated the genome-wide expression of UCRs in various normal and cancer samples, and we assessed the relationship between the genomic location of these sequences and the known regions involved in cancers.

[00018] Furthermore, we identified a functional role for miRNAs in the transcriptional regulation of cancer-associated UCRs.

[00019] Also described herein is evidence in cancer systems that a differentially expressed UCR could alter the functional characteristics of malignant cells.

[00020] Also described herein, by combining these data with the elaborate models involving miRNAs in human tumorigenesis, is a model in which alteration in both coding and non- coding RNAs cooperate in the initiation and progression of malignancy.

[00021] In one broad aspect, there is described herein methods for differentiate human cancers comprising using one or more transcribed ultraconserved regions(T-UCR) expression profiles where the association between the genomic location of UCRs and the analyzed cancer-related genomic elements is highly statistically significant and comparable to that reported for miRNA.

[00021a] In one aspect there is described herein a method to identify a relative cancer risk in a vertebrate comprising: obtaining a nucleic acid-containing test sample from a vertebrate subject; measuring, by laboratory analysis, a level of at least one transcribed ultraconserved region (T-UCR); and determining the relative risk for developing a cancer by comparing the measured levels, wherein a decrease in the level of the at least one T-UCR in the test sample, relative to the level of a corresponding T-UCR in a control sample, is indicative of the subject either having, or being at risk for developing, a cancer; wherein the association between the genomic location of UCRs and the analyzed cancer-related genomic elements is statistically significant and comparable to that reported for miRNAs.

[00021b] In one aspect there is described herein a method for assessing a functional regulatory pathway in which two or more types of ncRNAs interact and influence the phenotype comprising: obtaining a nucleic acid-containing sample from a cancer patient; and determining, by laboratory analysis, correlations between the expression of UCRs and miRNAs in the sample.

[00021c] In one aspect there is described herein a method of diagnosing whether a subject has, or is at risk for developing, a cancer linked to a cancer-associated chromosomal feature, comprising evaluating the status in the subject of at least one UCR gene located in close proximity to the cancer-associated chromosomal feature, by: (i) measuring in a test sample from said subject the level of at least one UCR gene product from the UCR gene in the test sample, wherein an alteration in the level of UCR gene product in the test sample relative to the level of corresponding UCR gene product in a control sample is indicative of the subject either having, or being at risk for developing, the cancer; (ii) analyzing the at least one UCR gene in the test sample for a deletion, mutation or amplification, wherein detection of a deletion, mutation and/or amplification in the UCR gene as compared to the corresponding UCR gene in the control sample is indicative of the subject either having, or being at risk for developing, the cancer; and/or (iii) measuring the copy number of the at least one UCR gene in the test sample, wherein a copy number other than two for an UCR gene on a somatic chromosome or sex chromosome in a female, or other than one for an UCR gene on a sex chromosome in a male, is indicative of the subject either having, or being at risk for developing, the cancer.

[00021d] In one aspect there is described herein a method of diagnosing whether a subject has, or is at risk for developing, a cancer, comprising: (1) reverse transcribing RNA from a test sample obtained from the subject to provide a set of target oligodeoxynucleotides; (2) hybridizing the target oligodeoxynucleotides to a microarray comprising one or more UCR specific probe oligonucleotides to provide a hybridization profile for the test sample; and (3) comparing the test sample hybridization profile to a hybridization profile generated from a control sample, wherein an alteration in the signal is indicative of the subject either having, or being at risk for developing, the cancer.

[00021e] In one aspect there is described herein a method of diagnosing whether a subject has, or is at risk for developing, a cancer associated with one or more adverse prognostic markers in a subject, comprising: (1) reverse transcribing RNA from a test sample obtained from the subject to provide a set of target oligodeoxynucleotides; (2) hybridizing the target oligodeoxynucleotides to a microarray comprising one or more UCR-specific probe oligonucleotides to provide a hybridization profile for said test sample; and (3) comparing the test sample hybridization profile to a hybridization profile generated from a control sample, wherein an alteration in the signal is indicative of the subject either having, or being at risk for developing, the cancer.

[00021f] In one aspect there is described herein a method of diagnosing whether a subject has, or is at risk for developing, a cancer, comprising analyzing in a test sample from said subject at least one UCR gene or gene product associated with a cancer, wherein detection of a mutation in the UCR gene or gene product, as compared to the corresponding UCR gene or gene product in a control sample, is indicative of the subject having, or being at risk for developing, the cancer.

[00021g] In one aspect there is described herein a method of treating cancer in a subject, comprising: (1) providing a subject who has a cancer associated with a cancer-associated chromosomal feature, in which at least one isolated UCR gene product from a UCR gene located in close proximity to the cancer-associated chromosomal feature is down-regulated or up-regulated in cancer cells of the subject as compared to control cells; and (2) (a) when the at least one isolated miR gene product is down-regulated in the cancer cells, administering to the subject an effective amount of at least one isolated miR gene product from the at least one UCR gene, such that proliferation of cancer cells in the subject is inhibited; or (b) when the at least one isolated UCR gene product is up-regulated in the cancer cells, administering to the subject an effective amount of at least one compound for inhibiting expression of the at least one UCR gene, such that proliferation of cancer cells in the subject is inhibited.

[00021h] In one aspect there is described herein a method of treating cancer associated with a cancer-associated chromosomal feature, comprising: (1) determining the amount of UC gene product expressed from at least one UCR gene located in close proximity to the cancer-associated chromosomal feature in cancer cells from a subject, relative to control cells; and (2) altering the amount of UC gene product expressed in the cancer cells by: (i) administering to the subject an effective amount of at least one isolated miR gene product from the UCR gene, if the amount of the UCR gene product expressed in the cancer cells is less than amount of the miR gene product expressed in control cells; or (ii) administering to the subject an effective amount of at least one compound for inhibiting expression of the at least one UCR gene, if the amount of the UCR gene product expressed in the cancer cells is greater than the amount of the UCR gene product expressed in control cells, such that proliferation of cancer cells in the subject is inhibited.

[00021i] In one aspect there is described herein a method for treating, preventing, reversing or limiting the severity of a cancer-related disease complication in an individual in need thereof, comprising: administering to the individual an agent that interferes with at

least one cancer-related disease response signaling pathway, in an amount sufficient to interfere with such signaling, wherein the agent comprises at least one UCR gene product.

[00021j] In one aspect there is described herein use of an agent that interferes with at least one lung cancer-related disease response signaling pathway, for the manufacture of a medicament for treating, preventing, reversing or limiting the severity of a cancer-related disease complication in an individual, wherein the agent comprises at least one UCR gene product.

[00021k] In one aspect there is described herein a method of treating, preventing, reversing or limiting the severity of a cancer-related disease complication in an individual in need thereof, comprising administering to the individual an agent that interferes with at least one cancer-related disease response cascade, wherein the agent comprises at least one UCR gene product.

[00021l] In one aspect there is described herein use of an agent that interferes with at least one cancer-related disease response cascade, for the manufacture of a medicament for treating, preventing, reversing or limiting the severity of a cancer-related disease complication in an individual, wherein the agent comprises at least one UCR gene product

[00022] Various objects and advantages of this invention will become apparent to those skilled in the art from the following detailed description of the preferred embodiment, when read in light of the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[00023] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[00024] **Figures 1A - 1E**. Transcriptional characteristics of various types of UCRs:

[00025] **Figure1A**. Northern blots showing the expression of various UCRs in normal tissues. In the case of uc.246(E) and uc.269A(N), the presence of the long transcript was confirmed by the RACE cloning experiments. For some tissues, duplicate samples were procured to confirm reproducibility. Normalization was performed with U6. The arrows on

the left side show the identified transcripts.

[00026]   **Figure 1B.** T-UCRs 291 and 73A expression (normalized to 18S rRNA) was
confirmed by qRT-PCR (graphs) and microarray analyses (Normalized number under the
graph) in normal CD5+/CD19+ lymphocytes and malignant CLL samples. P-values were
significant for both qRT-PCR and microarray data statistical comparison. Each box
represents the distribution of expression measured for normals (blue) and CLL patients (red),
ends of the boxes define the 25th and 75th percentiles, a line indicates the median, bars define
the 10th and 90th percentiles.

[00027]   **Figure 1C.** Number of UCRs expressed in one or more of 19 tissues, as revealed by
microarray analysis; UCR type (E, N, P) numbers are indicated. Four types of transcription
were found: ubiquitously expressed UCRs (in 18 or 19 out of 19 different tissues), UCRs
expressed in the majority of tissues (10 to 17), UCRs expressed in a minority of tissues (2 to
9) and tissue-specifically expressed UCRs.

[00028]   **Figure 1D.** Percentage of each UCR type (E, N, P) that is ubiquitously transcribed
(both uni- and bi-directionally) in all the analyzed tissues; the absolute numbers for each
UCR type are shown in the boxes.

[00029]   **Figure 1E.** Expression of the sense or antisense strand UCRs 73, 133 and 269,
relative to 18S rRNA, in CD19+ B cells from three different donors. Sense/antisense strand
specific real-time RT-PCR was used to validate the strand specific expression of the UCRs
observed with microarray analysis; the average +1- standard deviation of microarray results
for CDS+ samples is under each graph. Microarray probes are named as follows: the sense
genomic probe is named "+", while the probe to the complementary sequence is named "A+".

[00030]   **Figures 2A-2B.** Hierarchical clustering of tissues and tumors according to UCRs
expression. Unsupervised cluster of (**Figure 2A**) 22 normal human tissues and (**Figure
2A\B**) 133 leukemias and carcinomas made using the non-exonic UCRs of the chip. Some of
the T-UCRs that well differentiate the tissue types (**Figure 2A**) or carcinomas from
leukemias (**Figure 2B**) are expanded at the right. Samples are in columns, T-UCRs in rows.
A green colored gene is down-regulated compared to its median expression in all samples,
red is up-regulated and yellow means no variation. The complete UCRs profile of tissues and
tumors can be found in **Figures 5 and 6.**

[00031]   **Figures3A-3E.** T-UCRs represent direct targets of miRNAs (SEQ ID Nos.1-3, 2, 4-8

and 2, respectively, in order of appearance):

[00032] **Figure 3A.** Examples of sites of complementarity T-UCR::miRNA. The uc.348::
miR-155 pairing is shown as an example of low levels of complementarity in contrast with
the other 4 interacting paired genes for which higher levels of complementarity are found.

[00033] **Figure 3B.** The correlation by qRT-PCR for miR-155, uc.160 and uc.346A
expression in 9 CLL patients. Lymphocytes from four different individuals were used as
normal controls.

[00034] **Figure 3C.** The direct miRNA::T-UCR interaction. Relative repression of firefly
luciferase expression standardized to a transfection control, Renilla luciferase. pGL-3
(Promega) was used as the empty vector. All the experiments were performed four to eight
times in triplicate (n=12-24).

[00035] **Figure 3D.** The effects of miR-155 transfection in MEG-O1 cells on expression
levels of uc.160 and uc.346A. Effects were measured by qRT-PCR at 0, 24 and 48 hours
post-transfection.

[00036] **Figure 3E.** Two scatter plots between expression values of mir-24-1 and uc.160 and
of miR-155 and uc.346A are presented. The regression line shows the negative correlation
between these two genes. The name of the corresponding array probes are presented on the
Y and X axes. Both probes recognize the mature form of the miRNA gene.

[00037] **Figures 4A**-4D. T-UCR 73A(P) is acting as an oncogene in colon cancer cells:

[00038] **Figure 4A.** The expression inhibition by various siRNAs in COLO-320 cells. As
reference value we used a siRNA control from Dharmacon. The most effective two siRNAs
and a pool of four different siRNAs, including these two, were used.

[00039] **Figure 2B.** The antiproliferative effects of reduction in uc.73A(P) gene expression
using siRNA-uc73A in COLO-320 colorectal cancer cells. All the results represent the
median of three independent triplicate experiments. The levels of uc. 73A (P) expression
were measured by RT-PCR. Two asterisks indicate a statistically significant effect at $P<0.01$,
while one at $P<0.05$.

[00040] **Figure 4C.** Reduced levels of uc.73A(P) (using various siRNAs) results in enhanced
apoptosis as shown by the Annexin-V staining assay in COLO-329 cells. As reference value
we used a siRNA control from Dharmacon.

[00042] **Figure 4D.** Inhibition of uc.73A(P) by various siRNAs did not influence SW620 colon cancer cell survival. All the results represent the median of three independent triplicate experiments.

[00043] **Figure 5.** UCR expression in human normal and malignant tissues by Northern blot. The expression for uc.192(N) and uc.246(E) in normal mononuclear cells (MNC) and CLL samples is presented. Normalization was done with U6 probe. The arrows on the left side show the identified transcripts. Under the gel image there are the averages of UCR normalized expression values in CLL and MNC samples from microarray experiments; p-values were from ANOVA statistic.

[00044] **Figure 6.** UCR expression in human normal and malignant tissues by qRT-PCR. Relative gene expression by qRT-PCR in CD5+/CD19+ positive lymphocytes and human chronic lymphocytic leukemia (CLL) samples. UCR microarray values of CLL and CD5+ samples are indicated under the graph; p-values were from ANOVA statistic.

[00045] **Figure 7.** T-UCR expression profile of 22 normal human tissues. Clustering of tissues and UCRs revealed a distinct pattern of UCRs expression in normal human tissues. Samples are shown in columns, T-UCRs in rows. A green colored gene is down-regulated compared to its median expression in all samples, red is up-regulated and yellow means no variation.

[00046] **Figure 8.** T-UCR expression profile of 173 cancers and corresponding normal tissues. Samples from leukemia and normal blood cells are separated from cancer and tissue of epithelial origin. Samples are shown in columns, T-UCRs in rows. A green colored gene is down-regulated compared to its median expression in all samples, red is up-regulated and yellow means no variation.

[00047] **Figure 9.** The expression of uc.73A(P) gene in various colon cancer cell lines by quantitative RT-PCR. The expression in normal colon represents the median value of 4 different samples. For normalization we used beta-actin.

[00048] **Figure 10.** The uc.73A(P) inhibition by siRNA1 in COLO-320 and SW-620 cells at 48hrs. Comparable levels of inhibition in respect with a siRNA of control (Dharmacom) were achieved in both types of cells. In spite of this, the biological effects were seen only in COLO-320 cells, where the T-UCR is overexpressed about 2.5 times when compared with expression in normal colon.

[00049] **Figure 11.** Downregulation by small interfering of uc.73A(P) induces apoptosis in COLO-320 cells but not in SW-620 cells. Data obtained with caspase-3 assay in COLO-320 (**upper panel**), where a significant increase in apoptotic cells is found, and in the control cells SW620 (**lower panel**), where no difference could be found. COLO-320 express high levels of uc.73A(P), while in SW620 the expression is comparable with the normal colon levels.

[00050] **Figure 12 - Table 1.** Most significant differentially expressed UCRs in leukemias and carcinomas.

[00051] **Figure 13 - Table 2.** Mixed effect Poisson regression results as association of UCRs with regions of interest.

[00052] **Figure 14 - Table 3.** T-UCRs whose expression inversely correlates with complementary miRNA differentially expressed in CLL patients.

[00053] **Figure 15 - Table 4**. T-UCRs expression in 22 human normal tissues (3 in duplicate, from 2 different individuals).

[00054] **Figure 16 - Table 5**. T-UCRs differentially expressed in CLL, CRC and HCC identified by ANOVA analysis at $P<0.005$ (GeneSpring GX software).

[00055] **Figure 17 - Table 6**. Genomic location of UCRs is correlated with CAGR. (databases as in (Bejerano et al., 2004); (Calin et al., 2004)).

[00056] **Figure 18 - Table 7**. Negative correlations between the expression of miRNAs and T-UCRs in CLL patients. All validated negative correlation by FDR method at 0.01 threshold, or 1% of false positive results, and with an R correlation lower as 0.40 were considered.

DESCRIPTION OF EMBODIMENTS

[00057] As used herein, a "CAGR" includes any region of the genomic DNA that comprises a genetic or epigenetic change (or the potential for a genetic or epigenetic change) that differs from normal DNA, and which is correlated with a cancer. Exemplary genetic changes include single- and double-stranded breaks (including common breakpoint regions in or near possible oncogenes or tumor-suppressor genes); chromosomal translocations; mutations, deletions, insertions (including viral, plasmid or transposon integrations) and amplifications

(including gene duplications) in the DNA; minimal regions of loss-of-heterozygosity (LOH) suggestive of the presence of tumor-suppressor genes; and minimal regions of amplification suggestive of the presence of oncogenes. Exemplary epigenetic changes include any changes in DNA methylation patterns (e.g., DNA hyper- or hypo-methylation, especially in promoter regions).

[00058]   Many of the known miR genes in the human genome are in or near CAGRs, including 80 miR genes that are located exactly in minimal regions of LOH or minimal regions of amplification correlated to a variety of cancers. Other miR genes are located in or near breakpoint regions, deleted areas, or regions of amplification.

[00059]   For example, cancers associated with CAGRs include leukemia (e.g., AML, CLL, pro-lymphocytic leukemia), lung cancer (e.g., small cell and non-small cell lung carcinoma), esophageal cancer, gastric cancer, colorectal cancer, brain cancer (e.g., astrocytoma, glioma, glioblastoma, medulloblastoma, meningioma, neuroblastoma), bladder cancer, breast cancer, cervical cancer, epithelial cancer, nasopharyngeal cancer (e.g., oral or laryngeal squamous cell carcinoma), lymphoma (e.g., follicular lymphoma), uterine cancer (e.g., malignant fibrous histiocytoma), hepatic cancer (e.g., hepatocellular carcinoma), head-and-neck cancer (e.g., head-and-neck squamous cell carcinoma), renal cancer, male germ cell tumors, malignant mesothelioma, myelodysplastic syndrome, ovarian cancer, pancreatic or biliary cancer, prostate cancer, thyroid cancer (e.g., sporadic follicular thyroid tumors), and urothelial cancer.

[00060]   As used herein, a "FRA" includes any rare or common fragile site in a chromosome; e.g., one that can be induced by subjecting a cell to stress during DNA replication . For example, a rare FRA can be induced by subjecting the cell to folic acid deficiency during DNA replication. A common FRA can be induced by treating the cell with aphidocolin or 5-azacytidine during DNA replication. The identification or induction of chromosomal fragile sites is within the skill in the art; see, e.g., Arlt et al. (2003), Cytogenet. Genome Res. 100:92-100 and Arlt et al. (2002), Genes, Chromosomes and Cancer 33:82-92, the entire disclosures of which are herein incorporated by reference.

[00061]   Approximately 20% of the known human miR genes are located in (13 miRs) or within 3 Mb (22 miRs) of cloned FRAs. Indeed, the relative incidence of miR genes inside fragile sites occurs at a rate 9.12 times higher than in non-fragile sites. Moreover, after studying 113 fragile sites in a human karyotype, it was found that 61 miR genes are located in

the same chromosomal band as a FRA.

[00062]   For example, cancers associated with FRAs include bladder cancer, esophageal
cancer, lung cancer, stomach cancer, kidney cancer, cervical cancer, ovarian cancer, breast
cancer, lymphoma, Ewing sarcoma, hematopoietic tumors, solid tumors and leukemia.

[00063]   The following examples are included to demonstrate preferred embodiments of the
invention. It should be appreciated by those of skill in the art that the techniques disclosed in
the examples which follow represent techniques discovered by the inventor to function well
in the practice of the invention, and thus can be considered to constitute preferred modes for
its practice. However, those of skill in the art should, in light of the present disclosure,
appreciate that many changes can be made in the specific embodiments which are disclosed
and still obtain a like or similar result without departing from the spirit and scope of the
invention.

[00064]   **EXAMPLE 1**

[00065]   Genome-wide profiling reveals extensive transcription of ultraconserved regions
(UCRs) in normal human tissues.

[00066]   To investigate the involvement of UCRs in human cancers, we analyzed 481 genomic
regions longer than 200 bp (Bejerano et al., 2004b) by Northern blot, quantitative PCR (qRT-
PCR) and microarray.

[00067]   Both exonic (E) and non-exonic (N) UCR probes detected transcripts (in sense or
antisense - A, orientation) over a large range of lengths from various normal tissues (**Figure
lA** and **Figure 5**).

[00068]   The length of two of the transcripts was confirmed by cloning the cDNA by 5'- and 3'-
RACE for the exonic uc.246(E) from normal human colon and the non-exonic uc.269A(N)
from normal human bone marrow. Neither of these cDNAs contained open reading frames
(ORFs) of significant length, confirming their likely non-protein coding nature. These non-
spliced full-length cDNAs, that we named non-coding ultraconserved genes, nc-UCGs, are of
variable length (about 0.8 kb for the ultraconserved gene UCG.246 and about 1.8kb and
2.8kb for the ultraconserved gene UCG.269A).

[00069]   Transcription of these nc-UCGs may be initiated from poly-adenine rich genomic
regions, as was recently proposed for several long ncRNAs from mouse (Furuno et al., 2006).

[00070]   We compared the transcription levels of several UCRs from normal and disease tissue using microarray analysis followed by qRT-PCR and Northern blot confirmation. The expression of uc.291(P) and uc. 73A(P) was significantly higher in normal CD5+/CD 19+ lymphocytes than in CLL cells (P < 0.05) (**Figure 1B**). The data obtained with this microarray platform has been confirmed in various studies (Calin et al., 2005a; Yanaihara et al., 2006; Volinia et al., 2006).

[00071]   The strength of our data is reinforced by the fact that two independent sets of normal CD5 cells were included in microarray and quantitative RT-PCR experiments. When both uc.291(P) and uc.73A(P) were investigated by qRT-PCR and microarray in two different sets of CD5/CD19 positive B cells and malignant B cells, the differential expression was statistically significant by both assays (**Figure 1B**).

[00072]   Furthermore, qRT-PCR and Northern blotting for eleven and six UCRs, respectively, gave results that were concordant with microarray results (**Figure 5** and **Figure 6**).

[00073]   Using microarray analysis, we found that the majority of transcribed UCRs (that we named here T-UCRs) were expressed in normal human tissues both ubiquitously and in a tissue-specific manner (**Figure 1C**).

[00074]   About 34% of putative T-UCRs (325/962) had hybridization signals with an intensity over background (calculated as average signal of blank spots + 2 SD) in all 19 tissue samples. The highest number of T-UCRs was found in B cells, while the lowest was in ovary. About 93% of the UCRs (890 of 962) were expressed over background in at least one sample, and therefore we considered these as T-UCRs. The three different types of UCRs were transcribed with similar frequencies: 41% of exonic UCRs, 33% of possibly exonic UCRs and 30% of non-exonic UCRs.

[00075]   The microarray platform contains putative T-UCRs in both sense and anti-sense orientation. Eighty-four of the 962 UCRs (9%) were bidirectionally transcribed, while 241 were transcribed only from one strand, in all the normal tissues analyzed (**Figure 1D, Figure lE** and **Table 4**).

[00076]   Since identification of bidirectional transcription by microarray analysis may be hindered by trace contamination with genomic DNA, we performed a comparison of microarray results with strand-specific qRT-PCR for uc.2 69(N), uc.233(E) and uc. 73(P). In all three instances the data were concordant, showing predominant transcription from one

strand (**Figure 1E**).

[00077]   Of note, out of the 156 non-exonic T-UCRs expressed in all 19 tissues, 92 (-60%) are intergenic, while 64 are intronic. Of the latter, 37 are in the antisense orientation compared with the host gene, suggesting that about 83% (129/156) of the non-exonic T-UCRs did not represent intronic transcription of long precursor transcripts of known host genes, but bona fide independent noncoding transcripts.

[00078]   As with miRNAs (Liu et al., 2004), we performed a hierarchical clustering of T-UCR expression in hematopoietic tissues (represented by B lymphocytes, T lymphocytes and mononuclear cells, each collected from two healthy individuals) and non-hematopoietic tissues. The same types of tissue from different individuals were clustered as closest neighbors (**Figure 2A** and **Figure 7**).

[00079]   These findings demonstrate that UCRs represent, in a significant proportion of cases, non-coding transcripts in normal human tissues and that the expression of these T-UCRs is tissue-specific.

[00080]   **Distinct UCR signatures in human leukemias and carcinomas**

[00081]   Since extensive gene expression alterations in cancer cells have been widely described for both protein coding genes and miRNAs (Esquela-Kerscher and Slack, 2006; Calin and Croce, 2006a; Calin and Croce, 2006b; Lu et al., 2005), we investigated the expression of UCRs in a panel of 173 samples, including 133 human cancers and 40 corresponding normal tissues.

[00082]   Hierarchical clustering of the samples showed that various types of cancers clustered differently according to their developmental origins: the leukemias (CLL) and normal hematopoietic tissues were branched separately from the colorectal (CRC) and hepatocellular carcinomas (HCC) with their normal counterparts (**Figure 8**); moreover, specific groups of UCRs seemed to be differentially expressed in tumor types (**Figure 2B**).

[00083]   Since different tissues have specific UCR signatures, this clustering pattern could be the consequence of different tissue-specific origin of the tumors. Thus, we compared the expression of UCRs between the normal and tumor cells of the same origin. Out of 962 possible T-UCRs, 88 (9.1%) were differentially expressed at a highly statistically significant level (P<0.005) in at least one type of cancer (**Table 1** and **Table 5**).

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[00084] We found both down-regulated and up-regulated T-UCRs in cancers compared to the expression in corresponding normal tissues. By comparing each cancer type with the corresponding normal tissues, we found that the CLL signature was composed of 19 UCRs (8 up- and 11 down-regulated), the CRC signature of 61 UCRs (59 up- and 2 down-regulated), and the HCC signature of 8 UCRs (3 up- and 5 down-regulated) (**Table 5**).

[00085] Eighteen transcripts of the signatures were exonic UCRs (20%), 28 were possibly exonic UCRs (32%) and 42 were non-exonic UCRs (48%). Of the 18 exonic T-UCRs, 9 represented the anti-sense direction of the known host protein-coding gene transcripts. We therefore demonstrated that the T-UCR expression profiles can be used to differentiate human cancers.

[00086] **UCRs are frequently located at fragile sites and genomic regions involved in cancers**

[00087] We compared the genomic location of UCRs with that of previously reported non-random genetic alterations identified in human tumors and cloned fragile sites (FRA) as described (Calin et al., 2004b). We used the set of 186 miRNAs previously reported (Calin et al., 2004b) and a set of 297 zinc finger protein-coding genes (ZNF) (genome.ucsc.edu), a well known family of transcription factors shown to be associated with cancer (Huntley et al., 2006).

[00088] We previously reported that miRNA genes are frequently located at FRA sites, HOX genes clusters and genomic regions involved in cancer, such as minimal regions of loss of heterozygosity (LOH), and minimal regions of amplification, globally named cancer associated genomic regions (CAGR) (Calin et al., 2004b).

[00089] A recent study, using high-resolution array comparative genomic hybridization (aCGH), confirmed that miRNA loci exhibit genomic alterations at high frequency in human cancers (Zhang and al, 2006). Furthermore, by analyzing the miRNA expression in NCI-60 cell lines, another group found that the candidate tumor-suppressor and oncogenic miRNAs are located in CAGRs (Gaur et al, 2007).

[00090] Here, we show that the association between the genomic location of UCRs and the analyzed cancer-related genomic elements is highly statistically significant and comparable to that reported for miRNAs. The ZNF transcription factors did not show any significant association with any of the analyzed regions of interest (**Table 2** and **Table 6**).

[00091]   There was a similar lack of association for the smaller family of protein-coding genes involved in RNA splicing (80 genes, data not shown). For example, the probability for the association of UCRs or miRNAs with minimal LOH regions versus non-deleted genomic regions was less than 0.001 in both instances (IRR of 2.02 and 4.08, respectively). As an internal control, we used the human papilloma virus 16 (HPV 16) integration sites, which frequently occur in FRA sites. If UCRs are significantly associated with FRA, then we expected to fin an association with the HPV 16 integration site. This is exactly what we observed for both UCRs and miRNAs, but not for ZNF protein-coding genes (**Table 2**) or for the protein-coding genes involved in RNA splicing (data not shown).

[00092]   Additional data illustrate the importance of the genomic location of UCRs. First, we found that the ubiquitously expressed T-UCRs (expressed in 18 or 19 normal tissues in **Figure 1 C**) are significantly more frequently located in CAGRs (P<0.005, Fisher exact test) when compared with all other UCRs (97 out of 189 vs. 71 out of 292). Second, T-UCRs differentially expressed in human cancers are located in CAGRs specifically associated with that type of cancer. For example, the chromosomal region 13g21.33-g22.2 has been linked to susceptibility to familial CLL (Ng et al, 2007). No mutations were found in any of the 13 protein-coding genes screened within this interval.

[00093]   We identified a cluster of seven UCRs (uc.347 to uc.353) located within this CAGR. Two of them, uc.349A(P) and uc.352(N) are among the T-UCRs that are differentially expressed between normal and malignant B-CLL CD5 positive cells.

[00094]   This suggests, at least in this case, that it is not the protein-coding genes but the UCRs that represent the "unknown" culprits located in the CAGR. Together these data provide evidence that the UCRs are located in genomic regions altered during the malignant process, and suggest that T-UCRs could be candidate genes for cancer susceptibility.

[00095]   **Negative regulation of T-UCRs by direct interaction with microRNAs**

[00096]   In order to begin to functionally characterize some UCRs involved in human cancers, we performed a genome-wide expression study in the same set of CLL samples investigated above. We found that a signature of five UCRs, uc.269A(N), uc.160(N), uc.215(N), uc.346A(P) and uc.348(N), was able to differentiate between two main CLL prognosis groups previously differentiated by the expression of 70-kDa zeta-associated protein (ZAP-70).

[00097]   These five T-UCRs displayed variations in their expression level that was negatively correlated with the miRNA expression signature reported in CLL (Cahn et al., 2005a) (**Table 3**).

[00098]   While not wishing to be bound by theory, the inventor herein now believes that this finding raises the possibility of complex regulatory mechanisms between miRNAs and T-UCRs. We identified, by sequence alignments, that three out of the 5 UCRs have significant antisense complementarity with 5 out of the 13 miRNAs from the signature, giving rise to six possible interacting pairs: uc.160:: rniR-24, uc.160:: miR-155, uc.160:: miR-223, uc.160::miR-146a, uc.346A::miR-155, and uc.-348::miR-29b (**Figure 3A**).

[00099]   In this analyzed set of miRNA::UCR pairs, the 5'- end "6 base seed" complementarity rule described for miRNA::mRNA interaction was valid; furthermore, the levels of 3 '-end complementarity could be variable: more than 60% complementarity for miR-24:: uc160 or miR-155::uc.346A pairs to less than 25% for the miR-155:: uc.160 pair. As a control, when randomly generated combinations of five UCRs and 13 miRNAs were compared, the sense and antisense complementarity was not significant.

[000100]   Negative correlations between the microa7ay expression values of specific T-UCRs and predicted interactor miRNAs was confirmed by qRT-PCR for selected T-UCRs and miRNAs from lymphocytes of an independent set of CLL patients and normal controls (**Figure 3B**).

[000101]   We performed *in vitro* assays of miRNA::UCR interaction involving miR-155 which is overexpressed in the aggressive form of CLL (Calin et al., 2005) some lymphomas and carcinomas (Eis et al., 2005; Kluiver et al., 2005; Volinia et al., 2006), and miR-24-1 and miR29-b which carry mutations in primary transcripts from CLL patients (Calin et al., 2005a).

[000102]   We cloned the UCRs uc.160(N), uc.346A(P) and uc.348(N) in luciferase reporter vectors to assess the possible direct interaction with miR-155, miR-24-1 or miR-29-b. We observed consistent and reproducible reduction in luciferase expression with four miR::T-UCR pairings consistent with interactions taking place in vitro (Figure 3C).

[000103]   By contrast, uc.348(N) did not interact with miR155 as indicated by the luciferase assay, a result that is in concordance with the positive expression correlation of these two genes in CLL patients and the low sequence complementarity (**Figure 3A**).

[000104] **Interactions** *in vivo*

[000105] In order to determine if these interactions occur *in vivo*, we transfected miR-155 into MEG01 leukemia cells and assessed the levels of uc.346A and uc.160 (both well expressed in this cell line). At 24 hours after transfection, miR-155 significantly reduced the expression level of both T-UCRs; after 48 hours, the reduction of exogenous miR-155 levels was paralleled by an increase in T-UCR expression (**Figure 3D**).

[000106] This reversible effect supports a regulation of T-UCR by specific miRNAs. As this interaction was proven for the genes of the "ZAP-70 signature", we investigated the correlations between the expression of all miRNAs and T-UCRs at the genome-wide level in all 50 CLL patients. Interestingly, we found a significant negative correlation (at a false detection rate (FDR) of less than 0.01) between 87 miRNAs (out of 235 spotted on the chip, 37%) and T-UCRs expression levels (**Table 7**).

[000107] Furthermore, among the correlated genes we identified the miR-24-1:: uc.160 and the miR155:: uc346A(P) pairs, experimentally proven to interact (**Figure 3E**).

[000108] Moreover, miR-155 and uc.348, that did not interact experimentally, were not members of this list. Other pairs of possible interactors for which we identified positive luciferase assays were miR-15-a:: uc.78 and miR16:: uc. 78 (data not shown). Therefore, non-coding T-UCRs represent possible targets of miRNAs, and these interactions may have biological and prognostic significance for cancer patients.

[000109] **T-UCRs may act as Oncogenes**

[000110] To expand the functional characterization of T-UCR, we examined the biological effects of uc. 73A (P) in a cancer model. Since this is one of the most statistically significant up-regulated T-UCRs in colon cancers (P < 0.001), we decided to investigate the effects of its downregulation in COLO-320 colorectal cancer cells that expressed high levels of uc.73A(P). As a control we used the SW620 colon cancer cells in which the expression of this gene does not differ from normal colonic cells (**Figure 9**).

[000111] Two small interfering RNAs (siRNA1 and siRNA3), as well as a pool of four siRNAs (siRNApool), were designed to target uc. 73A(P) and transfected into COLO-320 and SW620 cells. There was significantly less expression of uc.73A(P) after 48 (**Figure 4A** and **Figure 10**), 72 and 144 hours (data not shown) in the COLO-320 cells treated with siRNAs 1, 3 and pool. The same was found also for SW-620 cells (**Figure 6**).

[000112] The growth of COLO-320 cells was significantly reduced after 144 hours of treatment with specific siRNA compared to both untreated (null) or siRNA-treated control cells ($P <$ 0.05 at 96 hrs and $P <$ 0.005 at 144hrs) (**Figure 4B**).

[000113] In comparison, proliferation of the SW620 control cells was not significantly changed ($P = 0.83$ and $P = 0.23$ at 96 and 144 hrs, respectively) (data not shown). Cell cycle studies revealed an increase in the sub-G1 fraction of cells (suggesting the presence of apoptotic cells, data not shown) in COLO-320 cells, but not in SW620 cells, a finding confirmed by the apoptosis-specific AnnexinV assay (**Figure 4C** and **Figure 4D**) and by caspase-3 assay (**Figure 11**).

[000114] Furthermore, the intensity of effects on cell proliferation and survival were proportional with the degree of inhibition by siRNAs (**Figure 4**).

[000115] These data suggest that in colorectal cancers, uc. 73A(P) behaves like an oncogene by increasing the number of malignant cells as a consequence of reduced apoptosis.

[000116] **DISCUSSION**

[000117] According to the dogma of molecular oncology, cancer is a genetic disease involving tumor-suppressor and oncogenic proteins (Bishop, 1991; Hunter, 1991; Weinberg, 1991). Recent findings strongly support the involvement of microRNAs in the pathogenesis of a majority of analyzed cancers, and add a new layer of complexity to the molecular architecture of human cancers (Calin et al., 2002; Esquela-Kerscher and Slack, 2006; Calin and Croce, 2006a). MiRNAs represent, however, just a particular group of ncRNAs involved in human cancers. It has been shown that antisense intronic ncRNA levels correlate with the degree of tumor differentiation in prostate cancer (Reis et al., 2005) and that MALAT-1 ncRNA expression predicts metastasis and survival in early stage non-small cell lung cancer (Ji et al., 2003), suggesting a deeper link between ncRNAs and tumor biology.

[000118] To clearly address this question, we investigated at the genomic level a full new class of ncRNAs, namely the transcribed non-coding ultraconserved regions (T-UCRs). We used bioinformatics tools to demonstrate that the UCRs are located in genomic regions targeted during the malignant process indicative of a putative involvement in human tumorigenesis.

[000119] As now shown herein, we were able to clone by RACE amplification cDNAs corresponding to uc.246(E) and uc.269A(N), proving that the UCRs are bona fide genes (named herein as nc-UCGs) that are expressed and can be cloned by standard methods.

[000120] Various expression techniques including Northern blot, qRT-PCR and genome-wide microarray profiling, proved that UCRs are frequently transcribed and that there are distinct signatures in human leukemias and carcinomas. We focused on chronic lymphocytic leukemia, the most frequent adult leukemia in the Western world (Chiorazzi et al., 2005), on colorectal carcinoma, one of the most common cancers in industrialized countries (de la Chapelle, 2004) and on hepatocellular carcinoma, the most rapidly increasing type of cancer in America (Wilson, 2005).

[000121] We found that for all the tumor types examined, the malignant cells have a unique spectrum of expressed UCRs when compared with the corresponding normal cells, suggesting that significant variations in T-UCR expression are involved in the malignant process.

[000122] Characterizing the functional significance of T-UCR alterations in human cancers is not a trivial task. A myriad of putative functions of T-UCRs can be hypothesized, including an antisense inhibitory role for protein coding genes or other non-codingRNAs, or a role as "aspecific" miRNAs, meaning miRNAs with peculiarities such as very long precursors (e.g. uc.339(P) which has a precursor length that is double the usual miRNA). This puzzle becomes more complicated by the fact that several UCRs do not act like genes and were found to have regulatory functions as enhancers (Nobrega et al., 2003; Pennacchio et al., 2006), while others represent exons of protein coding genes with known/unknown cancer connections. A particularly interesting region is the DA CHI locus that contains 7 UCRs in about 700kb (Bejerano et al., 2004b). Three of the UCRs from this region are differentially expressed in analyzed cancers, two of which are members of the CLL signature. The majority of scanned conserved regions from this locus in a mouse model are enhancers, including the uc.351(N) that was not expressed in any of the analyzed tissues in our study.

[000123] Interestingly, the only two regions that failed to have enhancer function are uc.348(N) and uc.352(N), both classified as non-coding and both differentially expressed in human cancers. Further increasing the interest in these specific T-UCRs, is the finding that this genomic region has been linked to susceptibility to familial CLL and that none of the known protein-coding genes were mutated (Ng et al, 2007).

[000124] Recently, it was found that short blocks of several tens of bp from the noncoding parts of the human genome (named pyknons) occur within nearly all known protein coding genes (Rigoutsos et al., 2006). While the pyknons are distinct from the UCRs, the ultraconserved

element containing the highest number of pyknons (four) was uc. 73(P), which we found to be one of the most differentially expressed T-UCRs in both CLL and CRC. These intriguing observations suggest a possible regulatory role for uc. 73(P) on the coding genes with complementary sequences.

[000125]   Further expanding the involvement of this T-UCR in human cancers, we were able to prove an oncogenic function for uc.73(P) in colon cancer, as diminution of its over-expression induced apoptosis and had antiproliferative effects specifically in colon cancer cells abnormally expressing this T-UCR.

[000126]   Our findings that another class of ncRNAs, the T-UCRs, is consistently altered at the genomic level in a high percentage of analyzed leukemias and carcinomas, support a model in which both coding and non-coding genes are involved and cooperate in human tumorigenesis (Calin and Croce, 2006b).

[000127]   Furthermore, correlations between the expression of UCRs and miRNAs in CLL patients raise the intriguing possibility of complex functional regulatory pathways in which two or more types of ncRNAs interact and influence the phenotype.

[000128]   We also demonstrated the existence of the miRNA::T-UCR interaction in which two different types of ncRNAs are interacting..

[000129]   We found that nc-UCGs are consistently altered at the genomic level in a high percentage of leukemias and carcinomas, and may interact with miRNAs in leukemias. The findings provide support for a model in which both coding and non-coding genes are involved in and cooperate in human tumorigenesis.

[000130]   **EXAMPLE I**

[000131]   EXPERIMENTAL PROCEDURES

[000132]   A)   RACE cloning and expression analysis by microarray, qRT-PCR and Northern blot

[000133]   1)   RACE cloning

[000134]   The expression of six UCRs (uc.47(N), uc.110(N), uc.192(N), uc.246(E), uc.269A(N) and uc.352(N)) was analyzed in brain, testis, bone marrow, small intestine, colon and liver tissue using various combinations of PCR primers designed to amplify short products. These products included 40-mers used for probes in microarray analysis and the complete >200bp

UCR sequence. Two of the UCR products, one exonic, uc.246(E) and one non-exonic, uc.269A(N), were cloned by Rapid Amplification of cDNA Ends (RACE) in both 5' and 3' directions. The sources of tissue from which sequences were cloned were bone marrow, leukocytes, fetal brain and colon according to the manufacturer protocol (Marathon-ready cDNAs, Clontech, Palo Alto, CA).

[000135] 2)   UCR expression study by microarray.

[000136] Total RNA was extracted with Trizol (Invitrogen, Carlsbad, CA) from 19 normal human tissues (Liu et al., 2004) and from 50 CLL samples from patients diagnosed with CLL. Informed consent was obtained from all patients at the CLL Research Consortium institutions in the US. As controls, CDS+ B cells from 6 healthy individuals (four distinct samples, two being pools from two different healthy individuals) and mononuclear cells (MNC) from 3 individuals were used as reported in (Calin et al., 2005a). RNA was also extracted from 78 primary colorectal carcinomas, 21 normal colonic mucosas, 9 primary hepatocellular carcinomas and 4 normal livers, collected at the University of Ferrara, University of Bologna and University Tor Vergata, Rome (Italy). All samples were obtained with written informed consent according to institutional guidelines for the protection of human subjects.

[000137] Microarray chips were developed with a total of 481 human UCR sequences as in (soe.ucsc.edu/-jill/ultra). For each UCR two 40-mer probes were designed, one corresponding to the sense genomic sequence (named "+") and the other to the complementary sequence (named "A+"). The design criteria were as described (Liu et al., 2004). Each oligo was printed in duplicate in two different slide locations, and therefore quadruplicate numerical values were available for analysis. Several thousand (3484) blank spots were used for background subtraction. RNA extraction and microarray experiments, consisting of the UCR microarray assembly, target preparation and array hybridization, were performed as described in detail elsewhere (Liu et al., 2004; Calin et al., 2004a).

[000138] Briefly, 5μg of RNA from each tissue sample was labeled with biotin by reverse transcription using random hexamers. Hybridization was carried out on the second version of our miRNA-chip (ArrayExpress accession number: A-MEXP-258) which contained the 962 UCR probes, 238 probes for mature miRNA and 143 probes for precursor miRNAs. Each oligo was printed in duplicate in two different slide locations. Hybridization signals were detected by biotin binding of a Streptavidin - Alexa647 conjugate (one-color signal) using a

GenePix 4000B scanner (Axon Instruments) . Images were quantified using the GenePix Pro 6.0 (Axon Instruments).

[000139]   Raw data were normalized and analyzed in GeneSpring GX 7.3 (Agilent Technologies, Santa Clara, CA). Expression data of the 22 tissue samples were normalized with Lowess function in Bioconductor (Limma package) and then were median centered using GeneSpring normalization; the threshold used to determine the level of UCR expression was calculated as the average of blank spots + 2 SD (standard deviation). Tumors were normalized using the on-chip and on-gene median normalization of the GeneSpring software. Hierarchical cluster analysis was done using average linkage and Pearson correlation as measures of similarity. Statistical comparisons of tumors and normal tissues were performed by filtering on fold change and then using the ANOVA (Analysis of Variance) statistic of the GeneSpring software and the Benjamin and Hochberg correction for reduction of false positives. The filter on fold-change was set on 1.2 because this threshold, already used for microRNAs analyzed with the same chip [see for examples (Cahn et al., 2005a; Cimmino et al., 2005; Iorio et al., 2005)], was demonstrated to reflect a real biological difference. The T-UCRs differentially expressed among CLL patients, grouped in accordance to 70-kDa zeta-associated protein (ZAP-70) expression, were identified by combining the ANOVA results with the SAM (Significance Analysis of Microarray) and PAM (Prediction Analysis of Microarrays) analysis. Their expression was compared to that of microRNAs (Calin et al., 2005a). All data were submitted using MIAMExpress to the ArrayExpress database and could be retrieve using the accession number E-TABM-184.

[000140]   3)   Quantitative RT-PCR for UCRs.

[000141] Quantitative RT-PCR was the first method we used to confirm the microarray results. We validated the microarray data for eleven UCRs, including uc. 73 (P)/73A (P) , uc.135(E), uc.160(N), uc.233(E)/233A(E), uc.269(N)/269A(N), uc.289(N), uc.291(P), and uc.346A(P) in various combinations of samples, including 15 to 17 randomly selected CLL samples from the array set of 50, and various normal CD 19+/CD5+ B cells and B and T lymphocyte controls by qRT-PCR. An additional set of 3 normal CD19+/CD5+ positive B cells, not used for microarray studies, was purchased from AllCells (Berkeley, CA), and used as an independent confirmation set. In all instances the qRT-PCR data confirmed the microarray data. RNA was treated with RNase-free DNase I and reverse transcribed to cDNA using random primers and SuperScript II reverse transcriptase. To determine if the sense or

antisense UCR transcript was expressed, total RNA was reverse transcribed using Thermoscript RT and a gene specific (i.e. sense or antisense) primer. RT conditions were as described (Schmittgen et al., 2004). cDNA was amplified using real-time PCR and SYBR green detection using PCR primers designed to amplify the same 40 bp regions as the oligo probe on the microarray. The relative amount of each UCR to 18S rRNA was determined using the equation $2"dcT$, where $dCT = (CTUCR- CT18s\ rRNA)$. Relative gene expression data were multiplied by 106 to simplify the presentation.

[000142] 4)   Northern blot analysis of T-UCRs.

[000143] We analyzed five UCRs, uc.110(N), uc.192(N), uc.246(E), uc.269A(N) and uc.352(N), by Northern blot, two of which were then cloned by RACE experiments. For a sixth one, the uc. 47(N), the data are not shown. Total RNA was electrophoresed on 15% PAA-urea gels (Calin et al., 2002). RNA sources included 11 normal tissues (breast, liver, lung, kidney and pancreas) in duplicate or triplicate (purchased from Ambion and Clontech) and 4 normal MNC samples and 16 CLL samples prepared in the laboratory. As this represents the investigation by Northern blot of UCR expression, we used multiple samples from the same tissues to confirm data reproducibility. The probes were designed to be identical with the oligonucleotides on the chip in order to detect the same transcripts as the microarray, and the hybridization was done as described (Calin et al., 2002).

[000144] B)   Databases and Statistical Analyses.

[000145] 1)   Databases for Genomic Locations.

[000146] The UCR databases used for all the studies reported here are as published (Bejerano et al., 2004b). We restricted our analyses to 481 segments longer than 200 base pairs (bp). The Fragile site (FRA) database and the cancer associated genomic regions (CAGR) databases are as previously published (Cain et al., 2004b).

[000147] 2)   Statistical Analyses for Genomic Locations.

[000148] To test hypotheses associating the incidence of ultra-conserved regions (UCRs) with fragile sites, amplified regions in cancer, and deletion regions in cancer, we utilized random effect Poisson and negative binomial regression models. Under these models, "events" were defined as the number of UCRs, and exposure "time" (i.e. fragile site versus non-fragile site) was defined as non-overlapping lengths of the region of interest. The "length" of a region was exact, if known, or estimated as 1Mb if unknown. For example, for each chromosome

the total length of all non-overlapping fragile sites was computed and was used as the exposure time for fragile sites. We then counted the number of UCRs occurring within fragile sites for each chromosome. The remaining length of each chromosome (total Mb - fragile sites Mb) was assumed to be non-fragile, and the remaining UCRs in each chromosome were assumed to occur in the non-fragile region. Then for each region, alternative random effects models, the zero-inflated Poisson and the zero-inflated negative binomial models were fitted, and, of the three, the best model was selected using the Akaike's Information Criteria (based on the log likelihood and number of parameters). This same approach was used for analysis of the data from expression of zinc finger proteins. The best fitting model for fragile sites with UCRs and LOH with zinc finger proteins was the zero-inflated negative binomial. For all other cases, the Poisson model is reported. When the number of categories with zero events was more than expected for a Poisson distribution, the zero-inflated negative binomial model was preferred. When the total number of events was too small for a region, the model likelihoods were unable to converge, and results are not reported. The random effect in the Poisson, zero-inflated Poisson and zero-inflated negative binomial regression models, was the individual chromosome, in that data within a chromosome was assumed to be correlated. The fixed effect in each model consisted of an indicator variable(s) for the type of region being compared. We report the incidence rate ratio (IRR), 2-sided 95% confidence interval of the incidence rate ratio, and 2-sided p-values for testing the hypothesis that the incident rate ratio is 1.0. An IRR significantly > 1 indicates an increase in the number of UCRs within a region over that expected by chance.

[000149]   The proportions of clustering of miRNAs and zinc finger proteins were compared using an asymptotic test of the difference in two independent proportions, where we report the difference, 95% confidence interval of the difference, and p-value. Of note, the ZNF transcription factor class of genes showed a significantly lower clustering (a cluster defined as the location of at least two genes from the same class at less than 50kb genomic distance) when compared with the microRNAs (32%, 95/297 clustered ZNF genes versus 48%, 90/186 clustered miRNAs, difference=16.4%, 95% CI=(7.5%, 25.2%), P<0.001). All computations were completed using STATA v7.0 and StatXact v7.0.

[000150]   3)   Statistical Analyses for negative correlations between microarray expression of UCRs and miRNAs.

[000151]   A detailed description is provided in the Example II and data therein. Briefly, the

input data was constituted by a list of T-UCRs and by a list of miRNAs (the "seeds") and the corresponding matrix of expression values. We calculated r, the Spearman rank coefficient of correlation for each pair of (miR, UC) genes; namely, we evaluate the P-values of the correlation tests and select the genes whose correlation value is significant at a given value of rejection. Given the high number of correlation tests performed, P-values were corrected for multiple testing by using the false detection rate (FDR), as in (Benjamini and Hochberg, 1995). In this way, P-values control the number of false positive over the number of truly null tests, while FDR controls the number of false positive over the number of significant tests.

[000152] C)   Functional studies

[000153] 1)   UCRs down-regulation by direct interaction with microRNAs.

[000154] The genomic sequences of uc.160, uc.346A and uc.348 were cloned into pGL3-control vector (Clontech) using the Xbal site immediately downstream from the stop codon of luciferase. Human megakaryocytic MEG-O1 and the cervical carcinoma HeLa cell lines were grown as recommended by the ATCC. Cells were co-transfected in 12-well plates using siPORT neoFX (Ambion) according to the manufacturer's protocol using 0.4 µg of the firefly luciferase reporter vector and 0.08 µg of the control vector containing Renilla luciferase, pRL-TK (Promega). For each well 10 nM of miRNA-sense precursor and scrambled oligonucleotides (Ambion) were used. Firefly and Renilla luciferase activities were measured consecutively using the Dual-luciferase assays (Promega) 24 hr after transfection. All experiments were performed in triplicate on four to six different days (n=12 to 18).

[000155] Expression of both the ultraconserved RNA and the mature miRNA was analyzed using real-time PCR. Expression of the UCR RNA was determined by real-time PCR as described above. Expression of the mature miRNA was performed using TaqMan looped primer assays to miR-155 (Applied Biosystems) as described (Chen et al., 2005). Mature miRNA expression was presented as 2-dCT where dCT = CTmiRNA - CTl ss rRNA); data was multiplied by 106 to simplify presentation.

[000156] For the patient correlation a set of 13 samples was used (including 9 CLL patients and 4 normal lymphocyte samples) and miR-155, uc.346A and uc.160 levels were analyzed as described herein. For the identification of the "in vivo" effects in MEG01 of miR-155

transfection, the levels of uc.346A and uc.160 were measured by qRT-PCR as described at 0, 24 and 48 hrs post-transfection with the pre-miRNA 155 (Ambion) using Lipofectamine reagent.

[000157]   2)   Effects on cancer cell proliferation by uc. 73A(P) inhibition.

[000158]   The siRNA against the uc. 73A(P) were designed using the Dharmacon algorithm (Dharmacon siDESIGN (harmacon.com/sidesign)) entering the complete sequence of the UCR. The eight highest rank target sequences were tested. The performance was assessed after 48, 72 and 144 hour post-transfection by semi-quantitative RT-PCR. The most effective two siRNAs and a pool of four different siRNAs, including these two, were used. We named these as siRNA1, siRNA3 and siRNApool. For the cell growth assay, the human colon cancer cell lines COLO-320 and SW620 were grown in RPMI1640 medium supplemented with 10% FBS and 1x104 cells were plated in 96-well plate a day before transfection. The cells were transfected with siRNA-uc.73A(P) at a final concentration of 200nM by using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. The siCONTROL Non-Targeting siRNA Pool (Dharmacon Research, LaFayette, CO, USA) was used as negative control. The transfection was repeated under the same conditions every two days, at 48 and 96 hour. To evaluate the cell number the CellTiter 96 Aqueous One Solution Cell Proliferation Assay (Promega U.S., Madison, WI, USA) was used. The readings were performed at 0, 48, 96, and 144 hours, respectively measuring the absorbance at 490nm using an ELISA plate reader (Spectra MAX, Molecular Devices, Sunnyvale, CA, USA). The cell growth assay was performed three times in triplicate for each treatment. The statistical differences between the number of cells at various time points with respect to time 0, was calculated using the t test.

[000159]   For both cell cycle and apoptosis assays, cells were plated in 6 well plates at 6x105 cells per well. The day after and then every 48 hrs, the cells were transfected with 200nM siRNA. The cells were collected and fixed in cold 70% ethanol for at least 30 minutes. The Propidium Iodide (PI) staining was performed at 48, 96, and 144 hours in a 50 μg/mL PI (Sigma Aldrich, St. Louis, MO) and 5 .ig/mL RNAse DNAse free (Roche Diagnostics, Indianapolis, IN, USA) PBS Solution. The apoptosis staining was performed with the Annexin V-FITC Apoptosis Detection Kit (BD Pharmingen, San Jose, CA, USA) and with the PE-conjugated monoclonal active Caspase-3 antibody apoptosis kit (BD Biosciences) at 0 and 144 hours according to the manufacturer's procedure using an FACS Calibur (BD

Biosciences, San Jose, CA, USA) to acquire the data. Each experiment was performed three times.

[000160]   The GeneBank accession numbers for the cloned T-UCRs described in this study are as followings: DQ644536 (UCG.246), DQ644537 (UCG.269A, short form), and DQ644538 (UCG.269A, long form).

[000161]   **EXAMPLE II**

[000162]   Experimental Procedures

[000163]   Statistical Analyses for negative correlations between microarray expression of UCRs and miRNAs.

[000164]   The input data were constituted by a list of UCGs and by a list of miRNAs (the "seeds") and the corresponding matrix of expression values. We calculated r, the Spearman rank coefficient of correlation, a non-parametric measure of data trend correlation based on rankings, for each pair of (miR, UCR) genes; namely, we evaluate the P-values of the correlation tests and selected the genes whose correlation value is significant at a given value of rejection. Evaluation of P-values was performed assuming that the correlation values are distributed using Student's t cumulative distribution, with a number of degrees of freedom corresponding to the number of samples in the microarray experiment. The P-values measure the 'goodness' of the single correlations (among couples of genes), therefore, to understand if the real correlation derives by chance or represents a biologically important information, we choose the method of permutations, changing the order of the samples for each row (miR or UCR) and calculating the correlations between pair of genes (miR, UCR) with different changed samples orders. We repeated the samples permutation and computed correlations 100 times, in this way, every real correlation has 100 random correlations to compare with. Using all ($100 * n° MIR * n° UC$) random correlations and real correlations, we recalculated P-values based on random correlations ranking and position of the real correlations.

[000165]   Given the high number of correlation tests performed, P-values were corrected for multiple testing by using the false detection rate (FDR), as defined by (Benjamini and Hochberg, 1995). In this way, P-values control the number of false positive over the number of truly null tests, while FDR controls the number of false positive over the number of significant tests. Several ways of estimating this number have been proposed, and we adopted the solution devised by Tom Nichols (see froi.sourceforge.net/documents/technical/

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matlab/FDR), that rescales the P-value obtained on a single test multiplying it by a combination of indexes related to the total number of tests performed. Correction was performed on a seed by seed basis, meaning that the genes in the seeds list were considered independent tests. This statistically validated tripe filtering allows the targeted extraction of a shortlist of candidate genes, thus saving resources for the following costly and time-consuming genetic analysis.

[000166]   To build a scatter plot between miR-24-1 and uc.160 expression values, we plotted a regression line by using MatLab function ROBUSTFIT to explain hypotheses of negative correlation between these two genes. Notice that only 11.67% (7/60) of points (pairs of expression values) are outlier.

[000167]   **EXAMPLE III**

[000168]   Additional Examples and Information

[000169]   As used herein miR and UCRs are used interchangeably; including in a non-limiting manner: a "miR gene product," "microRNA," "miR," or "miRNA" refers to the unprocessed (e.g., precursor) or processed (e.g., mature) RNA transcript from a miR gene.

[000170]   Diagnosis using UCRs (miRNAs)

[000171]   In one aspect, there is provided herein methods of diagnosing whether a subject has, or is at risk for developing, a cancer, comprising measuring the level of at least one UCR in a test sample from the subject and comparing the level of the miR gene product in the test sample to the level of a corresponding miR gene product in a control sample. As used herein, a "subject" can be any mammal that has, or is suspected of having, a cancer. In a preferred embodiment, the subject is a human who has, or is suspected of having, a cancer.

[000172]   The level of at least one miR gene product can be measured in a biological sample (e.g., cells, tissues) obtained from the subject. For example, a tissue sample (e.g., from a tumor) can be removed from a subject suspected of having a cancer-related disease by conventional biopsy techniques. In another embodiment, a blood sample can be removed from the subject, and blood cells (e.g., white blood cells) can be isolated for DNA extraction by standard techniques. The blood or tissue sample is preferably obtained from the subject prior to initiation of radiotherapy, chemotherapy or other therapeutic treatment. A corresponding control tissue or blood sample can be obtained from unaffected tissues of the subject, from a normal human individual or population of normal individuals, or from

cultured cells corresponding to the majority of cells in the subject's sample. The control tissue or blood sample is then processed along with the sample from the subject, so that the levels of miR gene product produced from a given miR gene in cells from the subject's sample can be compared to the corresponding miR gene product levels from cells of the control sample. A reference miR expression standard for the biological sample can also be used as a control.

[000173]   An alteration (*e.g.*, an increase or decrease) in the level of a miR gene product in the sample obtained from the subject, relative to the level of a corresponding miR gene product in a control sample, is indicative of the presence of a cancer-related disease in the subject.

[000174]   In one embodiment, the level of the at least one miR gene product in the test sample is greater than the level of the corresponding miR gene product in the control sample (i.e., expression of the miR gene product is "up-regulated"). As used herein, expression of a miR gene product is "up-regulated" when the amount of miR gene product in a cell or tissue sample from a subject is greater than the amount of the same gene product in a control cell or tissue sample.

[000175]   In another embodiment, the level of the at least one miR gene product in the test sample is less than the level of the corresponding miR gene product in the control sample (i.e., expression of the miR gene product is "down-regulated"). As used herein, expression of a miR gene is "down-regulated" when the amount of miR gene product produced from that gene in a cell or tissue sample from a subject is less than the amount produced from the same gene in a control cell or tissue sample.

[000176]   The relative miR gene expression in the control and normal samples can be determined with respect to one or more RNA expression standards. The standards can comprise, for example, a zero miR gene expression level, the miR gene expression level in a standard cell line, the miR gene expression level in unaffected tissues of the subject, or the average level of miR gene expression previously obtained for a population of normal human controls.

[000177]   The level of a miR gene product in a sample can be measured using any technique that is suitable for detecting RNA expression levels in a biological sample. Suitable techniques (e.g., Northern blot analysis, RT-PCR, *in situ* hybridization) for determining RNA expression levels in a biological sample (e.g., cells, tissues) are well known to those of skill

in the art. In a particular embodiment, the level of at least one miR gene product is detected

using Northern blot analysis. For example, total cellular RNA can be purified from cells by

homogenization in the presence of nucleic acid extraction buffer, followed by centrifugation.

Nucleic acids are precipitated, and DNA is removed by treatment with DNase and

precipitation. The RNA molecules are then separated by gel electrophoresis on agarose gels

according to standard techniques, and transferred to nitrocellulose filters. The RNA is then

immobilized on the filters by heating. Detection and quantification of specific RNA is

accomplished using appropriately labeled DNA or RNA probes complementary to the RNA

in question. See, for example, Molecular Cloning: A Laboratory Manual, J. Sambrook *et al.*,

eds., 2nd edition, Cold Spring Harbor Laboratory Press, 1989, Chapter 7, the entire disclosure

of which is incorporated by reference.

[000178]   Suitable probes for Northern blot hybridization of a given miR gene product can be

produced from the nucleic acid sequences and include, but are not limited to, probes having

at least about 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% or complete complementarity to a

miR gene product of interest. Methods for preparation of labeled DNA and RNA probes, and

the conditions for hybridization thereof to target nucleotide sequences, are described in

Molecular Cloning: A Laboratory Manual, J. Sambrook *et al.*, eds., 2nd edition, Cold Spring

Harbor Laboratory Press, 1989, Chapters 10 and 11, the disclosures of which are incorporated

herein by reference.

[000179]   In one non-limiting example, the nucleic acid probe can be labeled with, *e.g.*, a

radionuclide, such as ^{3}H, ^{32}P, ^{33}P, ^{14}C, or ^{35}S; a heavy metal; a ligand capable of functioning

as a specific binding pair member for a labeled ligand (*e.g.*, biotin, avidin or an antibody); a

fluorescent molecule; a chemiluminescent molecule; an enzyme or the like.

[000180]   Probes can be labeled to high specific activity by either the nick translation method of

Rigby *et al.* (1977), *J. Mol. Biol.* 113:237-251 or by the random priming method of Fienberg

et al. (1983), *Anal. Biochem.* 132:6-13, the entire disclosures of which are incorporated

herein by reference. The latter is the method of choice for synthesizing ^{32}P-labeled probes of

high specific activity from single-stranded DNA or from RNA templates. For example, by

replacing preexisting nucleotides with highly radioactive nucleotides according to the nick

translation method, it is possible to prepare ^{32}P-labeled nucleic acid probes with a specific

activity well in excess of 10^{8} cpm/microgram. Autoradiographic detection of hybridization

can then be performed by exposing hybridized filters to photographic film. Densitometric

scanning of the photographic films exposed by the hybridized filters provides an accurate measurement of miR gene transcript levels. Using another approach, miR gene transcript levels can be quantified by computerized imaging systems, such as the Molecular Dynamics 400-B 2D Phosphorimager available from Amersham Biosciences, Piscataway, NJ.

[000181] Where radionuclide labeling of DNA or RNA probes is not practical, the random-primer method can be used to incorporate an analogue, for example, the dTTP analogue 5-(N-(N-biotinyl-epsilon-aminocaproyl)-3-aminoallyl) deoxyuridine triphosphate, into the probe molecule. The biotinylated probe oligonucleotide can be detected by reaction with biotin-binding proteins, such as avidin, streptavidin, and antibodies (e.g., anti-biotin antibodies) coupled to fluorescent dyes or enzymes that produce color reactions.

[000182] In addition to Northern and other RNA hybridization techniques, determining the levels of RNA transcripts can be accomplished using the technique of *in situ* hybridization. This technique requires fewer cells than the Northern blotting technique, and involves depositing whole cells onto a microscope cover slip and probing the nucleic acid content of the cell with a solution containing radioactive or otherwise labeled nucleic acid (e.g., cDNA or RNA) probes. This technique is particularly well-suited for analyzing tissue biopsy samples from subjects. The practice of the *in situ* hybridization technique is described in more detail in U.S. Pat. No. 5,427,916, the entire disclosure of which is incorporated herein by reference.

[000183] In one non-limiting example, suitable probes for *in situ* hybridization of a given miR gene product can be produced from the nucleic acid sequences, and include, but are not limited to, probes having at least about 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% or complete complementarity to a miR gene product of interest, as described above.

[000184] The relative number of miR gene transcripts in cells can also be determined by reverse transcription of miR gene transcripts, followed by amplification of the reverse-transcribed transcripts by polymerase chain reaction (RT-PCR). The levels of miR gene transcripts can be quantified in comparison with an internal standard, for example, the level of mRNA from a "housekeeping" gene present in the same sample. A suitable "housekeeping" gene for use as an internal standard includes, e.g., myosin or glyceraldehyde-3-phosphate dehydrogenase (G3PDH). Methods for performing quantitative and semi-quantitative RT-PCR, and variations thereof, are well known to those of skill in the art.

[000185]   In some instances, it may be desirable to simultaneously determine the expression
    level of a plurality of different miR gene products in a sample. In other instances, it may be
    desirable to determine the expression level of the transcripts of all known miR genes
    correlated with a cancer. Assessing cancer-specific expression levels for hundreds of miR
    genes or gene products is time consuming and requires a large amount of total RNA (e.g., at
    least 20 µg for each Northern blot) and autoradiographic techniques that require radioactive
    isotopes.

[000186]   To overcome these limitations, an oligolibrary, in microchip format (i.e., a
    microarray), may be constructed containing a set of oligonucleotide (e.g.,
    oligodeoxynucleotides) probes that are specific for a set of miR genes. Using such a
    microarray, the expression level of multiple microRNAs in a biological sample can be
    determined by reverse transcribing the RNAs to generate a set of target
    oligodeoxynucleotides, and hybridizing them to probe the oligonucleotides on the microarray
    to generate a hybridization, or expression, profile. The hybridization profile of the test
    sample can then be compared to that of a control sample to determine which microRNAs
    have an altered expression level in cancer cells.

[000187]   As used herein, "probe oligonucleotide" or "probe oligodeoxynucleotide" refers to an
    oligonucleotide that is capable of hybridizing to a target oligonucleotide. "Target
    oligonucleotide" or "target oligodeoxynucleotide" refers to a molecule to be detected (e.g.,
    via hybridization). By "miR-specific probe oligonucleotide" or "probe oligonucleotide
    specific for a miR" is meant a probe oligonucleotide that has a sequence selected to hybridize
    to a specific miR gene product, or to a reverse transcript of the specific miR gene product.

[000188]   An "expression profile" or "hybridization profile" of a particular sample is essentially
    a fingerprint of the state of the sample; while two states may have any particular gene
    similarly expressed, the evaluation of a number of genes simultaneously allows the
    generation of a gene expression profile that is unique to the state of the cell. That is, normal
    tissue may be distinguished from cancerous (e.g., tumor) tissue, and within cancerous tissue,
    different prognosis states (for example, good or poor long term survival prospects) may be
    determined. By comparing expression profiles of the cancer tissue in different states,
    information regarding which genes are important (including both up- and down-regulation of
    genes) in each of these states is obtained. The identification of sequences that are
    differentially expressed in cancer tissue, as well as differential expression resulting in

different prognostic outcomes, allows the use of this information in a number of ways.

[000189]   In one non-limiting example, a particular treatment regime may be evaluated (e.g., to determine whether a chemotherapeutic drug acts to improve the long-term prognosis in a particular patient). Similarly, diagnosis may be done or confirmed by comparing patient samples with known expression profiles. Furthermore, these gene expression profiles (or individual genes) allow screening of drug candidates that suppress the cancer expression profile or convert a poor prognosis profile to a better prognosis profile.

[000190]   Accordingly, there is also provided herein methods of diagnosing whether a subject has, or is at risk for developing, a cancer, comprising reverse transcribing RNA from a test sample obtained from the subject to provide a set of target oligodeoxynucleotides, hybridizing the target oligodeoxynucleotides to a microarray comprising miRNA-specific probe oligonucleotides to provide a hybridization profile for the test sample, and comparing the test sample hybridization profile to a hybridization profile generated from a control sample or reference standard, wherein an alteration in the signal of at least one miRNA is indicative of the subject either having, or being at risk for developing, cancer.

[000191]   In one embodiment, the microarray comprises miRNA-specific probe oligonucleotides for a substantial portion of all known human miRNAs. In a particular embodiment, the microarray comprises miRNA-specific probe oligonucleotides for one or more miRNAs selected from the group consisting of miR29a, miR-29b, miR-29c and combinations thereof.

[000192]   The microarray can be prepared from gene-specific oligonucleotide probes generated from known miRNA sequences. The array may contain two different oligonucleotide probes for each miRNA, one containing the active, mature sequence and the other being specific for the precursor of the miRNA. The array may also contain controls, such as one or more mouse sequences differing from human orthologs by only a few bases, which can serve as controls for hybridization stringency conditions. tRNAs or other RNAs (e.g., rRNAs, mRNAs) from both species may also be printed on the microchip, providing an internal, relatively stable, positive control for specific hybridization. One or more appropriate controls for non-specific hybridization may also be included on the microchip. For this purpose, sequences are selected based upon the absence of any homology with any known miRNAs.

[000193]   The microarray may be fabricated using techniques known in the art. For example,

probe oligonucleotides of an appropriate length, e.g., 40 nucleotides, are 5'-amine modified at position C6 and printed using commercially available microarray systems, e.g., the GeneMachine OmniGrid™ 100 Microarrayer and Amersham CodeLink™ activated slides. Labeled cDNA oligomer corresponding to the target RNAs is prepared by reverse transcribing the target RNA with labeled primer. Following first strand synthesis, the RNA/DNA hybrids are denatured to degrade the RNA templates. The labeled target cDNAs thus prepared are then hybridized to the microarray chip under hybridizing conditions, e.g., 6X SSPE/30% formamide at 25°C for 18 hours, followed by washing in 0.75X TNT (Tris HCl/NaCl/Tween 20) at 37°C for 40 minutes. At positions on the array where the immobilized probe DNA recognizes a complementary target cDNA in the sample, hybridization occurs. The labeled target cDNA marks the exact position on the array where binding occurs, allowing automatic detection and quantification. The output consists of a list of hybridization events, indicating the relative abundance of specific cDNA sequences, and therefore the relative abundance of the corresponding complementary miRs, in the patient sample.

[000194] According to one embodiment, the labeled cDNA oligomer is a biotin-labeled cDNA, prepared from a biotin-labeled primer. The microarray is then processed by direct detection of the biotin-containing transcripts using, e.g., Streptavidin-Alexa647 conjugate, and scanned utilizing conventional scanning methods. Image intensities of each spot on the array are proportional to the abundance of the corresponding miR in the patient sample.

[000195] The use of the array has several advantages for miRNA expression detection. First, the global expression of several hundred genes can be identified in the same sample at one time point. Second, through careful design of the oligonucleotide probes, expression of both mature and precursor molecules can be identified. Third, in comparison with Northern blot analysis, the chip requires a small amount of RNA, and provides reproducible results using 2.5 μg of total RNA. The relatively limited number of miRNAs (a few hundred per species) allows the construction of a common microarray for several species, with distinct oligonucleotide probes for each. Such a tool allows for analysis of trans-species expression for each known miR under various conditions.

[000196] In addition to use for quantitative expression level assays of specific miRs, a microchip containing miRNA-specific probe oligonucleotides corresponding to a substantial portion of the miRNome, preferably the entire miRNome, may be employed to carry out miR

gene expression profiling, for analysis of miR expression patterns. Distinct miR signatures can be associated with established disease markers, or directly with a disease state.

[000197] According to the expression profiling methods described herein, total RNA from a sample from a subject suspected of having a cancer-related disease quantitatively reverse transcribed to provide a set of labeled target oligodeoxynucleotides complementary to the RNA in the sample. The target oligodeoxynucleotides are then hybridized to a microarray comprising miRNA-specific probe oligonucleotides to provide a hybridization profile for the sample. The result is a hybridization profile for the sample representing the expression pattern of miRNA in the sample. The hybridization profile comprises the signal from the binding of the target oligodeoxynucleotides from the sample to the miRNA-specific probe oligonucleotides in the microarray. The profile may be recorded as the presence or absence of binding (signal vs. zero signal).

[000198] More preferably, the profile recorded includes the intensity of the signal from each hybridization. The profile is compared to the hybridization profile generated from a normal, i.e., noncancerous, control sample. An alteration in the signal is indicative of the presence of, or propensity to develop, cancer in the subject.

[000199] Other techniques for measuring miR gene expression are also within the skill in the art, and include various techniques for measuring rates of RNA transcription and degradation.

[000200] There is also provided herein methods of determining the prognosis of a subject with a cancer, comprising measuring the level of at least one miR gene product, which is associated with a particular prognosis in a cancer-related disease (e.g., a good or positive prognosis, a poor or adverse prognosis), in a test sample from the subject.

[000201] According to these methods, an alteration in the level of a miR gene product that is associated with a particular prognosis in the test sample, as compared to the level of a corresponding miR gene product in a control sample, is indicative of the subject having a cancer with a particular prognosis. In one embodiment, the miR gene product is associated with an adverse (i.e., poor) prognosis. Examples of an adverse prognosis include, but are not limited to, low survival rate and rapid disease progression. In certain embodiments, the level of the at least one miR gene product is measured by reverse transcribing RNA from a test sample obtained from the subject to provide a set of target oligodeoxynucleotides, hybridizing the target oligodeoxynucleotides to a microarray that comprises miRNA-specific

probe oligonucleotides to provide a hybridization profile for the test sample, and comparing the test sample hybridization profile to a hybridization profile generated from a control sample.

[000202] Without wishing to be bound by any one theory, it is believed that alterations in the level of one or more miR gene products in cells can result in the deregulation of one or more intended targets for these miRs, which can lead to the formation of cancers. Therefore, altering the level of the miR gene product (e.g., by decreasing the level of a miR gene product that is up-regulated in cancer cells, by increasing the level of a miR gene product that is down-regulated in cancer cells) may successfully treat the cancer.

[000203] Accordingly, there is further provided herein methods of inhibiting tumorigenesis in a subject who has, or is suspected of having, a cancer wherein at least one miR gene product is deregulated (e.g., down-regulated, up-regulated) in the cancer cells of the subject. When the at least one isolated miR gene product is down-regulated in the cancer cells (e.g., miR-29 family), the method comprises administering an effective amount of the at least one isolated miR gene product, or an isolated variant or biologically-active fragment thereof, such that proliferation of cancer cells in the subject is inhibited.

[000204] For example, when a miR gene product is down-regulated in a cancer cell in a subject, administering an effective amount of an isolated miR gene product to the subject can inhibit proliferation of the cancer cell. The isolated miR gene product that is administered to the subject can be identical to the endogenous wild-type miR gene product (e.g., a miR gene product) that is down-regulated in the cancer cell or it can be a variant or biologically-active fragment thereof.

[000205] As defined herein, a "variant" of a miR gene product refers to a miRNA that has less than 100% identity to a corresponding wild-type miR gene product and possesses one or more biological activities of the corresponding wild-type miR gene product. Examples of such biological activities include, but are not limited to, inhibition of expression of a target RNA molecule (e.g., inhibiting translation of a target RNA molecule, modulating the stability of a target RNA molecule, inhibiting processing of a target RNA molecule) and inhibition of a cellular process associated with cancer (e.g., cell differentiation, cell growth, cell death). These variants include species variants and variants that are the consequence of one or more mutations (e.g., a substitution, a deletion, an insertion) in a miR gene. In certain embodiments, the variant is at least about 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%

identical to a corresponding wild-type miR gene product.

[000206]   As defined herein, a "biologically-active fragment" of a miR gene product refers to an RNA fragment of a miR gene product that possesses one or more biological activities of a corresponding wild-type miR gene product. As described above, examples of such biological activities include, but are not limited to, inhibition of expression of a target RNA molecule and inhibition of a cellular process associated with a cancer. In certain embodiments, the biologically-active fragment is at least about 5, 7, 10, 12, 15, or 17 nucleotides in length.

[000207]   In a particular embodiment, an isolated miR gene product can be administered to a subject in combination with one or more additional anti-cancer treatments. Suitable anti-cancer treatments include, but are not limited to, chemotherapy, radiation therapy and combinations thereof (e.g., chemoradiation).

[000208]   When the at least one isolated miR gene product is up-regulated in the cancer cells, the method comprises administering to the subject an effective amount of at least one compound for inhibiting expression of the at least one miR gene product, referred to herein as miR gene expression-inhibition compounds, such that proliferation of the cancer cells is inhibited. In a particular embodiment, the at least one miR expression-inhibition compound is specific for a miR gene product selected from the group consisting miR29 family, including miR-29a, miR-29b, miR-29c, and combinations thereof.

[000209]   The terms "treat", "treating" and "treatment", as used herein, refer to ameliorating symptoms associated with a disease or condition, for example, a cancer, including preventing or delaying the onset of the disease symptoms, and/or lessening the severity or frequency of symptoms of the disease or condition. The terms "subject", "patient" and "individual" are defined herein to include animals, such as mammals, including, but not limited to, primates, cows, sheep, goats, horses, dogs, cats, rabbits, guinea pigs, rats, mice or other bovine, ovine, equine, canine, feline, rodent, or murine species. In a preferred embodiment, the animal is a human.

[000210]   As used herein, an "effective amount" of an isolated miR gene product is an amount sufficient to inhibit proliferation of a cancer cell in a subject suffering from a cancer. One skilled in the art can readily determine an effective amount of a miR gene product to be administered to a given subject, by taking into account factors, such as the size and weight of the subject; the extent of disease penetration; the age, health and sex of the subject; the route of

administration; and whether the administration is regional or systemic.

[000211]   For example, an effective amount of an isolated miR gene product can be based on the approximate weight of a tumor mass to be treated. The approximate weight of a tumor mass can be determined by calculating the approximate volume of the mass, wherein one cubic centimeter of volume is roughly equivalent to one gram. An effective amount of the isolated miR gene product based on the weight of a tumor mass can be in the range of about 10-500 micrograms/gram of tumor mass. In certain embodiments, the tumor mass can be at least about 10 micrograms/gram of tumor mass, at least about 60 micrograms/gram of tumor mass or at least about 100 micrograms/gram of tumor mass.

[000212]   An effective amount of an isolated miR gene product can also be based on the approximate or estimated body weight of a subject to be treated. Preferably, such effective amounts are administered parenterally or enterally, as described herein. For example, an effective amount of the isolated miR gene product is administered to a subject can range from about 5 to about 3000 micrograms/kg of body weight, from about 700 - 1000 micrograms/kg of body weight, or greater than about 1000 micrograms/kg of body weight.

[000213]   One skilled in the art can also readily determine an appropriate dosage regimen for the administration of an isolated miR gene product to a given subject. For example, a miR gene product can be administered to the subject once (e.g., as a single injection or deposition). Alternatively, a miR gene product can be administered once or twice daily to a subject for a period of from about three to about twenty-eight days, more particularly from about seven to about ten days. In a particular dosage regimen, a miR gene product is administered once a day for seven days. Where a dosage regimen comprises multiple administrations, it is understood that the effective amount of the miR gene product administered to the subject can comprise the total amount of gene product administered over the entire dosage regimen.

[000214]   As used herein, an "isolated" miR gene product is one that is synthesized, or altered or removed from the natural state through human intervention. For example, a synthetic miR gene product, or a miR gene product partially or completely separated from the coexisting materials of its natural state, is considered to be "isolated." An isolated miR gene product can exist in substantially-purified form, or can exist in a cell into which the miR gene product has been delivered. Thus, a miR gene product that is deliberately delivered to, or expressed in, a cell is considered an "isolated" miR gene product. A miR gene product produced inside a cell from a miR precursor molecule is also considered to be an "isolated" molecule.

According to one particular embodiment, the isolated miR gene products described herein can be used for the manufacture of a medicament for treating a cancer in a subject (e.g., a human).

[000215]   Isolated miR gene products can be obtained using a number of standard techniques. For example, the miR gene products can be chemically synthesized or recombinantly produced using methods known in the art. In one embodiment, miR gene products are chemically synthesized using appropriately protected ribonucleoside phosphoramidites and a conventional DNA/RNA synthesizer. Commercial suppliers of synthetic RNA molecules or synthesis reagents include, e.g., Proligo (Hamburg, Germany), Dharmacon Research (Lafayette, CO, U.S.A.), Pierce Chemical (part of Perbio Science, Rockford, IL, U.S.A.), Glen Research (Sterling, VA, U.S.A.), ChemGenes (Ashland, MA, U.S.A.) and Cruachem (Glasgow, UK).

[000216]   Alternatively, the miR gene products can be expressed from recombinant circular or linear DNA plasmids using any suitable promoter. Suitable promoters for expressing RNA from a plasmid include, e.g., the U6 or H1 RNA pol III promoter sequences, or the cytomegalovirus promoters. Selection of other suitable promoters is within the skill in the art. The recombinant plasmids of the invention can also comprise inducible or regulatable promoters for expression of the miR gene products in cancer cells.

[000217]   The miR gene products that are expressed from recombinant plasmids can be isolated from cultured cell expression systems by standard techniques. The miR gene products that are expressed from recombinant plasmids can also be delivered to, and expressed directly in, the cancer cells. The use of recombinant plasmids to deliver the miR gene products to cancer cells is discussed in more detail below.

[000218]   The miR gene products can be expressed from a separate recombinant plasmid, or they can be expressed from the same recombinant plasmid. In one embodiment, the miR gene products are expressed as RNA precursor molecules from a single plasmid, and the precursor molecules are processed into the functional miR gene product by a suitable processing system, including, but not limited to, processing systems extant within a cancer cell. Other suitable processing systems include, e.g., the *in vitro* Drosophila cell lysate system (e.g., as described in U.S. Published Patent Application No. 2002/0086356 to Tuschl *et al.*, the entire disclosure of which is incorporated herein by reference) and the *E. coli* RNAse III system (e.g., as described in U.S. Published Patent Application No. 2004/0014113

to Yang *et al.*, the entire disclosure of which is incorporated herein by reference).

[000219] Selection of plasmids suitable for expressing the miR gene products, methods for inserting nucleic acid sequences into the plasmid to express the gene products, and methods of delivering the recombinant plasmid to the cells of interest are within the skill in the art. See, for example, Zeng *et al.* (2002), *Molecular Cell* 9:1327-1333; Tuschl (2002), *Nat. Biotechnol*, 20:446-448; Brummelkamp *et al.* (2002), *Science* 296:550-553; Miyagishi *et al.* (2002), *Nat. Biotechnol.* 20:497-500; Paddison *et al.* (2002), *Genes Dev.* 16:948-958; Lee *et al.* (2002), *Nat. Biotechnol.* 20:500-505; and Paul *et al.* (2002), *Nat. Biotechnol.* 20:505-508, the entire disclosures of which are incorporated herein by reference.

[000220] In one embodiment, a plasmid expressing the miR gene products comprises a sequence encoding a miR precursor RNA under the control of the CMV intermediate-early promoter. As used herein, "under the control" of a promoter means that the nucleic acid sequences encoding the miR gene product are located 3' of the promoter, so that the promoter can initiate transcription of the miR gene product coding sequences.

[000221] The miR gene products can also be expressed from recombinant viral vectors. It is contemplated that the miR gene products can be expressed from two separate recombinant viral vectors, or from the same viral vector. The RNA expressed from the recombinant viral vectors can either be isolated from cultured cell expression systems by standard techniques, or can be expressed directly in cancer cells. The use of recombinant viral vectors to deliver the miR gene products to cancer cells is discussed in more detail below.

[000222] The recombinant viral vectors of the invention comprise sequences encoding the miR gene products and any suitable promoter for expressing the RNA sequences. Suitable promoters include, but are not limited to, the U6 or H1 RNA pol III promoter sequences, or the cytomegalovirus promoters. Selection of other suitable promoters is within the skill in the art. The recombinant viral vectors of the invention can also comprise inducible or regulatable promoters for expression of the miR gene products in a cancer cell.

[000223] Any viral vector capable of accepting the coding sequences for the miR gene products can be used; for example, vectors derived from adenovirus (AV); adeno-associated virus (AAV); retroviruses (*e.g.,* lentiviruses (LV), Rhabdoviruses, murine leukemia virus); herpes virus, and the like. The tropism of the viral vectors can be modified by pseudotyping the vectors with envelope proteins or other surface antigens from other viruses, or by substituting

different viral capsid proteins, as appropriate.

[000224] For example, lentiviral vectors of the invention can be pseudotyped with surface proteins from vesicular stomatitis virus (VSV), rabies, Ebola, Mokola, and the like. AAV vectors of the invention can be made to target different cells by engineering the vectors to express different capsid protein serotypes. For example, an AAV vector expressing a serotype 2 capsid on a serotype 2 genome is called AAV 2/2. This serotype 2 capsid gene in the AAV 2/2 vector can be replaced by a serotype 5 capsid gene to produce an AAV 2/5 vector. Techniques for constructing AAV vectors that express different capsid protein serotypes are within the skill in the art; *see, e.g.*, Rabinowitz, J.E., *et al.* (2002), *J. Virol.* 76:791-801, the entire disclosure of which is incorporated herein by reference.

[000225] Selection of recombinant viral vectors suitable for use in the invention, methods for inserting nucleic acid sequences for expressing RNA into the vector, methods of delivering the viral vector to the cells of interest, and recovery of the expressed RNA products are within the skill in the art. See, for example, Dornburg (1995), *Gene Therapy* 2:301-310; Eglitis (1988), *Biotechniques* 6:608-614; Miller (1990), *Hum. Gene Therapy* 1:5-14; and Anderson (1998), *Nature* 392:25-30, the entire disclosures of which are incorporated herein by reference.

[000226] Particularly suitable viral vectors are those derived from AV and AAV. A suitable AV vector for expressing the miR gene products, a method for constructing the recombinant AV vector, and a method for delivering the vector into target cells, are described in Xia *et al.* (2002), *Nat. Biotech.* 20:1006-1010, the entire disclosure of which is incorporated herein by reference. Suitable AAV vectors for expressing the miR gene products, methods for constructing the recombinant AAV vector, and methods for delivering the vectors into target cells are described in Samulski *et al.* (1987), *J. Virol.* 61:3096-3101; Fisher *et al.* (1996), *J. Virol.*, 70:520-532; Samulski *et al.* (1989), *J. Virol.* 63:3822-3826; U.S. Pat. No. 5,252,479; U.S. Pat. No. 5,139,941; International Patent Application No. WO 94/13788; and International Patent Application No. WO 93/24641, the entire disclosures of which are incorporated herein by reference. In one embodiment, the miR gene products are expressed from a single recombinant AAV vector comprising the CMV intermediate early promoter.

[000227] In a certain embodiment, a recombinant AAV viral vector of the invention comprises a nucleic acid sequence encoding a miR precursor RNA in operable connection with a polyT termination sequence under the control of a human U6 RNA promoter. As used herein, "in

operable connection with a polyT termination sequence" means that the nucleic acid sequences encoding the sense or antisense strands are immediately adjacent to the polyT termination signal in the 5' direction. During transcription of the miR sequences from the vector, the polyT termination signals act to terminate transcription.

[000228] In other embodiments of the treatment methods of the invention, an effective amount of at least one compound that inhibits miR expression can be administered to the subject. As used herein, "inhibiting miR expression" means that the production of the precursor and/or active, mature form of miR gene product after treatment is less than the amount produced prior to treatment. One skilled in the art can readily determine whether miR expression has been inhibited in a cancer cell, using, for example, the techniques for determining miR transcript level discussed above for the diagnostic method. Inhibition can occur at the level of gene expression (i.e., by inhibiting transcription of a miR gene encoding the miR gene product) or at the level of processing (e.g., by inhibiting processing of a miR precursor into a mature, active miR).

[000229] As used herein, an "effective amount" of a compound that inhibits miR expression is an amount sufficient to inhibit proliferation of a cancer cell in a subject suffering from a cancer (e.g., a cancer). One skilled in the art can readily determine an effective amount of a miR expression-inhibition compound to be administered to a given subject, by taking into account factors, such as the size and weight of the subject; the extent of disease penetration; the age, health and sex of the subject; the route of administration; and whether the administration is regional or systemic.

[000230] For example, an effective amount of the expression-inhibition compound can be based on the approximate weight of a tumor mass to be treated, as described herein. An effective amount of a compound that inhibits miR expression can also be based on the approximate or estimated body weight of a subject to be treated, as described herein.

[000231] One skilled in the art can also readily determine an appropriate dosage regimen for administering a compound that inhibits miR expression to a given subject.

[000232] Suitable compounds for inhibiting miR gene expression include double-stranded RNA (such as short- or small-interfering RNA or "siRNA"), antisense nucleic acids, and enzymatic RNA molecules, such as ribozymes. Each of these compounds can be targeted to a given miR gene product and interfere with the expression of (e.g., inhibit translation of, induce

cleavage or destruction of) the target miR gene product.

[000233]   For example, expression of a given miR gene can be inhibited by inducing RNA interference of the miR gene with an isolated double-stranded RNA ("dsRNA") molecule which has at least 90%, for example at least 95%, at least 98%, at least 99%, or 100%, sequence homology with at least a portion of the miR gene product. In a particular embodiment, the dsRNA molecule is a "short or small interfering RNA" or "siRNA."

[000234]   siRNA useful in the present methods comprise short double-stranded RNA from about 17 nucleotides to about 29 nucleotides in length, preferably from about 19 to about 25 nucleotides in length. The siRNA comprise a sense RNA strand and a complementary antisense RNA strand annealed together by standard Watson-Crick base-pairing interactions (hereinafter "base-paired"). The sense strand comprises a nucleic acid sequence that is substantially identical to a nucleic acid sequence contained within the target miR gene product.

[000235]   As used herein, a nucleic acid sequence in an siRNA which is "substantially identical" to a target sequence contained within the target mRNA is a nucleic acid sequence that is identical to the target sequence, or that differs from the target sequence by one or two nucleotides. The sense and antisense strands of the siRNA can comprise two complementary, single-stranded RNA molecules, or can comprise a single molecule in which two complementary portions are base-paired and are covalently linked by a single-stranded "hairpin" area.

[000236]   The siRNA can also be altered RNA that differs from naturally-occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides. Such alterations can include addition of non-nucleotide material, such as to the end(s) of the siRNA or to one or more internal nucleotides of the siRNA, or modifications that make the siRNA resistant to nuclease digestion, or the substitution of one or more nucleotides in the siRNA with deoxyribonucleotides.

[000237]   One or both strands of the siRNA can also comprise a 3' overhang. As used herein, a "3' overhang" refers to at least one unpaired nucleotide extending from the 3'-end of a duplexed RNA strand. Thus, in certain embodiments, the siRNA comprises at least one 3' overhang of from 1 to about 6 nucleotides (which includes ribonucleotides or deoxyribonucleotides) in length, from 1 to about 5 nucleotides in length, from 1 to about 4

nucleotides in length, or from about 2 to about 4 nucleotides in length. In a particular embodiment, the 3' overhang is present on both strands of the siRNA, and is 2 nucleotides in length. For example, each strand of the siRNA can comprise 3' overhangs of dithymidylic acid ("TT") or diuridylic acid ("uu").

[000238] The siRNA can be produced chemically or biologically, or can be expressed from a recombinant plasmid or viral vector, as described above for the isolated miR gene products. Exemplary methods for producing and testing dsRNA or siRNA molecules are described in U.S. Published Patent Application No. 2002/0173478 to Gewirtz and in U.S. Published Patent Application No. 2004/0018176 to Reich *et al.*, the entire disclosures of both of which are incorporated herein by reference.

[000239] Expression of a given miR gene can also be inhibited by an antisense nucleic acid. As used herein, an "antisense nucleic acid" refers to a nucleic acid molecule that binds to target RNA by means of RNA-RNA, RNA-DNA or RNA-peptide nucleic acid interactions, which alters the activity of the target RNA. Antisense nucleic acids suitable for use in the present methods are single-stranded nucleic acids (*e.g.*, RNA, DNA, RNA-DNA chimeras, peptide nucleic acid (PNA)) that generally comprise a nucleic acid sequence complementary to a contiguous nucleic acid sequence in a miR gene product. The antisense nucleic acid can comprise a nucleic acid sequence that is 50-100% complementary, 75-100% complementary, or 95-100% complementary to a contiguous nucleic acid sequence in a miR gene product.

[000240] Without wishing to be bound by any theory, it is believed that the antisense nucleic acids activate RNase H or another cellular nuclease that digests the miR gene product/antisense nucleic acid duplex.

[000241] Antisense nucleic acids can also contain modifications to the nucleic acid backbone or to the sugar and base moieties (or their equivalent) to enhance target specificity, nuclease resistance, delivery or other properties related to efficacy of the molecule. Such modifications include cholesterol moieties, duplex intercalators, such as acridine, or one or more nuclease-resistant groups.

[000242] Antisense nucleic acids can be produced chemically or biologically, or can be expressed from a recombinant plasmid or viral vector, as described above for the isolated miR gene products. Exemplary methods for producing and testing are within the skill in the art; *see, e.g.*, Stein and Cheng (1993), *Science* 261:1004 and U.S. Pat. No. 5,849,902 to

Woolf *et al.,* the entire disclosures of which are incorporated herein by reference.

[000243] Expression of a given miR gene can also be inhibited by an enzymatic nucleic acid. As used herein, an "enzymatic nucleic acid" refers to a nucleic acid comprising a substrate binding region that has complementarity to a contiguous nucleic acid sequence of a miR gene product, and which is able to specifically cleave the miR gene product. The enzymatic nucleic acid substrate binding region can be, for example, 50-100% complementary, 75-100% complementary, or 95-100% complementary to a contiguous nucleic acid sequence in a miR gene product. The enzymatic nucleic acids can also comprise modifications at the base, sugar, and/or phosphate groups.

[000244] Exemplary enzymatic nucleic acids for use in the present methods include *de novo* methyltransferases, including DNMT3A and DNMT3B, as described in the Examples herein.

[000245] The enzymatic nucleic acids can be produced chemically or biologically, or can be expressed from a recombinant plasmid or viral vector, as described above for the isolated miR gene products. Exemplary methods for producing and testing dsRNA or siRNA molecules are described in Werner and Uhlenbeck (1995), *Nucl. Acids Res.* 23:2092-96; Hammann *et al.* (1999), *Antisense and Nucleic Acid Drug Dev.* 9:25-31; and U.S. Pat. No. 4,987,071 to Cech *et al*, the entire disclosures of which are incorporated herein by reference.

[000246] Administration of at least one miR gene product, or at least one compound for inhibiting miR expression, will inhibit the proliferation of cancer cells in a subject who has a cancer.

[000247] As used herein, to "inhibit the proliferation of a cancer cell" means to kill the cell, or permanently or temporarily arrest or slow the growth of the cell. Inhibition of cancer cell proliferation can be inferred if the number of such cells in the subject remains constant or decreases after administration of the miR gene products or miR gene expression-inhibition compounds. An inhibition of cancer cell proliferation can also be inferred if the absolute number of such cells increases, but the rate of tumor growth decreases.

[000248] The number of cancer cells in the body of a subject can be determined by direct measurement, or by estimation from the size of primary or metastatic tumor masses. For example, the number of cancer cells in a subject can be measured by immunohistological methods, flow cytometry, or other techniques designed to detect characteristic surface markers of cancer cells.

[000249] The size of a tumor mass can be ascertained by direct visual observation, or by diagnostic imaging methods, such as X-ray, magnetic resonance imaging, ultrasound, and scintigraphy. Diagnostic imaging methods used to ascertain size of the tumor mass can be employed with or without contrast agents, as is known in the art. The size of a tumor mass can also be ascertained by physical means, such as palpation of the tissue mass or measurement of the tissue mass with a measuring instrument, such as a caliper.

[000250] The miR gene products or miR gene expression-inhibition compounds can be administered to a subject by any means suitable for delivering these compounds to cancer cells of the subject. For example, the miR gene products or miR expression-inhibition compounds can be administered by methods suitable to transfect cells of the subject with these compounds, or with nucleic acids comprising sequences encoding these compounds.

[000251] In one embodiment, the cells are transfected with a plasmid or viral vector comprising sequences encoding at least one miR gene product or miR gene expression-inhibition compound.

[000252] Transfection methods for eukaryotic cells are well known in the art, and include, e.g., direct injection of the nucleic acid into the nucleus or pronucleus of a cell; electroporation; liposome transfer or transfer mediated by lipophilic materials; receptor-mediated nucleic acid delivery, bioballistic or particle acceleration; calcium phosphate precipitation, and transfection mediated by viral vectors.

[000253] For example, cells can be transfected with a liposomal transfer compound, e.g., DOTAP (N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethyl-ammonium methylsulfate, Boehringer-Mannheim) or an equivalent, such as LIPOFECTIN. The amount of nucleic acid used is not critical to the practice of the invention; acceptable results may be achieved with 0.1-100 micrograms of nucleic acid/10^5 cells. For example, a ratio of about 0.5 micrograms of plasmid vector in 3 micrograms of DOTAP per 10^5 cells can be used.

[000254] A miR gene product or miR gene expression-inhibition compound can also be administered to a subject by any suitable enteral or parenteral administration route. Suitable enteral administration routes for the present methods include, e.g., oral, rectal, or intranasal delivery. Suitable parenteral administration routes include, e.g., intravascular administration (e.g., intravenous bolus injection, intravenous infusion, intra-arterial bolus injection, intra-arterial infusion and catheter instillation into the vasculature); peri- and intra-tissue injection

(e.g., peri-tumoral and intra-tumoral injection, intra-retinal injection, or subretinal injection); subcutaneous injection or deposition, including subcutaneous infusion (such as by osmotic pumps); direct application to the tissue of interest, for example by a catheter or other placement device (e.g., a retinal pellet or a suppository or an implant comprising a porous, non-porous, or gelatinous material); and inhalation. Particularly suitable administration routes are injection, infusion and direct injection into the tumor.

[000255] In the present methods, a miR gene product or miR gene product expression-inhibition compound can be administered to the subject either as naked RNA, in combination with a delivery reagent, or as a nucleic acid (e.g., a recombinant plasmid or viral vector) comprising sequences that express the miR gene product or miR gene product expression-inhibition compound. Suitable delivery reagents include, e.g., the Mirus Transit TKO lipophilic reagent; lipofectin; lipofectamine; cellfectin; polycations (e.g., polylysine), and liposomes.

[000256] Recombinant plasmids and viral vectors comprising sequences that express the miR gene products or miR gene expression-inhibition compounds, and techniques for delivering such plasmids and vectors to cancer cells, are discussed herein and/or are well known in the art.

[000257] In a particular embodiment, liposomes are used to deliver a miR gene product or miR gene expression-inhibition compound (or nucleic acids comprising sequences encoding them) to a subject. Liposomes can also increase the blood half-life of the gene products or nucleic acids. Suitable liposomes for use in the invention can be formed from standard vesicle-forming lipids, which generally include neutral or negatively charged phospholipids and a sterol, such as cholesterol. The selection of lipids is generally guided by consideration of factors, such as the desired liposome size and half-life of the liposomes in the blood stream. A variety of methods are known for preparing liposomes, for example, as described in Szoka et al. (1980), Ann. Rev. Biophys. Bioeng. 9:467; and U.S. Pat. Nos. 4,235,871, 4,501,728, 4,837,028, and 5,019,369, the entire disclosures of which are incorporated herein by reference.

[000258] The liposomes for use in the present methods can comprise a ligand molecule that targets the liposome to cancer cells. Ligands that bind to receptors prevalent in cancer cells, such as monoclonal antibodies that bind to tumor cell antigens, are preferred.

[000259]   The liposomes for use in the present methods can also be modified so as to avoid clearance by the mononuclear macrophage system ("MMS") and reticuloendothelial system ("RES"). Such modified liposomes have opsonization-inhibition moieties on the surface or incorporated into the liposome structure. In a particularly preferred embodiment, a liposome of the invention can comprise both an opsonization-inhibition moiety and a ligand.

[000260]   Opsonization-inhibiting moieties for use in preparing the liposomes of the invention are typically large hydrophilic polymers that are bound to the liposome membrane. As used herein, an opsonization-inhibiting moiety is "bound" to a liposome membrane when it is chemically or physically attached to the membrane, e.g., by the intercalation of a lipid-soluble anchor into the membrane itself, or by binding directly to active groups of membrane lipids. These opsonization-inhibiting hydrophilic polymers form a protective surface layer that significantly decreases the uptake of the liposomes by the MMS and RES; e.g., as described in U.S. Pat. No. 4,920,016, the entire disclosure of which is incorporated herein by reference.

[000261]   Opsonization-inhibiting moieties suitable for modifying liposomes are preferably water-soluble polymers with a number-average molecular weight from about 500 to about 40,000 daltons, and more preferably from about 2,000 to about 20,000 daltons. Such polymers include polyethylene glycol (PEG) or polypropylene glycol (PPG) derivatives; e.g., methoxy PEG or PPG, and PEG or PPG stearate; synthetic polymers, such as polyacrylamide or poly N-vinyl pyrrolidone; linear, branched, or dendrimeric polyamidoamines; polyacrylic acids; polyalcohols, e.g., polyvinylalcohol and polyxylitol to which carboxylic or amino groups are chemically linked, as well as gangliosides, such as ganglioside GM1. Copolymers of PEG, methoxy PEG, or methoxy PPG, or derivatives thereof, are also suitable. In addition, the opsonization-inhibiting polymer can be a block copolymer of PEG and either a polyamino acid, polysaccharide, polyamidoamine, polyethyleneamine, or polynucleotide. The opsonization-inhibiting polymers can also be natural polysaccharides containing amino acids or carboxylic acids, e.g., galacturonic acid, glucuronic acid, mannuronic acid, hyaluronic acid, pectic acid, neuraminic acid, alginic acid, carrageenan; aminated polysaccharides or oligosaccharides (linear or branched); or carboxylated polysaccharides or oligosaccharides, e.g., reacted with derivatives of carbonic acids with resultant linking of carboxylic groups. Preferably, the opsonization-inhibiting moiety is a PEG, PPG, or a derivative thereof. Liposomes modified with PEG or PEG-derivatives are sometimes called

"PEGylated liposomes."

[000262] The opsonization-inhibiting moiety can be bound to the liposome membrane by any one of numerous well-known techniques. For example, an N-hydroxysuccinimide ester of PEG can be bound to a phosphatidyl-ethanolamine lipid-soluble anchor, and then bound to a membrane. Similarly, a dextran polymer can be derivatized with a stearylamine lipid-soluble anchor via reductive amination using Na(CN)BH$_3$ and a solvent mixture, such as tetrahydrofuran and water in a 30:12 ratio at 60 °C.

[000263] Liposomes modified with opsonization-inhibition moieties remain in the circulation much longer than unmodified liposomes. For this reason, such liposomes are sometimes called "stealth" liposomes. Stealth liposomes are known to accumulate in tissues fed by porous or "leaky" microvasculature. Thus, tissue characterized by such microvasculature defects, for example, tumors, will efficiently accumulate these liposomes; see Gabizon, *et al.* (1988), Proc. Natl. Acad. Sci., U.S.A., 18:6949-53. In addition, the reduced uptake by the RES lowers the toxicity of stealth liposomes by preventing significant accumulation of the liposomes in the liver and spleen. Thus, liposomes that are modified with opsonization-inhibition moieties are particularly suited to deliver the miR gene products or miR gene expression-inhibition compounds (or nucleic acids comprising sequences encoding them) to tumor cells.

[000264] The miR gene products or miR gene expression-inhibition compounds can be formulated as pharmaceutical compositions, sometimes called "medicaments," prior to administering them to a subject, according to techniques known in the art. Accordingly, the invention encompasses pharmaceutical compositions for treating a cancer.

[000265] In one embodiment, the pharmaceutical composition comprises at least one isolated miR gene product, or an isolated variant or biologically-active fragment thereof, and a pharmaceutically-acceptable carrier. In a particular embodiment, the at least one miR gene product corresponds to a miR gene product that has a decreased level of expression in cancer cells relative to suitable control cells.

[000266] In other embodiments, the pharmaceutical compositions of the invention comprise at least one miR expression-inhibition compound. In a particular embodiment, the at least one miR gene expression-inhibition compound is specific for a miR gene whose expression is greater in cancer cells than control cells.

[000267] Pharmaceutical compositions of the present invention are characterized as being at least sterile and pyrogen-free. As used herein, "pharmaceutical compositions" include formulations for human and veterinary use. Methods for preparing pharmaceutical compositions of the invention are within the skill in the art, for example as described in Remington's Pharmaceutical Science, 17th ed., Mack Publishing Company, Easton, Pa. (1985), the entire disclosure of which is incorporated herein by reference.

[000268] The present pharmaceutical compositions comprise at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising sequences encoding them) (e.g., 0.1 to 90% by weight), or a physiologically-acceptable salt thereof, mixed with a pharmaceutically-acceptable carrier. In certain embodiments, the pharmaceutical compositions of the invention additionally comprise one or more anti-cancer agents (e.g., chemotherapeutic agents). The pharmaceutical formulations of the invention can also comprise at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising sequences encoding them), which are encapsulated by liposomes and a pharmaceutically-acceptable carrier. In one embodiment, the pharmaceutical composition comprises a miR gene or gene product that is one or more of miR29a, miR-29b and miR-29c.

[000269] Especially suitable pharmaceutically-acceptable carriers are water, buffered water, normal saline, 0.4% saline, 0.3% glycine, hyaluronic acid and the like.

[000270] In a particular embodiment, the pharmaceutical compositions of the invention comprise at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising sequences encoding them) that is resistant to degradation by nucleases.

[000271] One skilled in the art can readily synthesize nucleic acids that are nuclease resistant, for example, by incorporating one or more ribonucleotides that is modified at the 2'-position into the miR gene product. Suitable 2'-modified ribonucleotides include those modified at the 2'-position with fluoro, amino, alkyl, alkoxy, and O-allyl.

[000272] **Pharmaceutical Compositions**

[000273] Pharmaceutical compositions of the invention can also comprise conventional pharmaceutical excipients and/or additives. Suitable pharmaceutical excipients include stabilizers, antioxidants, osmolality adjusting agents, buffers, and pH adjusting agents.

Suitable additives include, e.g., physiologically biocompatible buffers (e.g., tromethamine hydrochloride), additions of chelants (such as, for example, DTPA or DTPA-bisamide) or calcium chelate complexes (such as, for example, calcium DTPA, CaNaDTPA-bisamide), or, optionally, additions of calcium or sodium salts (for example, calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate). Pharmaceutical compositions of the invention can be packaged for use in liquid form, or can be lyophilized.

[000274] For solid pharmaceutical compositions of the invention, conventional nontoxic solid pharmaceutically-acceptable carriers can be used; for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like.

[000275] For example, a solid pharmaceutical composition for oral administration can comprise any of the carriers and excipients listed above and 10-95%, preferably 25%-75%, of the at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising sequences encoding them). A pharmaceutical composition for aerosol (inhalational) administration can comprise 0.01-20% by weight, preferably 1%-10% by weight, of the at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising sequences encoding them) encapsulated in a liposome as described above, and a propellant. A carrier can also be included as desired; e.g., lecithin for intranasal delivery.

[000276] The pharmaceutical compositions of the invention can further comprise one or more anti-cancer agents. In a particular embodiment, the compositions comprise at least one miR gene product or miR gene expression-inhibition compound (or at least one nucleic acid comprising sequences encoding them) and at least one chemotherapeutic agent. Chemotherapeutic agents that are suitable for the methods of the invention include, but are not limited to, DNA-alkylating agents, anti-tumor antibiotic agents, anti-metabolic agents, tubulin stabilizing agents, tubulin destabilizing agents, hormone antagonist agents, topoisomerase inhibitors, protein kinase inhibitors, HMG-CoA inhibitors, CDK inhibitors, cyclin inhibitors, caspase inhibitors, metalloproteinase inhibitors, antisense nucleic acids, triple-helix DNAs, nucleic acids aptamers, and molecularly-modified viral, bacterial and exotoxic agents. Examples of suitable agents for the compositions of the present invention include, but are not limited to, cytidine arabinoside, methotrexate, vincristine, etoposide (VP-16), doxorubicin (adriamycin), cisplatin (CDDP), dexamethasone, arglabin,

cyclophosphamide, sarcolysin, methylnitrosourea, fluorouracil, 5-fluorouracil (5FU),
vinblastine, camptothecin, actinomycin-D, mitomycin C, hydrogen peroxide, oxaliplatin,
irinotecan, topotecan, leucovorin, carmustine, streptozocin, CPT-11, taxol, tamoxifen,
dacarbazine, rituximab, daunorubicin, 1-β-D-arabinofuranosylcytosine, imatinib, fludarabine,
docetaxel, FOLFOX4.

[000277] **Inhibitors of Tumorigenesis**

[000278] There is also provided herein methods of identifying an inhibitor of tumorigenesis,
comprising providing a test agent to a cell and measuring the level of at least one miR gene
product in the cell. In one embodiment, the method comprises providing a test agent to a cell
and measuring the level of at least one miR gene product associated with decreased
expression levels in cancer cells. An increase in the level of the miR gene product in the cell
after the agent is provided, relative to a suitable control cell (e.g., agent is not provided), is
indicative of the test agent being an inhibitor of tumorigenesis.

[000279] In other embodiments, the method comprises providing a test agent to a cell and
measuring the level of at least one miR gene product associated with increased expression
levels in cancer cells. A decrease in the level of the miR gene product in the cell after the
agent is provided, relative to a suitable control cell (e.g., agent is not provided), is indicative
of the test agent being an inhibitor of tumorigenesis. In a particular embodiment, at least one
miR gene product associated with increased expression levels in cancer cells is selected from
the group consisting of miR29a, miR-29b, miR-29c, and combinations thereof.

[000280] Suitable agents include, but are not limited to drugs (e.g., small molecules, peptides),
and biological macromolecules (e.g., proteins, nucleic acids). The agent can be produced
recombinantly, synthetically, or it may be isolated (i.e., purified) from a natural source.
Various methods for providing such agents to a cell (e.g., transfection) are well known in the
art, and several of such methods are described hereinabove. Methods for detecting the
expression of at least one miR gene product (e.g., Northern blotting, *in situ* hybridization,
RT-PCR, expression profiling) are also well known in the art. Several of these methods are
also described hereinabove.

[000281] **EXAMPLE IV**

[000282] **Methods, Reagents and Kits for Diagnosing, Staging, Prognosing, Monitoring
and Treating Cancer-Related Diseases.**

[000283]   It is to be understood that all examples herein are to be considered non-limiting in their scope. Various aspects are described in further detail in the following subsections.

[000284]   **Diagnostic Methods**

[000285]   In one embodiment, there is provided a diagnostic method of assessing whether a patient has a cancer-related disease or has higher than normal risk for developing a cancer-related disease, comprising the steps of comparing the level of expression of a marker in a patient sample and the normal level of expression of the marker in a control, e.g., a sample from a patient without a cancer-related disease.

[000286]   A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with a cancer-related disease or has higher than normal risk for developing a cancer-related disease.

[000287]   The markers are selected such that the positive predictive value of the methods is at least about 10%, and in certain non-limiting embodiments, about 25%, about 50% or about 90%. Also preferred for use in the methods are markers that are differentially expressed, as compared to normal cells, by at least two-fold in at least about 20%, and in certain non-limiting embodiments, about 50% or about 75%.

[000288]   In one diagnostic method of assessing whether a patient is afflicted with a cancer-related disease (e.g., new detection ("screening"), detection of recurrence, reflex testing), the method comprises comparing: a) the level of expression of a marker in a patient sample, and b) the normal level of expression of the marker in a control non-cancer-related disease sample. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with a cancer-related disease.

[000289]   There is also provided diagnostic methods for assessing the efficacy of a therapy for inhibiting a cancer-related disease in a patient. Such methods comprise comparing: a) expression of a marker in a first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, and b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy. A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the therapy is efficacious for inhibiting a cancer-related disease in the patient.

[000290]   It will be appreciated that in these methods the "therapy" may be any therapy for treating a cancer-related disease including, but not limited to, pharmaceutical compositions, gene therapy and biologic therapy such as the administering of antibodies and chemokines. Thus, the methods described herein may be used to evaluate a patient before, during and after therapy, for example, to evaluate the reduction in disease state.

[000291]   In certain aspects, the diagnostic methods are directed to therapy using a chemical or biologic agent. These methods comprise comparing: a) expression of a marker in a first sample obtained from the patient and maintained in the presence of the chemical or biologic agent, and b) expression of the marker in a second sample obtained from the patient and maintained in the absence of the agent. A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the agent is efficacious for inhibiting a cancer-related disease in the patient. In one embodiment, the first and second samples can be portions of a single sample obtained from the patient or portions of pooled samples obtained from the patient.

[000292]   **Methods for Assessing Prognosis**

[000293]   There is also provided a monitoring method for assessing the progression of a cancer-related disease in a patient, the method comprising: a) detecting in a patient sample at a first time point, the expression of a marker; b) repeating step a) at a subsequent time point in time; and c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of a cancer-related disease in the patient. A significantly higher level of expression of the marker in the sample at the subsequent time point from that of the sample at the first time point is an indication that the cancer-related disease has progressed, whereas a significantly lower level of expression is an indication that the cancer-related disease has regressed.

[000294]   There is further provided a diagnostic method for determining whether a cancer-related disease has worsened or is likely to worsen in the future, the method comprising comparing: a) the level of expression of a marker in a patient sample, and b) the normal level of expression of the marker in a control sample. A significantly higher level of expression in the patient sample as compared to the normal level is an indication that the cancer-related disease has worsened or is likely to worsen in the future.

[000295]   **Methods for Assessing Inhibitory, Therapeutic and/or Harmful Compositions**

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[000296]   There is also provided a test method for selecting a composition for inhibiting a cancer-related disease in a patient. This method comprises the steps of: a) obtaining a sample comprising cells from the patient; b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions; c) comparing expression of a marker in each of the aliquots; and d) selecting one of the test compositions which significantly reduces the level of expression of the marker in the aliquot containing that test composition, relative to the levels of expression of the marker in the presence of the other test compositions.

[000297]   There is additionally provided a test method of assessing the harmful potential of a compound in causing a cancer-related disease. This method comprises the steps of: a) maintaining separate aliquots of cells in the presence and absence of the compound; and b) comparing expression of a marker in each of the aliquots. A significantly higher level of expression of the marker in the aliquot maintained in the presence of the compound, relative to that of the aliquot maintained in the absence of the compound, is an indication that the compound possesses such harmful potential.

[000298]   In addition, there is further provided a method of inhibiting a cancer-related disease in a patient. This method comprises the steps of: a) obtaining a sample comprising cells from the patient; b) separately maintaining aliquots of the sample in the presence of a plurality of compositions; c) comparing expression of a marker in each of the aliquots; and d) administering to the patient at least one of the compositions which significantly lowers the level of expression of the marker in the aliquot containing that composition, relative to the levels of expression of the marker in the presence of the other compositions.

[000299]   The level of expression of a marker in a sample can be assessed, for example, by detecting the presence in the sample of: the corresponding marker protein or a fragment of the protein (e.g. by using a reagent, such as an antibody, an antibody derivative, an antibody fragment or single-chain antibody, which binds specifically with the protein or protein fragment) the corresponding marker nucleic acid (e.g. a nucleotide transcript, or a complement thereof), or a fragment of the nucleic acid (e.g. by contacting transcribed polynucleotides obtained from the sample with a substrate having affixed thereto one or more nucleic acids having the entire or a segment of the nucleic acid sequence or a complement thereof) a metabolite which is produced directly (i.e., catalyzed) or indirectly by the corresponding marker protein.

[000300]   Any of the aforementioned methods may be performed using at least one or a plurality

(e.g., 2, 3, 5, or 10 or more) of cancer-related disease markers. In such methods, the level of expression in the sample of each of a plurality of markers, at least one of which is a marker, is compared with the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with a cancer-related disease. A significantly altered (i.e., increased or decreased as specified in the above-described methods using a single marker) level of expression in the sample of one or more markers, or some combination thereof, relative to that marker's corresponding normal or control level, is an indication that the patient is afflicted with a cancer-related disease. For all of the aforementioned methods, the marker(s) are selected such that the positive predictive value of the method is at least about 10%.

[000301] **Examples of Candidate Agents**

[000302] The candidate agents may be pharmacologic agents already known in the art or may be agents previously unknown to have any pharmacological activity. The agents may be naturally arising or designed in the laboratory. They may be isolated from microorganisms, animals or plants, or may be produced recombinantly, or synthesized by any suitable chemical method. They may be small molecules, nucleic acids, proteins, peptides or peptidomimetics. In certain embodiments, candidate agents are small organic compounds having a molecular weight of more than 50 and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins. Candidate agents are also found among biomolecules including, but not limited to: peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof.

[000303] Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. There are, for example, numerous means available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides and oligopeptides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means, and may be used to produce combinatorial libraries. In certain embodiments, the candidate agents can be obtained using any of the numerous approaches in combinatorial library methods art, including, by non-limiting example: biological libraries; spatially

addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection.

[000304]   In certain further embodiments, certain pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification, etc. to produce structural analogs.

[000305]   The same methods for identifying therapeutic agents for treating a cancer-related disease can also be used to validate lead compounds/agents generated from in vitro studies.

[000306]   The candidate agent may be an agent that up- or down-regulates one or more cancer-related disease response pathways. In certain embodiments, the candidate agent may be an antagonist that affects such pathway.

[000307]   **Methods for Treating a Cancer-related Disease**

[000308]   There is provided herein methods for treating, inhibiting, relieving or reversing a cancer-related disease response. In the methods described herein, an agent that interferes with a signaling cascade is administered to an individual in need thereof, such as, but not limited to, cancer-related disease patients in whom such complications are not yet evident and those who already have at least one cancer-related disease response.

[000309]   In the former instance, such treatment is useful to prevent the occurrence of such cancer-related disease response and/or reduce the extent to which they occur. In the latter instance, such treatment is useful to reduce the extent to which such cancer-related disease response occurs, prevent their further development or reverse the cancer-related disease response.

[000310]   In certain embodiments, the agent that interferes with the cancer-related disease response cascade may be an antibody specific for such response.

[000311]   **Expression of Markers**

[000312]   Expression of a marker can be inhibited in a number of ways, including, by way of a non-limiting example, an antisense oligonucleotide can be provided to the cancer-related disease cells in order to inhibit transcription, translation, or both, of the marker(s). Alternately, a polynucleotide encoding an antibody, an antibody derivative, or an antibody fragment which specifically binds a marker protein, and operably linked with an appropriate

promoter/regulator region, can be provided to the cell in order to generate intracellular antibodies which will inhibit the function or activity of the protein. The expression and/or function of a marker may also be inhibited by treating the cancer-related disease cell with an antibody, antibody derivative or antibody fragment that specifically binds a marker protein. Using the methods described herein, a variety of molecules, particularly including molecules sufficiently small that they are able to cross the cell membrane, can be screened in order to identify molecules which inhibit expression of a marker or inhibit the function of a marker protein. The compound so identified can be provided to the patient in order to inhibit cancer-related disease cells of the patient.

[000313] Any marker or combination of markers, as well as any certain markers in combination with the markers, may be used in the compositions, kits and methods described herein. In general, it is desirable to use markers for which the difference between the level of expression of the marker in cancer-related disease cells and the level of expression of the same marker in normal cells is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the marker, it is desirable that the difference be at least greater than the standard error of the assessment method, and, in certain embodiments, a difference of at least 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 100-, 500-, 1000-fold or greater than the level of expression of the same marker in normal tissue.

[000314] It is recognized that certain marker proteins are secreted to the extracellular space surrounding the cells. These markers are used in certain embodiments of the compositions, kits and methods, owing to the fact that such marker proteins can be detected in a cancer-associated body fluid sample, which may be more easily collected from a human patient than a tissue biopsy sample. In addition, in vivo techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

[000315] In order to determine whether any particular marker protein is a secreted protein, the marker protein is expressed in, for example, a mammalian cell, such as a human cell line, extracellular fluid is collected, and the presence or absence of the protein in the extracellular fluid is assessed (e.g. using a labeled antibody which binds specifically with the protein).

[000316] It will be appreciated that patient samples containing tissue and/or fluid cells may be used in the methods described herein. In these embodiments, the level of expression of the

marker can be assessed by assessing the amount (e.g., absolute amount or concentration) of the marker in a sample. The cell sample can, of course, be subjected to a variety of post-collection preparative and storage techniques (e.g., nucleic acid and/or protein extraction, fixation, storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the sample.

[000317] It will also be appreciated that the markers may be shed from the cells into the digestive system, the blood stream and/or interstitial spaces. The shed markers can be tested, for example, by examining the serum or plasma.

[000318] The compositions, kits and methods can be used to detect expression of marker proteins having at least one portion which is displayed on the surface of cells which express it. For example, immunological methods may be used to detect such proteins on whole cells, or computer-based sequence analysis methods may be used to predict the presence of at least one extracellular domain (i.e., including both secreted proteins and proteins having at least one cell-surface domain). Expression of a marker protein having at least one portion which is displayed on the surface of a cell which expresses it may be detected without necessarily lysing the cell (e.g., using a labeled antibody which binds specifically with a cell-surface domain of the protein).

[000319] Expression of a marker may be assessed by any of a wide variety of methods for detecting expression of a transcribed nucleic acid or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods and nucleic acid amplification methods.

[000320] In a particular embodiment, expression of a marker is assessed using an antibody (e.g., a radio-labeled, chromophore-labeled, fluorophore-labeled or enzyme-labeled antibody), an antibody derivative (e.g., an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair), or an antibody fragment (e.g., a single-chain antibody, an isolated antibody hypervariable domain, etc.) which binds specifically with a marker protein or fragment thereof, including a marker protein which has undergone all or a portion of its normal post-translational modification.

[000321] In another particular embodiment, expression of a marker is assessed by preparing

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mRNA/cDNA (i.e., a transcribed polynucleotide) from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a marker nucleic acid, or a fragment thereof. cDNA can, optionally, be amplified using any of a variety of polymerase chain reaction methods prior to hybridization with the reference polynucleotide; preferably, it is not amplified. Expression of one or more markers can likewise be detected using quantitative PCR to assess the level of expression of the marker(s). Alternatively, any of the many methods of detecting mutations or variants (e.g., single nucleotide polymorphisms, deletions, etc.) of a marker may be used to detect occurrence of a marker in a patient.

[000322] In a related embodiment, a mixture of transcribed polynucleotides obtained from the sample is contacted with a substrate having fixed thereto a polynucleotide complementary to or homologous with at least a portion (e.g., at least 7, 10, 15, 20, 25, 30, 40, 50, 100, 500, or more nucleotide residues) of a marker nucleic acid. If polynucleotides complementary to or homologous with are differentially detectable on the substrate (e.g., detectable using different chromophores or fluorophores, or fixed to different selected positions), then the levels of expression of a plurality of markers can be assessed simultaneously using a single substrate (e.g., a "gene chip" microarray of polynucleotides fixed at selected positions). When a method of assessing marker expression is used which involves hybridization of one nucleic acid with another, it is desired that the hybridization be performed under stringent hybridization conditions.

[000323] **Biomarker Assays**

[000324] In certain embodiments, the biomarker assays can be performed using mass spectrometry or surface plasmon resonance. In various embodiment, the method of identifying an agent active against a l cancer-related disease can include a) providing a sample of cells containing one or more markers or derivative thereof; b) preparing an extract from said cells; c) mixing said extract with a labeled nucleic acid probe containing a marker binding site; and, d) determining the formation of a complex between the marker and the nucleic acid probe in the presence or absence of the test agent. The determining step can include subjecting said extract/nucleic acid probe mixture to an electrophoretic mobility shift assay.

[000325] In certain embodiments, the determining step comprises an assay selected from an enzyme linked immunoabsorption assay (ELISA), fluorescence based assays and ultra high

throughput assays, for example surface plasmon resonance (SPR) or fluorescence correlation spectroscopy (FCS) assays. In such embodiments, the SPR sensor is useful for direct real-time observation of biomolecular interactions since SPR is sensitive to minute refractive index changes at a metal-dielectric surface. SPR is a surface technique that is sensitive to changes of 10^5 to 10^{-6} refractive index (RI) units within approximately 200 nm of the SPR sensor/sample interface. Thus, SPR spectroscopy is useful for monitoring the growth of thin organic films deposited on the sensing layer.

[000326] Because the compositions, kits, and methods rely on detection of a difference in expression levels of one or more markers, it is desired that the level of expression of the marker is significantly greater than the minimum detection limit of the method used to assess expression in at least one of normal cells and cancer-affected cells.

[000327] It is understood that by routine screening of additional patient samples using one or more of the markers, it will be realized that certain of the markers are over-expressed in cells of various types, including specific cancer-related diseases.

[000328] In addition, as a greater number of patient samples are assessed for expression of the markers and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that altered expression of certain of the markers are strongly correlated with a cancer-related disease and that altered expression of other markers are strongly correlated with other diseases. The compositions, kits, and methods are thus useful for characterizing one or more of the stage, grade, histological type, and nature of a cancer-related disease in patients.

[000329] When the compositions, kits, and methods are used for characterizing one or more of the stage, grade, histological type, and nature of a cancer-related disease in a patient, it is desired that the marker or panel of markers is selected such that a positive result is obtained in at least about 20%, and in certain embodiments, at least about 40%, 60%, or 80%, and in substantially all patients afflicted with a cancer-related disease of the corresponding stage, grade, histological type, or nature. The marker or panel of markers invention can be selected such that a positive predictive value of greater than about 10% is obtained for the general population (in a non-limiting example, coupled with an assay specificity greater than 80%).

[000330] When a plurality of markers are used in the compositions, kits, and methods, the level of expression of each marker in a patient sample can be compared with the normal level of

expression of each of the plurality of markers in non-cancer samples of the same type, either in a single reaction mixture (i.e. using reagents, such as different fluorescent probes, for each marker) or in individual reaction mixtures corresponding to one or more of the markers. In one embodiment, a significantly increased level of expression of more than one of the plurality of markers in the sample, relative to the corresponding normal levels, is an indication that the patient is afflicted with a cancer-related disease. When a plurality of markers is used, 2, 3, 4, 5, 8, 10, 12, 15, 20, 30, or 50 or more individual markers can be used; in certain embodiments, the use of fewer markers may be desired.

[000331] In order to maximize the sensitivity of the compositions, kits, and methods (i.e. by interference attributable to cells of non-tissue and/or fluid origin in a patient sample), it is desirable that the marker used therein be a marker which has a restricted tissue distribution, e.g., normally not expressed in a non-tissue cells.

[000332] It is recognized that the compositions, kits, and methods will be of particular utility to patients having an enhanced risk of developing a cancer-related disease and their medical advisors. Patients recognized as having an enhanced risk of developing a cancer-related disease include, for example, patients having a familial history of a cancer-related disease.

[000333] The level of expression of a marker in normal human cells can be assessed in a variety of ways. In one embodiment, this normal level of expression is assessed by assessing the level of expression of the marker in a portion of cells which appear to be normal and by comparing this normal level of expression with the level of expression in a portion of the cells which is suspected of being abnormal. Alternately, and particularly as further information becomes available as a result of routine performance of the methods described herein, population-average values for normal expression of the markers may be used. In other embodiments, the "normal" level of expression of a marker may be determined by assessing expression of the marker in a patient sample obtained from a non-cancer-afflicted patient, from a patient sample obtained from a patient before the suspected onset of a cancer-related disease in the patient, from archived patient samples, and the like.

[000334] There is also provided herein compositions, kits, and methods for assessing the presence of cancer-related disease cells in a sample (e.g. an archived tissue sample or a sample obtained from a patient). These compositions, kits, and methods are substantially the same as those described above, except that, where necessary, the compositions, kits, and methods are adapted for use with samples other than patient samples. For example, when the

sample to be used is a parafinized, archived human tissue sample, it can be necessary to adjust the ratio of compounds in the compositions, in the kits, or the methods used to assess levels of marker expression in the sample.

[000335] **Methods of Producing Antibodies**

[000336] There is also provided herein a method of making an isolated hybridoma which produces an antibody useful for assessing whether a patient is afflicted with a cancer-related disease. In this method, a protein or peptide comprising the entirety or a segment of a marker protein is synthesized or isolated (e.g. by purification from a cell in which it is expressed or by transcription and translation of a nucleic acid encoding the protein or peptide in vivo or in vitro). A vertebrate, for example, a mammal such as a mouse, rat, rabbit, or sheep, is immunized using the protein or peptide. The vertebrate may optionally (and preferably) be immunized at least one additional time with the protein or peptide, so that the vertebrate exhibits a robust immune response to the protein or peptide. Splenocytes are isolated from the immunized vertebrate and fused with an immortalized cell line to form hybridomas, using any of a variety of methods. Hybridomas formed in this manner are then screened using standard methods to identify one or more hybridomas which produce an antibody which specifically binds with the marker protein or a fragment thereof. There is also provided herein hybridomas made by this method and antibodies made using such hybridomas.

[000337] **Methods of Assessing Efficacy**

[000338] There is also provided herein a method of assessing the efficacy of a test compound for inhibiting cancer-related disease cells. As described herein, differences in the level of expression of the markers correlate with the abnormal state of the cells. Although it is recognized that changes in the levels of expression of certain of the markers likely result from the abnormal state of the cells, it is likewise recognized that changes in the levels of expression of other of the markers induce, maintain, and promote the abnormal state of those cells. Thus, compounds which inhibit a cancer-related disease in a patient will cause the level of expression of one or more of the markers to change to a level nearer the normal level of expression for that marker (i.e. the level of expression for the marker in normal cells).

[000339] This method thus comprises comparing expression of a marker in a first cell sample and maintained in the presence of the test compound and expression of the marker in a second cell sample and maintained in the absence of the test compound. A significantly

reduced expression of a marker in the presence of the test compound is an indication that the test compound inhibits a cancer-related disease. The cell samples may, for example, be aliquots of a single sample of normal cells obtained from a patient, pooled samples of normal cells obtained from a patient, cells of a normal cell line, aliquots of a single sample of cancer-related disease cells obtained from a patient, pooled samples of cancer-related disease cells obtained from a patient, cells of a cancer-related disease cell line, or the like.

[000340]   In one embodiment, the samples are cancer-related disease cells obtained from a patient and a plurality of compounds believed to be effective for inhibiting various cancer-related diseases are tested in order to identify the compound which is likely to best inhibit the cancer-related disease in the patient.

[000341]   This method may likewise be used to assess the efficacy of a therapy for inhibiting a cancer-related disease in a patient. In this method, the level of expression of one or more markers in a pair of samples (one subjected to the therapy, the other not subjected to the therapy) is assessed. As with the method of assessing the efficacy of test compounds, if the therapy induces a significantly lower level of expression of a marker then the therapy is efficacious for inhibiting a cancer-related disease. As above, if samples from a selected patient are used in this method, then alternative therapies can be assessed in vitro in order to select a therapy most likely to be efficacious for inhibiting a cancer-related disease in the patient.

[000342]   **Methods for Assessing Harmful Potentials**

[000343]   As described herein, the abnormal state of human cells is correlated with changes in the levels of expression of the markers. There is also provided a method for assessing the harmful potential of a test compound. This method comprises maintaining separate aliquots of human cells in the presence and absence of the test compound. Expression of a marker in each of the aliquots is compared. A significantly higher level of expression of a marker in the aliquot maintained in the presence of the test compound (relative to the aliquot maintained in the absence of the test compound) is an indication that the test compound possesses a harmful potential. The relative harmful potential of various test compounds can be assessed by comparing the degree of enhancement or inhibition of the level of expression of the relevant markers, by comparing the number of markers for which the level of expression is enhanced or inhibited, or by comparing both.

[000344] **Isolated Proteins and Antibodies**

[000345] One aspect pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

[000346] An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein").

[000347] When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

[000348] Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein can be a polypeptide which

is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein. In certain embodiments, useful proteins are substantially identical (e.g., at least about 40%, and in certain embodiments, 50%, 60%, 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

[000349]   In addition, libraries of segments of a marker protein can be used to generate a variegated population of polypeptides for screening and subsequent selection of variant marker proteins or segments thereof.

[000350]   **Predictive Medicine**

[000351]   There is also provided herein uses of the animal models and markers in the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, there is also provided herein diagnostic assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing a cancer-related disease. Such assays can be used for prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the cancer-related disease.

[000352]   In another aspect, the methods are useful for at least periodic screening of the same individual to see if that individual has been exposed to chemicals or toxins that change his/her expression patterns.

[000353]   Yet another aspect pertains to monitoring the influence of agents (e.g., drugs or other compounds administered either to inhibit a cancer-related disease or to treat or prevent any other disorder (e.g., in order to understand any system effects that such treatment may have) on the expression or activity of a marker in clinical trials.

[000354]   **Pharmacogenomics**

[000355]   The markers are also useful as pharmacogenomic markers. As used herein, a "pharmacogenomic marker" is an objective biochemical marker whose expression level correlates with a specific clinical drug response or susceptibility in a patient. The presence or

quantity of the pharmacogenomic marker expression is related to the predicted response of the patient and more particularly the patient's tumor to therapy with a specific drug or class of drugs. By assessing the presence or quantity of the expression of one or more pharmacogenomic markers in a patient, a drug therapy which is most appropriate for the patient, or which is predicted to have a greater degree of success, may be selected.

[000356] **Monitoring Clinical Trials**

[000357] Monitoring the influence of agents (e.g., drug compounds) on the level of expression of a marker can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for a cancer-related disease.

[000358] In one non-limiting embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one or more selected markers in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly.

[000359] For example, increased expression of the marker gene(s) during the course of treatment may indicate ineffective dosage and the desirability of increasing the dosage. Conversely, decreased expression of the marker gene(s) may indicate efficacious treatment and no need to change dosage.

[000360] **Electronic Apparatus Readable Media, Systems, Arrays and Methods of Using Same**

[000361] As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be read and accessed directly by an electronic apparatus. Such media can include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage

media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; and general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or configured for having recorded thereon a marker as described herein.

[000362]   As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet; electronic appliances such as personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

[000363]   As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can readily adopt any method for recording information on media to generate materials comprising the markers described herein.

[000364]   A variety of software programs and formats can be used to store the marker information of the present invention on the electronic apparatus readable medium. Any number of data processor structuring formats (e.g., text file or database) may be employed in order to obtain or create a medium having recorded thereon the markers. By providing the markers in readable form, one can routinely access the marker sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences which match a particular target sequence or target motif.

[000365]   Thus, there is also provided herein a medium for holding instructions for performing a method for determining whether a subject has a cancer-related disease or a pre-disposition to a cancer-related disease, wherein the method comprises the steps of determining the presence or absence of a marker and based on the presence or absence of the marker, determining whether the subject has a cancer-related disease or a pre-disposition to a cancer-related disease and/or recommending a particular treatment for a cancer-related disease or pre-cancer-related disease condition.

[000366]   There is also provided herein an electronic system and/or in a network, a method for determining whether a subject has a cancer-related disease or a pre-disposition to a cancer-related disease associated with a marker wherein the method comprises the steps of determining the presence or absence of the marker, and based on the presence or absence of the marker, determining whether the subject has a cancer-related disease or a pre-disposition to a cancer-related disease, and/or recommending a particular treatment for the cancer-related disease or pre-cancer-related disease condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject.

[000367]   Also provided herein is a network, a method for determining whether a subject has a cancer-related disease or a pre-disposition to a cancer-related disease associated with a marker, the method comprising the steps of receiving information associated with the marker, receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or a cancer-related disease, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a cancer-related disease or a pre-disposition to a cancer-related disease. The method may further comprise the step of recommending a particular treatment for the cancer-related disease or pre-cancer-related disease condition.

[000368]   There is also provided herein a business method for determining whether a subject has a cancer-related disease or a pre-disposition to a cancer-related disease, the method comprising the steps of receiving information associated with the marker, receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or a cancer-related disease, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a cancer-related disease or a pre-disposition to a cancer-related disease. The method may further comprise the step of recommending a particular treatment for the cancer-related disease or pre-cancer-related disease condition.

[000369]   **Arrays**

[000370]   There is also provided herein an array that can be used to assay expression of one or more genes in the array. In one embodiment, the array can be used to assay gene expression in a tissue to ascertain tissue specificity of genes in the array. In this manner, up to about 7000 or more genes can be simultaneously assayed for expression. This allows a profile to be

developed showing a battery of genes specifically expressed in one or more tissues.

[000371] In addition to such qualitative determination, there is provided herein the quantitation of gene expression. Thus, not only tissue specificity, but also the level of expression of a battery of genes in the tissue is ascertainable. Thus, genes can be grouped on the basis of their tissue expression per se and level of expression in that tissue. This is useful, for example, in ascertaining the relationship of gene expression between or among tissues. Thus, one tissue can be perturbed and the effect on gene expression in a second tissue can be determined. In this context, the effect of one cell type on another cell type in response to a biological stimulus can be determined.

[000372] Such a determination is useful, for example, to know the effect of cell-cell interaction at the level of gene expression. If an agent is administered therapeutically to treat one cell type but has an undesirable effect on another cell type, the method provides an assay to determine the molecular basis of the undesirable effect and thus provides the opportunity to co-administer a counteracting agent or otherwise treat the undesired effect. Similarly, even within a single cell type, undesirable biological effects can be determined at the molecular level. Thus, the effects of an agent on expression of other than the target gene can be ascertained and counteracted.

[000373] In another embodiment, the array can be used to monitor the time course of expression of one or more genes in the array. This can occur in various biological contexts, as disclosed herein, for example development of a cancer-related disease, progression of a cancer-related disease, and processes, such as cellular transformation associated with a cancer-related disease.

[000374] The array is also useful for ascertaining the effect of the expression of a gene or the expression of other genes in the same cell or in different cells. This provides, for example, for a selection of alternate molecular targets for therapeutic intervention if the ultimate or downstream target cannot be regulated.

[000375] The array is also useful for ascertaining differential expression patterns of one or more genes in normal and abnormal cells. This provides a battery of genes that could serve as a molecular target for diagnosis or therapeutic intervention.

[000376] **Surrogate Markers**

[000377] The markers may serve as surrogate markers for one or more disorders or disease

states or for conditions leading up to a cancer-related disease state. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder. The presence or quantity of such markers is independent of the disease. Therefore, these markers may serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies, or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is reached.

[000378] The markers are also useful as pharmacodynamic markers. As used herein, a "pharmacodynamic marker" is an objective biochemical marker which correlates specifically with drug effects. The presence or quantity of a pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a pharmacodynamic marker may be indicative of the concentration of the drug in a biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug may be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker may be related to the presence or quantity of the metabolic product of a drug, such that the presence or quantity of the marker is indicative of the relative breakdown rate of the drug *in vivo*.

[000379] Pharmacodynamic markers are of particular use in increasing the sensitivity of detection of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug may be sufficient to activate multiple rounds of marker transcription or expression, the amplified marker may be in a quantity which is more readily detectable than the drug itself. Also, the marker may be more easily detected due to the nature of the marker itself; for example, using the methods described herein, antibodies may be employed in an immune-based detection system for a protein marker, or marker-specific radiolabeled probes may be used to detect a mRNA marker. Furthermore, the use of a pharmacodynamic marker may offer mechanism-based prediction of risk due to drug treatment beyond the range of possible direct observations.

[000380] **Protocols for Testing**

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[000381]   The method of testing for cancer-related diseases comprises, for example measuring the expression level of each marker gene in a biological sample from a subject over time and comparing the level with that of the marker gene in a control biological sample.

[000382]   When the marker gene is one of the genes described herein and the expression level is differentially expressed (for examples, higher or lower than that in the control), the subject is judged to be affected with a cancer-related disease. When the expression level of the marker gene falls within the permissible range, the subject is unlikely to be affected with a cancer-related disease.

[000383]   The standard value for the control may be pre-determined by measuring the expression level of the marker gene in the control, in order to compare the expression levels. For example, the standard value can be determined based on the expression level of the above-mentioned marker gene in the control. For example, in certain embodiments, the permissible range is taken as ± 2S.D. based on the standard value. Once the standard value is determined, the testing method may be performed by measuring only the expression level in a biological sample from a subject and comparing the value with the determined standard value for the control.

[000384]   Expression levels of marker genes include transcription of the marker genes to mRNA, and translation into proteins. Therefore, one method of testing for a cancer-related disease is performed based on a comparison of the intensity of expression of mRNA corresponding to the marker genes, or the expression level of proteins encoded by the marker genes.

[000385]   **Probes**

[000386]   The measurement of the expression levels of marker genes in the testing for a cancer-related disease can be carried out according to various gene analysis methods. Specifically, one can use, for example, a hybridization technique using nucleic acids that hybridize to these genes as probes, or a gene amplification technique using DNA that hybridize to the marker genes as primers.

[000387]   The probes or primers used for the testing can be designed based on the nucleotide sequences of the marker genes. The identification numbers for the nucleotide sequences of the respective marker genes are describer herein.

[000388]   Further, it is to be understood that genes of higher animals generally accompany

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polymorphism in a high frequency. There are also many molecules that produce isoforms comprising mutually different amino acid sequences during the splicing process. Any gene associated with a cancer-related disease that has an activity similar to that of a marker gene is included in the marker genes, even if it has nucleotide sequence differences due to polymorphism or being an isoform.

[000389] It is also to be understood that the marker genes can include homologs of other species in addition to humans. Thus, unless otherwise specified, the expression "marker gene" refers to a homolog of the marker gene unique to the species or a foreign marker gene which has been introduced into an individual.

[000390] Also, it is to be understood that a "homolog of a marker gene" refers to a gene derived from a species other than a human, which can hybridize to the human marker gene as a probe under stringent conditions. Such stringent conditions are known to one skilled in the art who can select an appropriate condition to produce an equal stringency experimentally or empirically.

[000391] A polynucleotide comprising the nucleotide sequence of a marker gene or a nucleotide sequence that is complementary to the complementary strand of the nucleotide sequence of a marker gene and has at least 15 nucleotides, can be used as a primer or probe. Thus, a "complementary strand" means one strand of a double stranded DNA with respect to the other strand and which is composed of A:T (U for RNA) and G:C base pairs.

[000392] In addition, "complementary" means not only those that are completely complementary to a region of at least 15 continuous nucleotides, but also those that have a nucleotide sequence homology of at least 40% in certain instances, 50% in certain instances, 60% in certain instances, 70% in certain instances, at least 80%, 90%, and 95% or higher. The degree of homology between nucleotide sequences can be determined by an algorithm, BLAST, etc.

[000393] Such polynucleotides are useful as a probe to detect a marker gene, or as a primer to amplify a marker gene. When used as a primer, the polynucleotide comprises usually 15 bp to 100 bp, and in certain embodiments 15 bp to 35 bp of nucleotides. When used as a probe, a DNA comprises the whole nucleotide sequence of the marker gene (or the complementary strand thereof), or a partial sequence thereof that has at least 15 bp nucleotides. When used as a primer, the 3' region must be complementary to the marker gene, while the 5' region can

be linked to a restriction enzyme-recognition sequence or a tag.

[000394] "Polynucleotides" may be either DNA or RNA. These polynucleotides may be either synthetic or naturally-occurring. Also, DNA used as a probe for hybridization is usually labeled. Those skilled in the art readily understand such labeling methods. Herein, the term "oligonucleotide" means a polynucleotide with a relatively low degree of polymerization. Oligonucleotides are included in polynucleotides.

[000395] <u>Tests for Cancer-related Diseases</u>

[000396] Tests for a cancer-related disease using hybridization techniques can be performed using, for example, Northern hybridization, dot blot hybridization, or the DNA microarray technique. Furthermore, gene amplification techniques, such as the RT-PCR method may be used. By using the PCR amplification monitoring method during the gene amplification step in RT-PCR, one can achieve a more quantitative analysis of the expression of a marker gene.

[000397] In the PCR gene amplification monitoring method, the detection target (DNA or reverse transcript of RNA) is hybridized to probes that are labeled with a fluorescent dye and a quencher which absorbs the fluorescence. When the PCR proceeds and Taq polymerase degrades the probe with its 5'-3' exonuclease activity, the fluorescent dye and the quencher draw away from each other and the fluorescence is detected. The fluorescence is detected in real time. By simultaneously measuring a standard sample in which the copy number of a target is known, it is possible to determine the copy number of the target in the subject sample with the cycle number where PCR amplification is linear. Also, one skilled in the art recognizes that the PCR amplification monitoring method can be carried out using any suitable method.

[000398] The method of testing for a cancer-related disease can be also carried out by detecting a protein encoded by a marker gene. Hereinafter, a protein encoded by a marker gene is described as a "marker protein." For such test methods, for example, the Western blotting method, the immunoprecipitation method, and the ELISA method may be employed using an antibody that binds to each marker protein.

[000399] Antibodies used in the detection that bind to the marker protein may be produced by any suitable technique. Also, in order to detect a marker protein, such an antibody may be appropriately labeled. Alternatively, instead of labeling the antibody, a substance that specifically binds to the antibody, for example, protein A or protein G, may be labeled to

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detect the marker protein indirectly. More specifically, such a detection method can include the ELISA method.

[000400] A protein or a partial peptide thereof used as an antigen may be obtained, for example, by inserting a marker gene or a portion thereof into an expression vector, introducing the construct into an appropriate host cell to produce a transformant, culturing the transformant to express the recombinant protein, and purifying the expressed recombinant protein from the culture or the culture supernatant. Alternatively, the amino acid sequence encoded by a gene or an oligopeptide comprising a portion of the amino acid sequence encoded by a full-length cDNA are chemically synthesized to be used as an immunogen.

[000401] Furthermore, a test for a cancer-related disease can be performed using as an index not only the expression level of a marker gene but also the activity of a marker protein in a biological sample. Activity of a marker protein means the biological activity intrinsic to the protein. Various methods can be used for measuring the activity of each protein.

[000402] Even if a patient is not diagnosed as being affected with a cancer-related disease in a routine test in spite of symptoms suggesting these diseases, whether or not such a patient is suffering from a cancer-related disease can be easily determined by performing a test according to the methods described herein.

[000403] More specifically, in certain embodiments, when the marker gene is one of the genes described herein, an increase or decrease in the expression level of the marker gene in a patient whose symptoms suggest at least a susceptibility to a cancer-related disease indicates that the symptoms are primarily caused by a cancer-related disease.

[000404] In addition, the tests are useful to determine whether a cancer-related disease is improving in a patient. In other words, the methods described herein can be used to judge the therapeutic effect of a treatment for a cancer-related disease. Furthermore, when the marker gene is one of the genes described herein, an increase or decrease in the expression level of the marker gene in a patient, who has been diagnosed as being affected by a cancer-related disease, implies that the disease has progressed more.

[000405] The severity and/or susceptibility to a cancer-related disease may also be determined based on the difference in expression levels. For example, when the marker gene is one of the genes described herein, the degree of increase in the expression level of the marker gene is correlated with the presence and/or severity of a cancer-related disease.

[000406] **Control of Expression of Marker**

[000407] In addition, the expression itself of a marker gene can be controlled by introducing a mutation(s) into the transcriptional regulatory region of the gene. Those skilled in the art understand such amino acid substitutions. Also, the number of amino acids that are mutated is not particularly restricted, as long as the activity is maintained. Normally, it is within 50 amino acids, in certain non-limiting embodiments, within 30 amino acids, within 10 amino acids, or within 3 amino acids. The site of mutation may be any site, as long as the activity is maintained.

[000408] **Screening Methods**

[000409] In yet another aspect, there is provided herein screening methods for candidate compounds for therapeutic agents to treat a cancer-related disease. One or more marker genes are selected from the group of genes described herein. A therapeutic agent for a cancer-related disease can be obtained by selecting a compound capable of increasing or decreasing the expression level of the marker gene(s).

[000410] It is to be understood that the expression "a compound that increases the expression level of a gene" refers to a compound that promotes any one of the steps of gene transcription, gene translation, or expression of a protein activity. On the other hand, the expression "a compound that decreases the expression level of a gene", as used herein, refers to a compound that inhibits any one of these steps.

[000411] In particular aspects, the method of screening for a therapeutic agent for a cancer-related disease can be carried out either *in vivo* or *in vitro*. This screening method can be performed, for example, by (1) administering a candidate compound to an animal subject; (2) measuring the expression level of a marker gene(s) in a biological sample from the animal subject; or (3) selecting a compound that increases or decreases the expression level of a marker gene(s) as compared to that in a control with which the candidate compound has not been contacted.

[000412] In still another aspect, there is provided herein a method to assess the efficacy of a candidate compound for a pharmaceutical agent on the expression level of a marker gene(s) by contacting an animal subject with the candidate compound and monitoring the effect of the compound on the expression level of the marker gene(s) in a biological sample derived from the animal subject. The variation in the expression level of the marker gene(s) in a

biological sample derived from the animal subject can be monitored using the same technique as used in the testing method described above. Furthermore, based on the evaluation, a candidate compound for a pharmaceutical agent can be selected by screening.

[000413] **Kits**

[000414] In another aspect, there is provided various diagnostic and test kits. In one embodiment, a kit is useful for assessing whether a patient is afflicted with a cancer-related disease. The kit comprises a reagent for assessing expression of a marker. In another embodiment, a kit is useful for assessing the suitability of a chemical or biologic agent for inhibiting a cancer-related disease in a patient. Such a kit comprises a reagent for assessing expression of a marker, and may also comprise one or more of such agents.

[000415] In a further embodiment, the kits are useful for assessing the presence of cancer-related disease cells or treating cancer-related diseases. Such kits comprise an antibody, an antibody derivative or an antibody fragment, which binds specifically with a marker protein or a fragment of the protein. Such kits may also comprise a plurality of antibodies, antibody derivatives or antibody fragments wherein the plurality of such antibody agents binds specifically with a marker protein or a fragment of the protein.

[000416] In an additional embodiment, the kits are useful for assessing the presence of cancer-related disease cells, wherein the kit comprises a nucleic acid probe that binds specifically with a marker nucleic acid or a fragment of the nucleic acid. The kit may also comprise a plurality of probes, wherein each of the probes binds specifically with a marker nucleic acid, or a fragment of the nucleic acid.

[000417] The compositions, kits and methods described herein can have the following uses, among others: 1) assessing whether a patient is afflicted with a cancer-related disease; 2) assessing the stage of a cancer-related disease in a human patient; 3) assessing the grade of a cancer-related disease in a patient; 4) assessing the nature of a cancer-related disease in a patient; 5) assessing the potential to develop a cancer-related disease in a patient; 6) assessing the histological type of cells associated with a cancer-related disease in a patient; 7) making antibodies, antibody fragments or antibody derivatives that are useful for treating a cancer-related disease and/or assessing whether a patient is afflicted with a cancer-related disease; 8) assessing the presence of cancer-related disease cells; 9) assessing the efficacy of one or more test compounds for inhibiting a cancer-related disease in a patient; 10) assessing the efficacy

of a therapy for inhibiting a cancer-related disease in a patient; 11) monitoring the progression of a cancer-related disease in a patient; 12) selecting a composition or therapy for inhibiting a cancer-related disease in a patient; 13) treating a patient afflicted with a cancer-related disease; 14) inhibiting a cancer-related disease in a patient; 15) assessing the harmful potential of a test compound; and 16) preventing the onset of a cancer-related disease in a patient at risk for developing a cancer-related disease.

[000418] The kits are useful for assessing the presence of cancer-related disease cells (e.g. in a sample such as a patient sample). The kit comprises a plurality of reagents, each of which is capable of binding specifically with a marker nucleic acid or protein. Suitable reagents for binding with a marker protein include antibodies, antibody derivatives, antibody fragments, and the like. Suitable reagents for binding with a marker nucleic acid (e.g. a genomic DNA, an MRNA, a spliced MRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon probes, and the like.

[000419] The kits may optionally comprise additional components useful for performing the methods described herein. By way of example, the kit may comprise fluids (e.g. SSC buffer) suitable for annealing complementary nucleic acids or for binding an antibody with a protein with which it specifically binds, one or more sample compartments, an instructional material which describes performance of the method, a sample of normal cells, a sample of cancer-related disease cells, and the like.

[000420]

[000421] **Animal Model**

[000422] Non-human animal model can be produced for assessment of at least one cancer-related disease. The method includes exposing the animal to repeated doses of at least one chemical believed to cause the cancer if interest. In certain aspects, the method further includes collecting one or more selected samples from the animal; and comparing the collected sample to one or more indicia of potential cancer initiation or development.

[000423] A method of producing the animal model includes: maintaining the animal in a specific chemical-free environment and sensitizing the animal with at least one chemical believed to cause the cancer. In certain embodiments, at least a part of the animal is

sensitized by multiple sequential exposures.

[000424]   A method of screening for an agent for effectiveness against at least one cancer-related disease generally includes: administering at least one agent to a test animal, determining whether the agent reduces or aggravates one or more symptoms of the cancer-related disease; correlating a reduction in one or more symptoms with effectiveness of the agent against the cancer-related disease; or correlating a lack of reduction in one or more symptoms with ineffectiveness of the agent. The animal model is useful for assessing one or more metabolic pathways that contribute to at least one of initiation, progression, severity, pathology, aggressiveness, grade, activity, disability, mortality, morbidity, disease sub-classification or other underlying pathogenic or pathological feature of at least one cancer-related disease. The analysis can be by one or more of: hierarchical clustering, signature network construction, mass spectroscopy proteomic analysis, surface plasmon resonance, linear statistical modeling, partial least squares discriminant analysis, and multiple linear regression analysis.

[000425]   The animal model can be assessed for at least one cancer-related disease, by examining an expression level of one or more markers, or a functional equivalent thereto.

[000426]   The animal models can be used for the screening of therapeutic agents useful for treating or preventing a cancer-related disease. Accordingly, the methods are useful for identifying therapeutic agents for treating or preventing a cancer-related disease. The methods comprise administering a candidate agent to an animal model made by the methods described herein, assessing at least one cancer-related disease response in the animal model as compared to a control animal model to which the candidate agent has not been administered. If at least one cancer-related disease response is reduced in symptoms or delayed in onset, the candidate agent is an agent for treating or preventing the cancer-related disease.

[000427]   The animal models for a cancer-related disease can include an animal where the expression level of one or more marker genes or a gene functionally equivalent to the marker gene has been elevated in the animal model. A "functionally equivalent gene" as used herein generally is a gene that encodes a protein having an activity similar to a known activity of a protein encoded by the marker gene. A representative example of a functionally equivalent gene includes a counterpart of a marker gene of a subject animal, which is intrinsic to the animal.

[000428]   The animal model for a cancer-related disease is useful for detecting physiological changes due to a cancer-related disease. In certain embodiments, the animal model is useful to reveal additional functions of marker genes and to evaluate drugs whose targets are the marker genes.

[000429]   In one embodiment, an animal model for a cancer-related disease can be created by controlling the expression level of a counterpart gene or administering a counterpart gene. The method can include creating an animal model for a cancer-related disease by controlling the expression level of a gene selected from the group of genes described herein. In another embodiment, the method can include creating an animal model for a cancer-related disease by administering the protein encoded by a gene described herein, or administering an antibody against the protein. It is to be also understood, that in certain other embodiments, the marker can be over-expressed such that the marker can then be measured using appropriate methods.

[000430]   In another embodiment, an animal model for a cancer-related disease can be created by introducing a gene selected from such groups of genes, or by administering a protein encoded by such a gene.

[000431]   In another embodiment, a cancer-related disease can be induced by suppressing the expression of a gene selected from such groups of genes or the activity of a protein encoded by such a gene. An antisense nucleic acid, a ribozyme, or an RNAi can be used to suppress the expression. The activity of a protein can be controlled effectively by administering a substance that inhibits the activity, such as an antibody.

[000432]   The animal model is useful to elucidate the mechanism underlying a cancer-related disease and also to test the safety of compounds obtained by screening. For example, when an animal model develops the symptoms of a cancer-related disease, or when a measured value involved in a certain a cancer-related disease alters in the animal, a screening system can be constructed to explore compounds having activity to alleviate the disease.

[000433]   As used herein, the expression "an increase in the expression level" refers to any one of the following: where a marker gene introduced as a foreign gene is expressed artificially; where the transcription of a marker gene intrinsic to the subject animal and the translation thereof into the protein are enhanced; or where the hydrolysis of the protein, which is the translation product, is suppressed. As used herein, the expression "a decrease in the expression level" refers to either the state in which the transcription of a marker gene of the

subject animal and the translation thereof into the protein are inhibited, or the state in which the hydrolysis of the protein, which is the translation product, is enhanced. The expression level of a gene can be determined, for example, by a difference in signal intensity on a DNA chip. Furthermore, the activity of the translation product--the protein--can be determined by comparing with that in the normal state.

[000434] It is also within the contemplated scope that the animal model can include transgenic animals, including, for example animals where a marker gene has been introduced and expressed artificially; marker gene knockout animals; and knock-in animals in which another gene has been substituted for a marker gene. A transgenic animal, into which an antisense nucleic acid of a marker gene, a ribozyme, a polynucleotide having an RNAi effect, or a DNA functioning as a decoy nucleic acid or such has been introduced, can be used as the transgenic animal. Such transgenic animals also include, for example, animals in which the activity of a marker protein has been enhanced or suppressed by introducing a mutation(s) into the coding region of the gene, or the amino acid sequence has been modified to become resistant or susceptible to hydrolysis. Mutations in an amino acid sequence include substitutions, deletions, insertions, and additions.

THERAPEUTIC APPLICATIONS

[0227] The invention is widely applicable to a variety of situations where it is desirable to be able to regulate the level of gene expression, such as by turning gene expression "on" and "off", in a rapid, efficient and controlled manner without causing pleiotropic effects or cytotoxicity. The invention may be particularly useful for gene therapy purposes in humans, in treatments for either genetic or acquired diseases. The general approach of gene therapy involves the introduction of one or more nucleic acid molecules into cells such that one or more gene products encoded by the introduced genetic material are produced in the cells to restore or enhance a functional activity. For reviews on gene therapy approaches Anderson, et al. (1992; Miller et al. (1992); Friedmann et al. (1989); and Cournoyer et al. (1990). However, current gene therapy vectors typically utilize constitutive regulatory elements which are responsive to endogenous transcriptions factors. These vector systems do not allow for the ability

to modulate the level of gene expression in a subject. In contrast, the regulatory system of the invention provides this ability.

[0228] To use the system of the invention for gene therapy purposes, at least one DNA molecule is introduced into cells of a subject in need of gene therapy (e.g., a human subject suffering from a genetic or acquired disease) to modify the cells. The cells are modified to comprise: 1) nucleic acid encoding an inducible regulator of the invention in a form suitable for expression of the inducible regulator in the host cells; and 2) an siRNA (e.g., for therapeutic purposes) operatively linked to a tissue-specific promoter such as an s-ship1 promoter. A single DNA molecule encoding components of the regulatory system of the invention can be used, or alternatively, separate DNA molecules encoding each component can be used. The cells of the subject can be modified ex vivo and then introduced into the subject or the cells can be directly modified in vivo by conventional techniques for introducing nucleic acid into cells. Thus, the regulatory system of the invention offers the advantage over constitutive regulatory systems of allowing for modulation of the level of gene expression depending upon the requirements of the therapeutic situation.

[0229] Genes of particular interest to be knocked down or knocked out in cells of a subject for treatment of genetic or acquired diseases include those encoding a deleterious gene product, such as an abnormal protein. Examples of non-limiting specific diseases include anemia, blood-related cancers, Parkinson's disease, and diabetes.

[0230] The present invention can be applied to develop autologous or allogeneic cell lines for therapeutical purposes. For example, gene therapy applications of particular interest in cell and/or organ transplantation are utilized with the present invention. In exemplary embodiments, downregulation of transplantation antigens (such as, for example, by downregulation of beta2-microglobulin expression via siRNA) allows for transplantation of allogeneic cells while minimizing the risk of rejection by the patient's immune system. The present invention would allow for a switch off of the

RNAi in case of adverse effects (e.g. uncontrollable replication of the transplanted cells).

[0231] Cells types that can be subjected to the present invention include hematopoietic stem cells, myoblasts, hepatocytes, lymphocytes, airway epithelium, skin epithelium, islets, dopaminergic neurons, keratinocytes, and so forth. For further descriptions of cell types, genes and methods for gene therapy see e.g., Armentano et al. (1990); Wolff et al. (1990); Chowdhury et al. (1991); Ferry et al. (1991); Quantin et al (1992); Dai et al. (1992); van Beusechem et al. (1992); Rosenfeld et al. (1992); Kay et al. (1992); Cristiano et al (1993); Hwu et al (1993); and Herz and Gerard (1993).

[0232] In particular embodiments of the present invention, there is a method of treating any disease condition amenable to treatment with an s-ship promoter. In specific embodiments, the method comprises preparing a polynucleotide construct having a region encoding a therapeutic or diagnostic (marker) gene that is operably linked to a promoter, wherein the gene encoded by the construct is for the treatment of the disease condition.

[0233] A. Pharmaceutical Formulations, Delivery, and Treatment Regimens

[0234] In an embodiment of the present invention, methods of treatment are contemplated. An effective amount of the pharmaceutical composition, generally, is defined as that amount sufficient to detectably and repeatedly to ameliorate, reduce, minimize or limit the extent of the disease or its symptoms. More rigorous definitions may apply, including elimination, eradication or cure of disease.

[0235] The routes of administration will vary, naturally, with the location and nature of the lesion, and include, e.g., intradermal, transdermal, parenteral, intravenous, intramuscular, intranasal, subcutaneous, percutaneous, intratracheal, intraperitoneal, intratumoral, perfusion, lavage, direct injection, and oral administration and formulation.

[0236] Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U.S. Pat. No. 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0237] For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous, intratumoral and intraperitoneal administration. In this connection, sterile aqueous media that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one

dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA Office of Biologics standards.

[0238] Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0239] The compositions disclosed herein may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug release capsules and the like.

[0240] As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0241] The phrase "pharmaceutically-acceptable" or "pharmacologically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human. The preparation of an aqueous composition that contains a protein as an active ingredient is well understood in the art. Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared.

[0242] B. Combination Treatments

[0243] The compounds and methods of the present invention may be used in the context of traditional therapies. In order to increase the effectiveness of a treatment with the compositions of the present invention, it may be desirable to combine these compositions with other agents effective in the treatment of those diseases and conditions. For example, the treatment of a cancer may be implemented with therapeutic compounds of the present invention and other anti-cancer therapies, such as anti-cancer agents or surgery. Likewise, the treatment of a vascular disease or condition may involve both the present invention and conventional vascular agents or therapies.

[0244] Various combinations may be employed; for example, a host cell of the present invention is "A" and the secondary anti-cancer agent/therapy is "B": TABLE-US-

00005 A/B/A B/A/B B/B/A A/A/B A/B/B B/A/A A/B/B/B B/A/B/B B/B/B/A

B/B/A/B A/A/B/B A/B/A/B A/B/B/A B/B/A/A B/A/B/A B/A/A/B A/A/A/B B/A/A/A

A/B/A/A A/A/B/A

[0245] Administration of the therapeutic expression constructs of the present

invention to a patient will follow general protocols for the administration of that

particular secondary therapy, taking into account the toxicity, if any, of the treatment.

It is expected that the treatment cycles would be repeated as necessary. It also is

contemplated that various standard therapies, as well as surgical intervention, may be

applied in combination with the described therapy.

[000435]   All patents, patent applications and references cited herein are incorporated in their

entirety by reference. While the invention has been described and exemplified in sufficient

detail for those skilled in this art to make and use it, various alternatives, modifications and

improvements should be apparent without departing from the spirit and scope of the

invention. One skilled in the art readily appreciates that the present invention is well adapted

to carry out the objects and obtain the ends and advantages mentioned, as well as those

inherent therein.

[000436]   The methods and reagents described herein are representative of preferred

embodiments, are exemplary, and are not intended as limitations on the scope of the

invention. Modifications therein and other uses will occur to those skilled in the art. These

modifications are encompassed within the spirit of the invention and are defined by the scope

of the claims. It will also be readily apparent to a person skilled in the art that varying

substitutions and modifications may be made to the invention disclosed herein without

departing from the scope and spirit of the invention.

[000437]   It should be understood that although the present invention has been specifically

disclosed by preferred embodiments and optional features, modifications and variations of the

concepts herein disclosed may be resorted to by those skilled in the art, and that such

modifications and variations are considered to be within the scope of this invention as defined

by the appended claims.

[000438]   While the invention has been described with reference to various and preferred

embodiments, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the essential scope of the invention. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the invention without departing from the essential scope thereof.

[000439] Therefore, it is intended that the invention not be limited to the particular embodiment disclosed herein contemplated for carrying out this invention, but that the invention will include all embodiments falling within the scope of the claims.

[000440] All of the compositions and/or methods and/or apparatus disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and/or apparatus and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents that are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

[000441] Throughout this disclosure, various publications, patents and published patent specifications are referenced by an identifying citation. The disclosures of these publications, patents and published patent specifications are hereby incorporated by reference into the present disclosure to more fully describe the state of the art to which this invention pertains.

[000442] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art (e.g., in cell culture, molecular genetics, nucleic acid chemistry, hybridization techniques and biochemistry). Standard techniques are used for molecular, genetic and biochemical methods which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, Molecular Cloning A Laboratory Manual, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press: 1989); DNA Cloning, Volumes I and II (Glover ed., 1985); Oligonucleotide Synthesis (Gait ed., 1984); Mullis et al. U.S. Pat. No: 4,683,195; Nucleic Acid Hybridization (Hames & Higgins eds., 1984); Transcription And

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Immunochemical Methods In Cell And Molecular Biology (Mayer and Walker, eds.,

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(Weir and Blackwell, eds., 1986); The Laboratory Rat, editor in chief: Mark A. Suckow;

authors: Sharp and LaRegina. CRC Press, Boston, 1988, which are incorporated herein by

reference) and chemical methods.

[000443] REFERENCES

[000444] The publication and other material used herein to illuminate the invention or provide

additional details respecting the practice of the invention, are incorporated be reference

herein, and for convenience are provided in the following bibliography.

[000445] Citation of the any of the documents recited herein is not intended as an admission

that any of the foregoing is pertinent prior art. All statements as to the date or representation

as to the contents of these documents is based on the information available to the applicant

and does not constitute any admission as to the correctness of the dates or contents of these

documents.

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CLAIMS

1.   A method to identify a relative cancer risk in a vertebrate comprising:

obtaining a nucleic acid-containing test sample from a vertebrate subject;

measuring, by laboratory analysis, a level of at least one transcribed ultraconserved region (T-UCR); and

determining the relative risk for developing a cancer by comparing the measured levels, wherein a decrease in the level of the at least one T-UCR in the test sample, relative to the level of a corresponding T-UCR in a control sample, is indicative of the subject either having, or being at risk for developing, a cancer;

wherein the association between the genomic location of UCRs and the analyzed cancer-related genomic elements is statistically significant and comparable to that reported for miRNAs.

2.   The method of claim 1, wherein the at least one T-UCR is located in a cancer associated genomic region (CAGR) specifically associated with a particular type of cancer.

3.   The method of claim 1, wherein the at least one T-UCR comprises a cluster of seven UCRs (uc.347 to uc.353) located within a CAGR.

4.   The method claim 1, wherein the at least one T-UCR comprises uc.349A(P) and uc.352(N), and the cancer comprises B-CLL.

5.   The method of claim 1, wherein the at least one UCR is located in genomic regions altered during the malignant process.

6.   The method of claim 1, wherein the at least one T-UCR is a candidate gene for cancer susceptibility.

7.   The method of claim 1, wherein a signature of five UCRs, uc.269A(N), uc.160(N), uc.215(N), uc.346A(P) and uc.348(N), is used to differentiate between two CLL prognosis groups.

8.   The method of claim 7, wherein three out of the 5 UCRs have significant antisense complementarity with 5 out of the 13 miRNAs from the signature, giving rise to six possible interacting pairs: uc.160:: miR-24, uc.160:: miR-155, uc.160:: miR-223, uc.160::miR-146a, uc.346A::miR-155, and uc.-348::miR-29b.

9.   The method of claim 8, wherein the UCRs are located in genomic regions targeted during the malignant process and are indicative of putative involvement in human tumorigenesis.

10.   A method of claim 1, wherein the at least one T-UCR has an oncogenic function for uc.73(P) in colon cancer, wherein diminution of its over-expression induces apoptosis and has antiproliferative effects in colon cancer cells abnormally expressing the T-UCR.

11.   A method for assessing a functional regulatory pathway in which two or more types of ncRNAs interact and influence the phenotype comprising:
        obtaining a nucleic acid-containing sample from a cancer patient; and
        determining, by laboratory analysis, correlations between the expression of UCRs and miRNAs in the sample.

12.   The method of claim 11, wherein the cancer is CLL.

13.   The method of claim 12, wherein the correlation comprises the existence of the miRNA::T-UCR interaction.

14.   The method of claim 11, wherein one or more nc-UCGs are altered at the

genomic level in a cancer patient.

15. The method of claim 14, wherein the cancer patient has leukemia

16. A method of diagnosing whether a subject has, or is at risk for developing, a cancer linked to a cancer-associated chromosomal feature, comprising evaluating the status in the subject of at least one UCR gene located in close proximity to the cancer-associated chromosomal feature, by:

(i) measuring in a test sample from said subject the level of at least one UCR gene product from the UCR gene in the test sample, wherein an alteration in the level of UCR gene product in the test sample relative to the level of corresponding UCR gene product in a control sample is indicative of the subject either having, or being at risk for developing, the cancer;

(ii) analyzing the at least one UCR gene in the test sample for a deletion, mutation or amplification, wherein detection of a deletion, mutation and/or amplification in the UCR gene as compared to the corresponding UCR gene in the control sample is indicative of the subject either having, or being at risk for developing, the cancer; and/or

(iii) measuring the copy number of the at least one UCR gene in the test sample, wherein a copy number other than two for an UCR gene on a somatic chromosome or sex chromosome in a female, or other than one for an UCR gene on a sex chromosome in a male, is indicative of the subject either having, or being at risk for developing, the cancer.

17. The method of claim 16, wherein the cancer-associated chromosomal feature is selected from the group consisting of: a cancer-associated genomic region; a chromosomal fragile site; a human papillomavirus integration site; and a homeobox gene or gene cluster.

18. The method of claim 1, wherein the cancer is selected from the group consisting of: bladder cancer; esophageal cancer; lung cancer; stomach cancer; kidney cancer; cervical cancer; ovarian cancer; breast cancer; lymphoma; Ewing sarcoma; hematopoietic tumors; solid tumors; gastric cancer; colorectal cancer; brain cancer; epithelial cancer; nasopharyngeal cancer; uterine cancer; hepatic cancer; head-and-neck cancer; renal cancer;

male germ cell tumors; malignant mesothelioma; myelodysplastic syndrome; pancreatic or biliary cancer; prostate cancer; thyroid cancer; urothelial cancer; renal cancer; Wilm's tumor; small cell lung cancer; melanoma; skin cancer; osteosarcoma; neuroblastoma; leukemia (acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia); glioblastoma multiforme; medulloblastoma; lymphoplasmacytoid lymphoma; and rhabdomyosarcoma.

19.   The method of claim 17, wherein the cancer-associated chromosomal feature is a chromosomal fragile site.

20.   The method of claim 1, wherein the at least one UCR is selected from the group consisting of: a cluster of seven UCRs (uc.347 to uc.353); and combinations thereof.

21.   The method of claim 17, wherein the cancer is a leukemia.

22.   A method of diagnosing whether a subject has, or is at risk for developing, a cancer, comprising: (1) reverse transcribing RNA from a test sample obtained from the subject to provide a set of target oligodeoxynucleotides; (2) hybridizing the target oligodeoxynucleotides to a microarray comprising one or more UCR specific probe oligonucleotides to provide a hybridization profile for the test sample; and (3) comparing the test sample hybridization profile to a hybridization profile generated from a control sample, wherein an alteration in the signal is indicative of the subject either having, or being at risk for developing, the cancer.

23.   The method of claim 22, wherein the cancer is a cancer associated with a cancer-associated chromosomal feature.

24.   The method of claim 22, wherein the cancer is B-cell chronic lymphocytic leukemia.

25.   A method of diagnosing whether a subject has, or is at risk for developing, a

cancer associated with one or more adverse prognostic markers in a subject, comprising: (1) reverse transcribing RNA from a test sample obtained from the subject to provide a set of target oligodeoxynucleotides; (2) hybridizing the target oligodeoxynucleotides to a microarray comprising one or more UCR-specific probe oligonucleotides to provide a hybridization profile for said test sample; and (3) comparing the test sample hybridization profile to a hybridization profile generated from a control sample, wherein an alteration in the signal is indicative of the subject either having, or being at risk for developing, the cancer.

26. The method of claim 25, wherein the cancer is B-cell chronic lymphocytic leukemia.

27. A method of diagnosing whether a subject has, or is at risk for developing, a cancer, comprising analyzing in a test sample from said subject at least one UCR gene or gene product associated with a cancer, wherein detection of a mutation in the UCR gene or gene product, as compared to the corresponding UCR gene or gene product in a control sample, is indicative of the subject having, or being at risk for developing, the cancer.

28. The method of claim 27, wherein the at least one miR gene or gene product is a miR gene selected from the group consisting wherein the UCR gene is selected from the group consisting of: a cluster of seven UCRs (uc.347 to uc.353); and combinations thereof

29. The method of claim 28, wherein the cancer is B-cell chronic lymphocytic leukemia.

30. A method of treating cancer in a subject, comprising:

(1) providing a subject who has a cancer associated with a cancer-associated chromosomal feature, in which at least one isolated UCR gene product from a UCR gene located in close proximity to the cancer-associated chromosomal feature is down-regulated or up-regulated in cancer cells of the subject as compared to control cells; and

(2) (a) when the at least one isolated miR gene product is down-regulated in the

cancer cells, administering to the subject an effective amount of at least one isolated miR gene product from the at least one UCR gene, such that proliferation of cancer cells in the subject is inhibited; or (b) when the at least one isolated UCR gene product is up-regulated in the cancer cells, administering to the subject an effective amount of at least one compound for inhibiting expression of the at least one UCR gene, such that proliferation of cancer cells in the subject is inhibited.

31.   The method of claim 30, wherein the cancer-associated chromosomal feature is selected from the group consisting of a cancer-associated genomic region, and a chromosomal fragile site.

32.   A method of treating cancer associated with a cancer-associated chromosomal feature, comprising:

(1) determining the amount of UC gene product expressed from at least one UCR gene located in close proximity to the cancer-associated chromosomal feature in cancer cells from a subject, relative to control cells; and

(2) altering the amount of UC gene product expressed in the cancer cells by:

(i) administering to the subject an effective amount of at least one isolated miR gene product from the UCR gene, if the amount of the UCR gene product expressed in the cancer cells is less than amount of the miR gene product expressed in control cells; or

(ii) administering to the subject an effective amount of at least one compound for inhibiting expression of the at least one UCR gene, if the amount of the UCR gene product expressed in the cancer cells is greater than the amount of the UCR gene product expressed in control cells, such that proliferation of cancer cells in the subject is inhibited.

33.   The method of claim 32, wherein the cancer-associated chromosomal feature is selected from the group consisting of a cancer-associated genomic region, and a chromosomal fragile site.

34.   The method of claim 33, wherein the cancer-associated chromosomal feature is

a chromosomal fragile site.

35.   The method of claim 34, wherein the cancer-associated chromosomal feature is a cancer-associated genomic region.

36.   The method of any of the preceding claims, wherein the cancer is selected from the group consisting of: leukemia; lung cancer; esophageal cancer; gastric cancer; colorectal cancer; brain cancer; bladder cancer; breast cancer; cervical cancer; epithelial cancer; nasopharyngeal cancer; lymphoma; uterine cancer; hepatic cancer; head-and-neck cancer; renal cancer; male germ cell tumors; malignant mesothelioma; myelodysplastic syndrome; ovarian cancer; pancreatic or biliary cancer; prostate cancer; thyroid cancer; and urothelial cancer.

37.   A method for treating, preventing, reversing or limiting the severity of a cancer-related disease complication in an individual in need thereof, comprising:

administering to the individual an agent that interferes with at least one cancer-related disease response signaling pathway, in an amount sufficient to interfere with such signaling,

wherein the agent comprises at least one UCR gene product.

38.   Use of an agent that interferes with at least one lung cancer-related disease response signaling pathway, for the manufacture of a medicament for treating, preventing, reversing or limiting the severity of a cancer-related disease complication in an individual,

wherein the agent comprises at least one UCR gene product.

39.   A method of treating, preventing, reversing or limiting the severity of a cancer-related disease complication in an individual in need thereof, comprising

administering to the individual an agent that interferes with at least one cancer-related disease response cascade,

wherein the agent comprises at least one UCR gene product.

40.   Use of an agent that interferes with at least one cancer-related disease response cascade, for the manufacture of a medicament for treating, preventing, reversing or limiting the severity of a cancer-related disease complication in an individual, wherein the agent comprises at least one UCR gene product.

The Ohio State University Research Foundation

Patent Attorneys for the Applicant/Nominated Person

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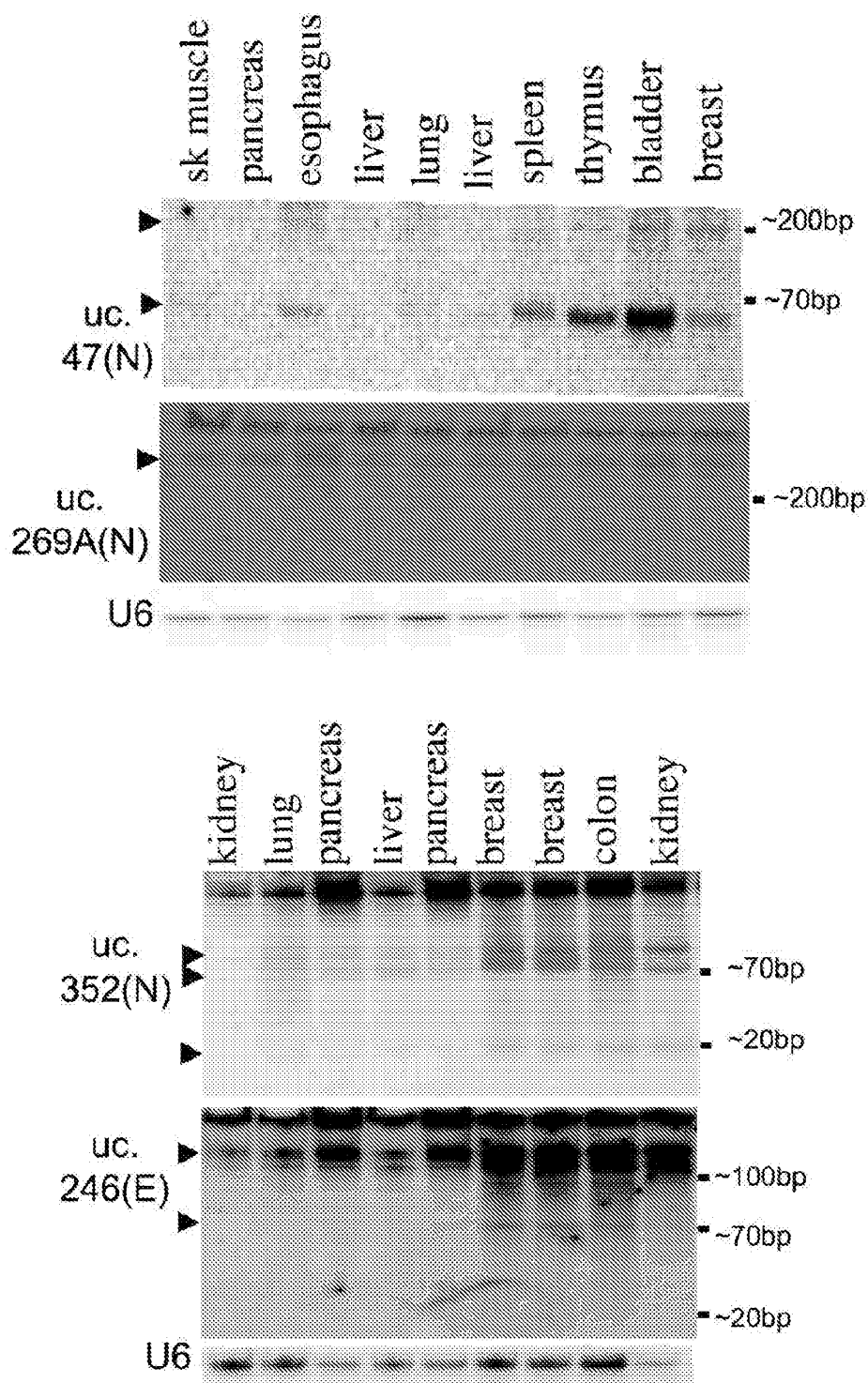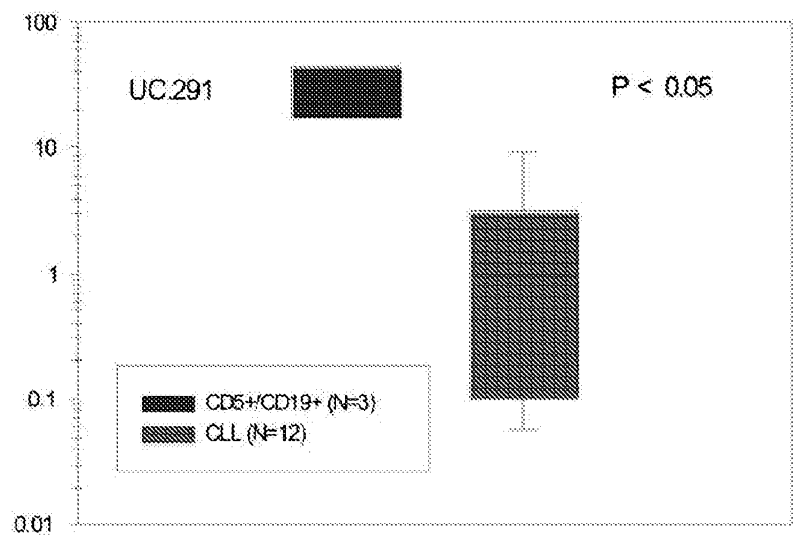
Figure 1A

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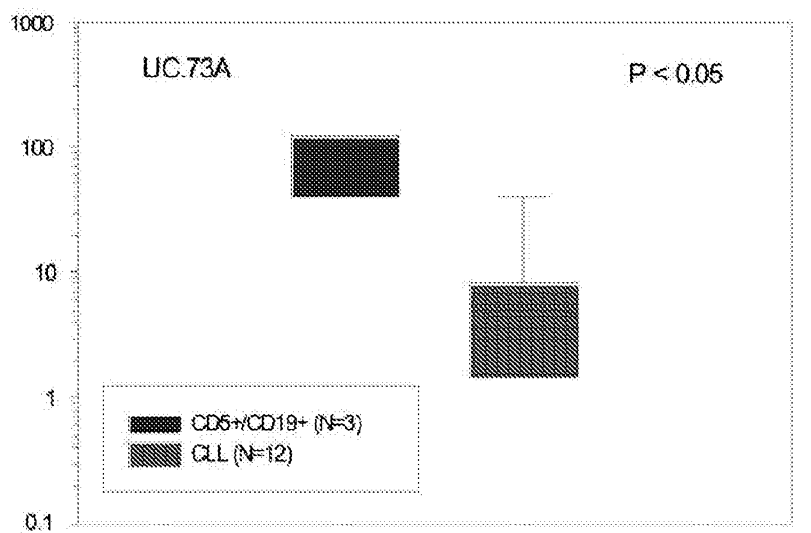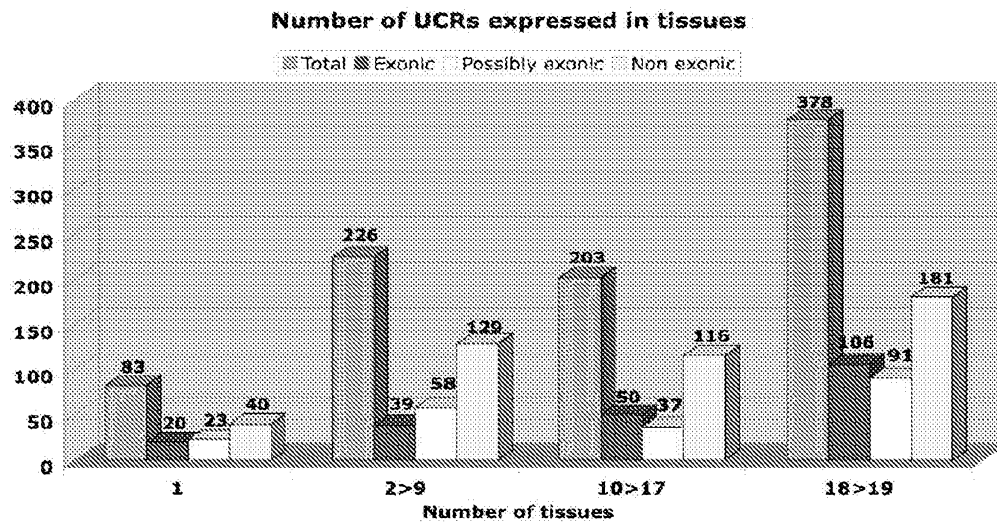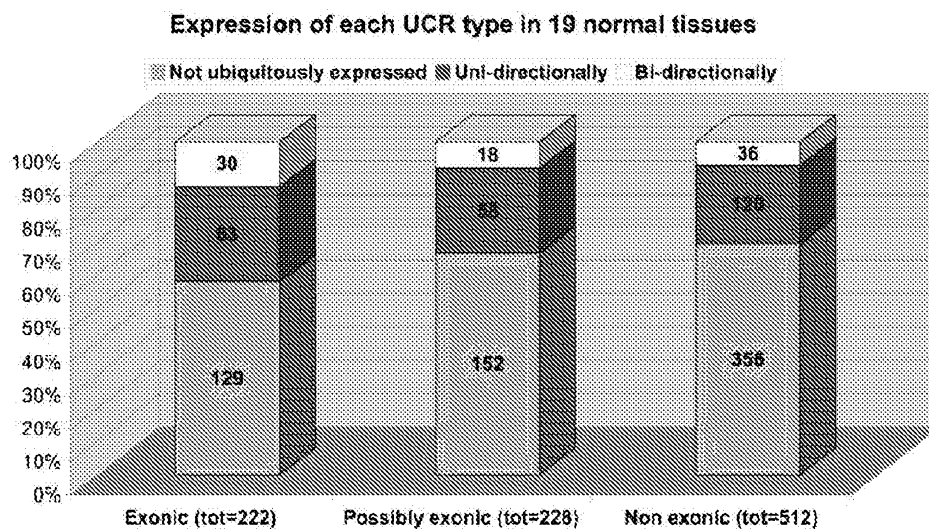
Figure 1B

Figure 1C

Figure1D

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Figure 1E

Figure 2A

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Figure 2B

Legend of samples: HCC   CRC   CLL

Figure 2B continued
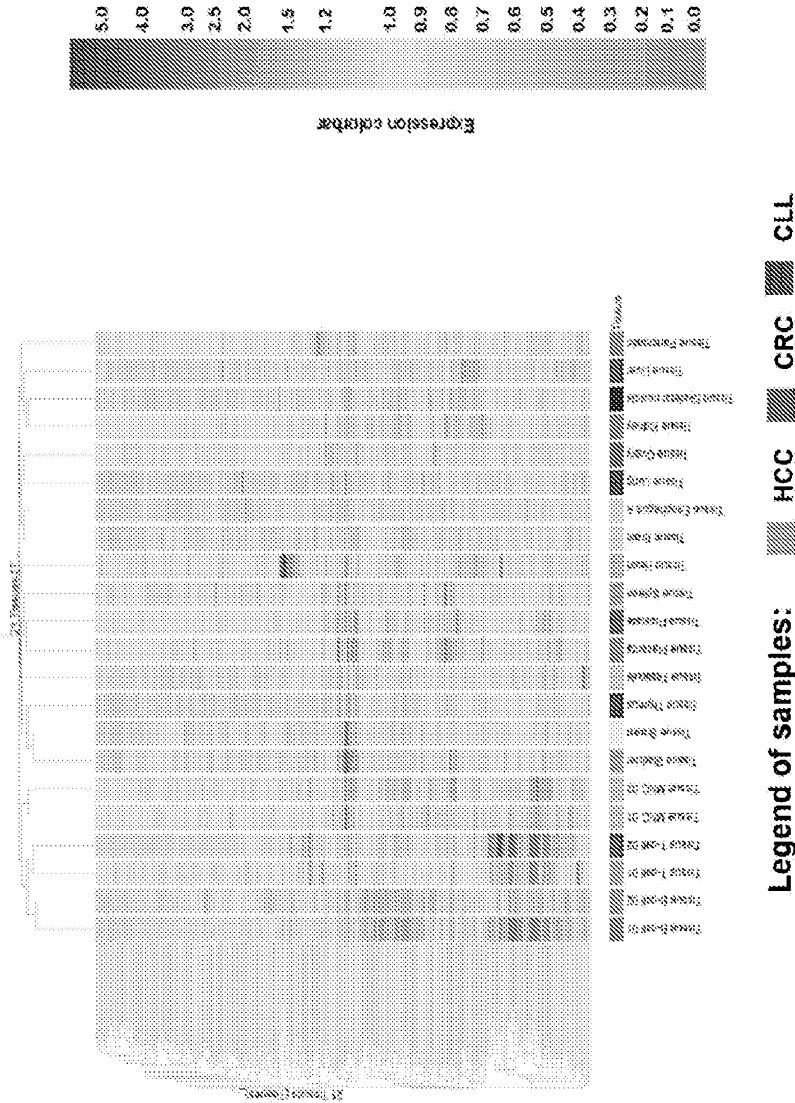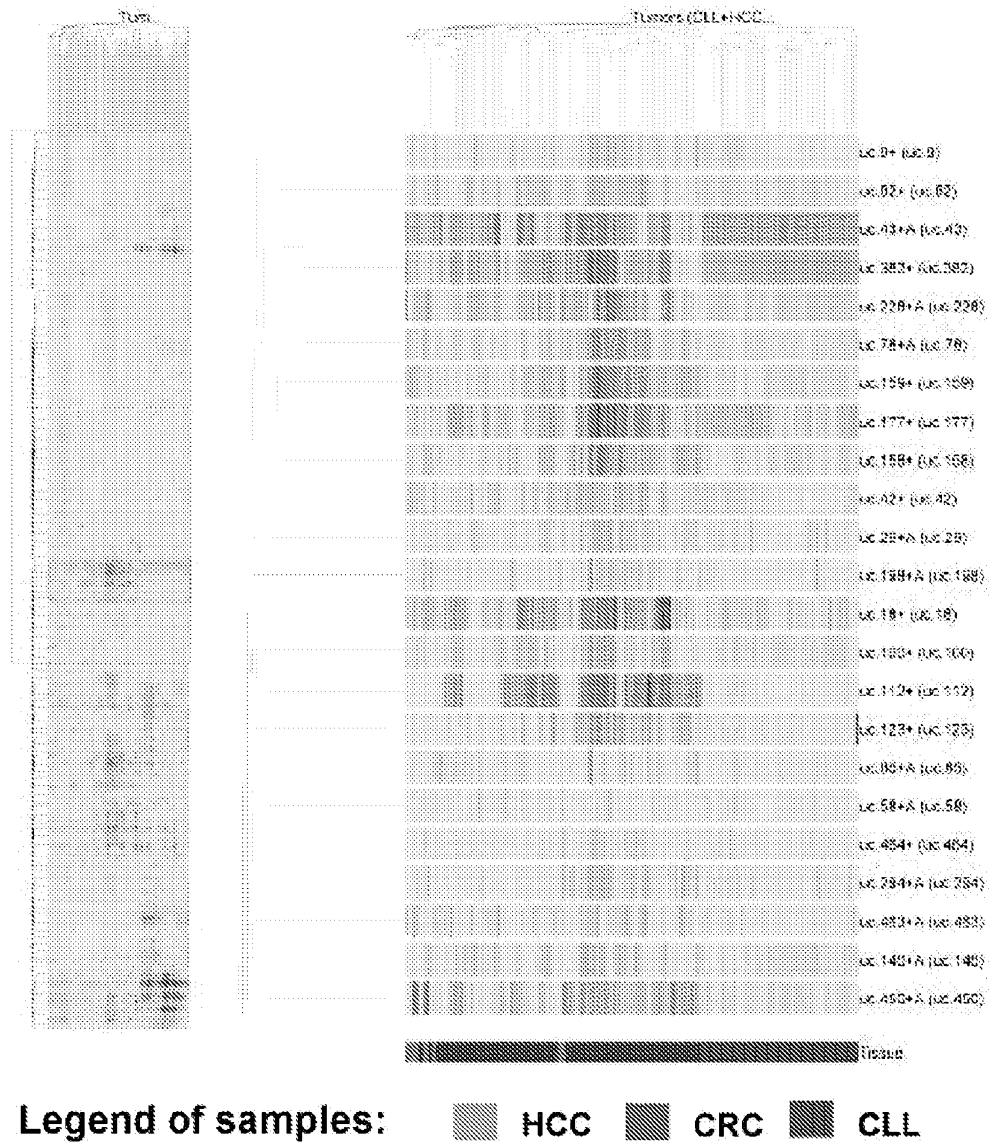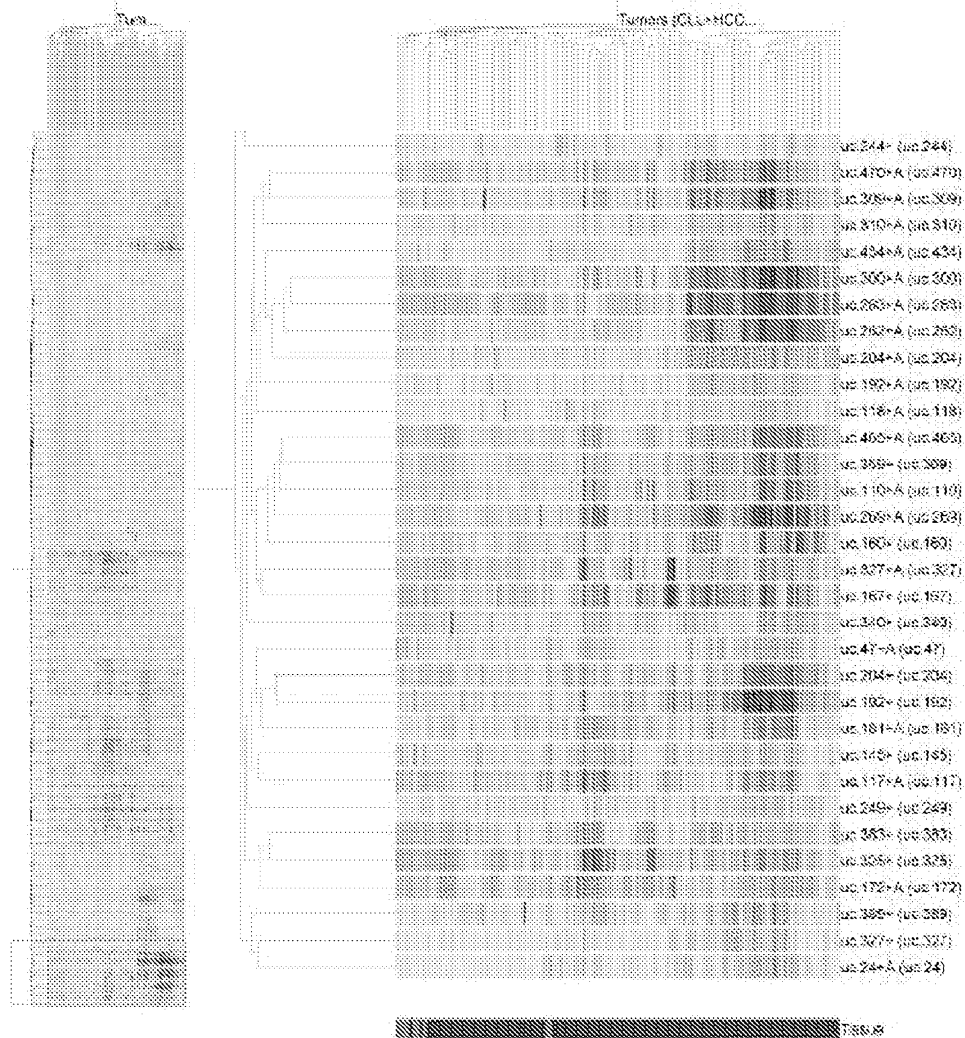
```
5'- ACTTCCCCCT:TCTATTA:TAGCATTAGCAACG   uc.346A
(bp.158)
      3' -GGGGATAG:TGCTATACGTAATT          miR-155

5'- TCAATGCACTATTGC:AAGAGCATTATTGCAT      uc.160 (bp.184)
    3' -GGGGATAG:TCCTATACGTAATT           miR-155

5'- CCGCCATGTACCTGC:CTACTTAGCCCAAGGG      uc.160 (bp.136)
    3'- GACAAGGACGACTTGACTCGGT            miR-24

5'- CTAATGAGACTGAGTTTACA::GTGCCATAGA      uc.348 (bp.170)
    3'- TTGTGACTAAAGTTACCACGAT            miR-29b

5'- TGGAGATAC:AACAAGA:TAACATTAATGAGT      uc.348 (bp.111)
    3' -GGGCATAG:TGCTATACGTAATT           miR-155
```

Figure 3A
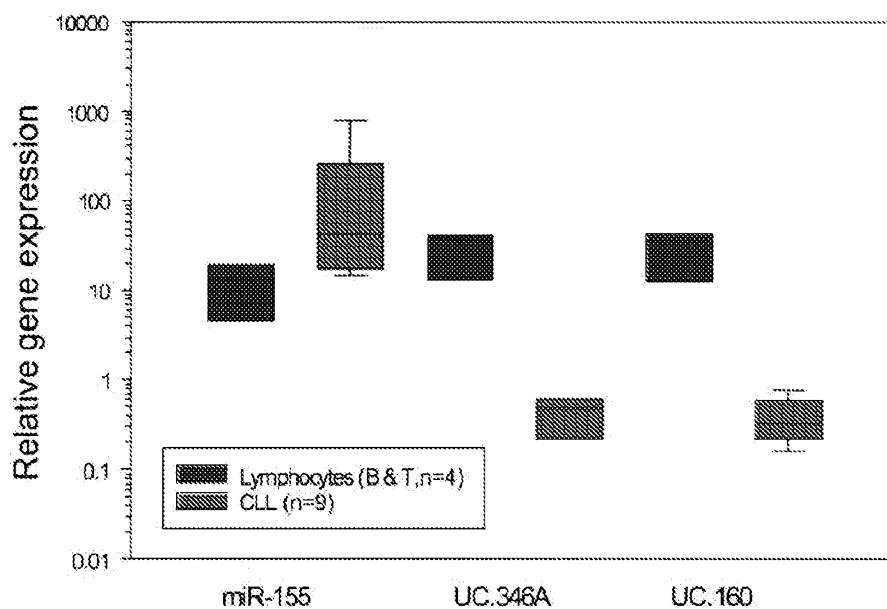
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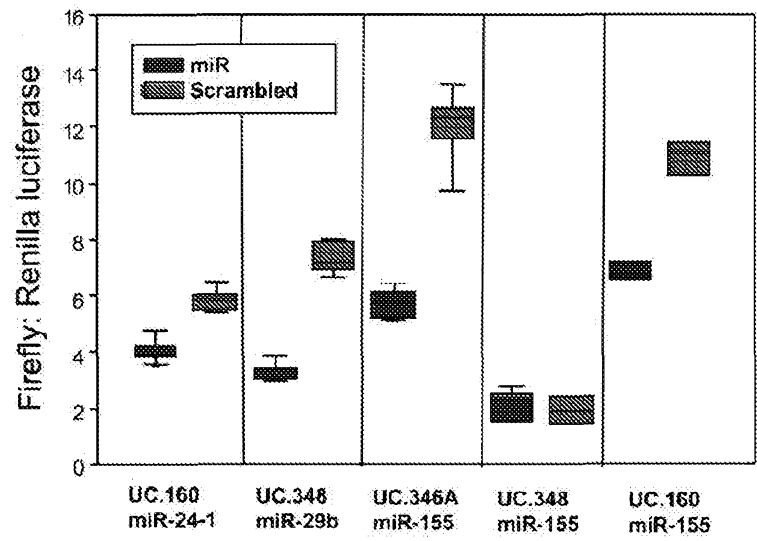
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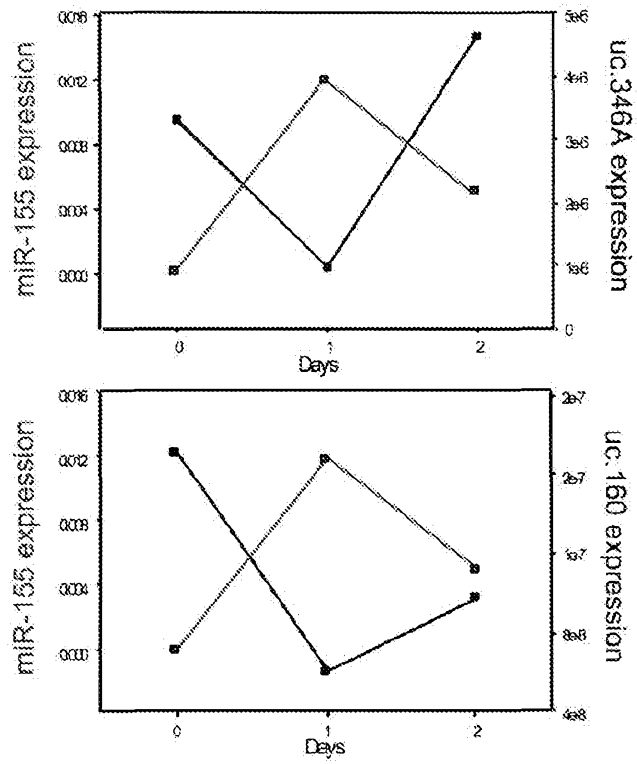
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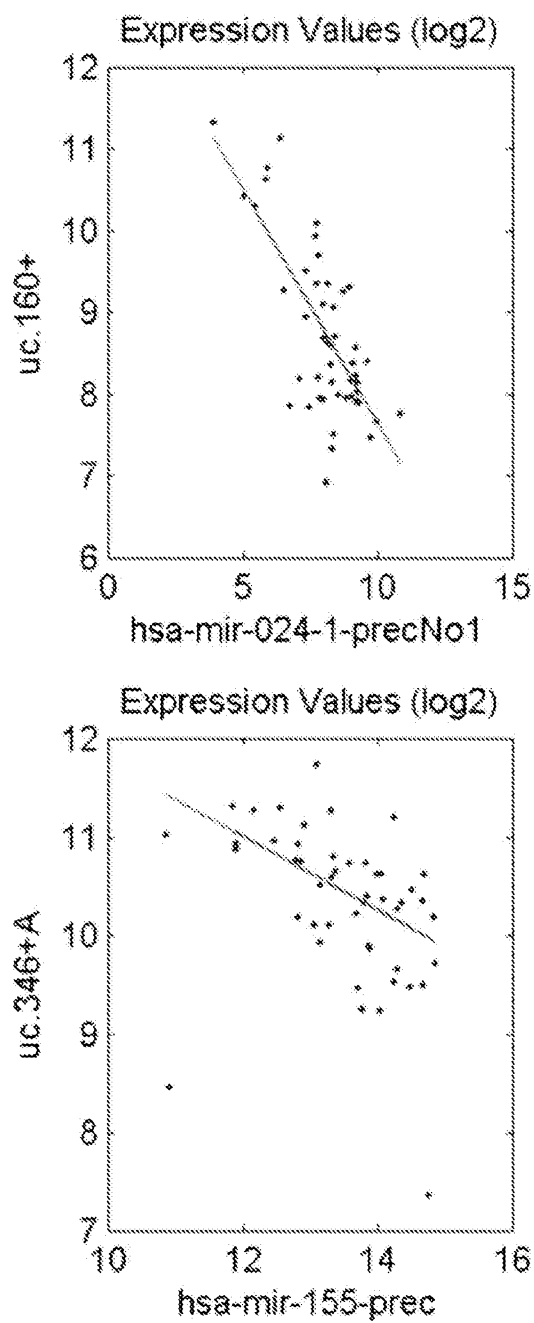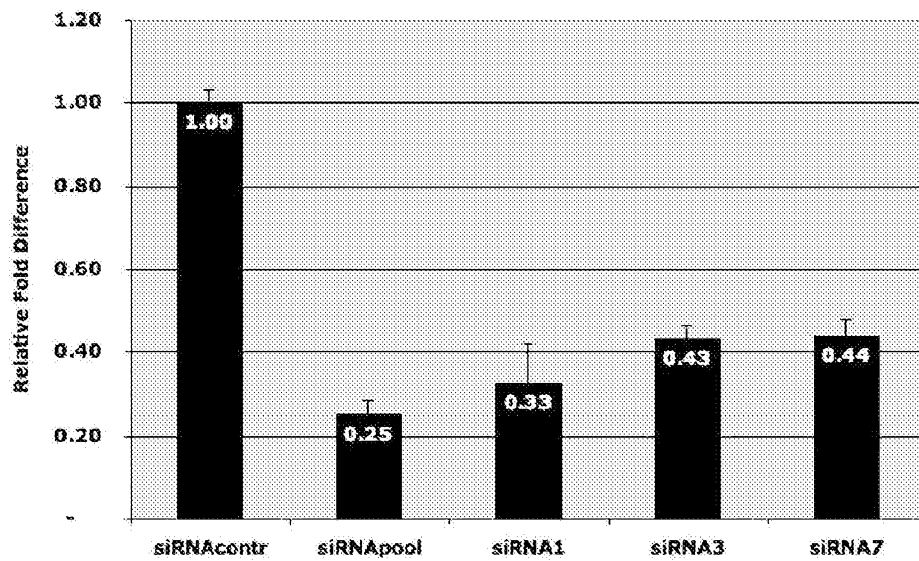
Figure 3E

Figure 4A

Figure 4B

Figure 4C

Figure 4D

Figure 5

Array data	UCR name UC. 135	p-value < 0.01	CD5+/CD19+ (N = 5) Normalized 1.10	CLL (N = 12) Normalized 0.935

Array data	UCR name UC. 289	p-value < 0.01	CD5+/CD19+ (N = 3) Normalized 3.78	CLL (N = 12) Normalized 0.771

Figure 6

Figure 7

Figure 8

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UC.73+A Expression

Figure 9

UC.73+A Expression at 48hr
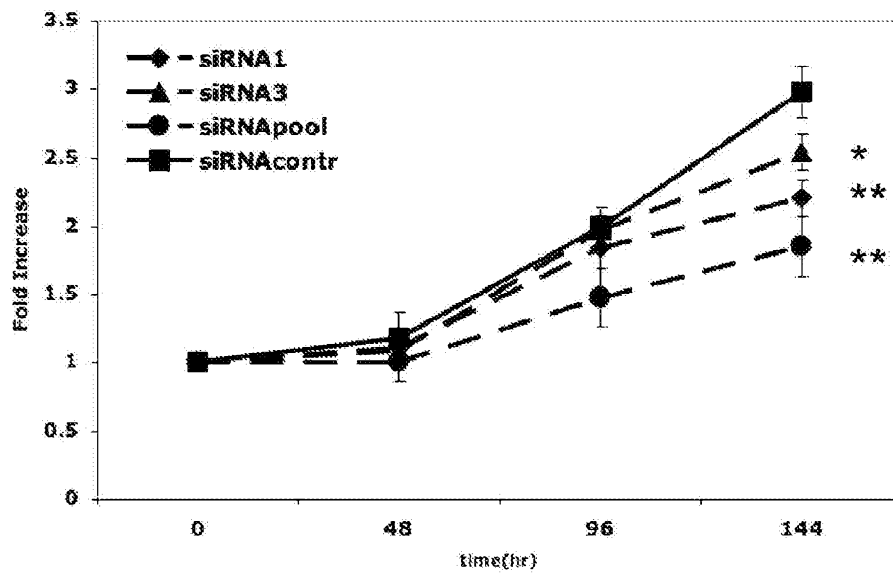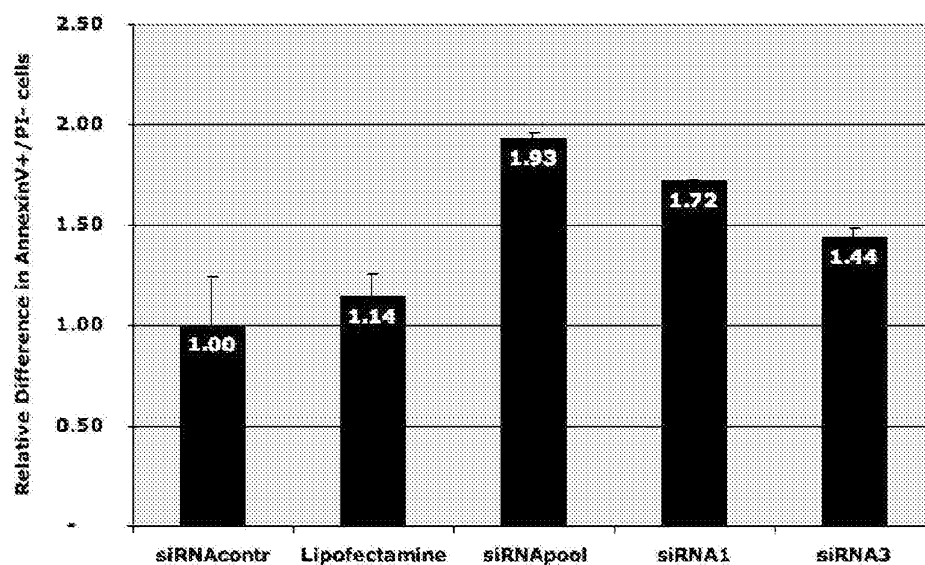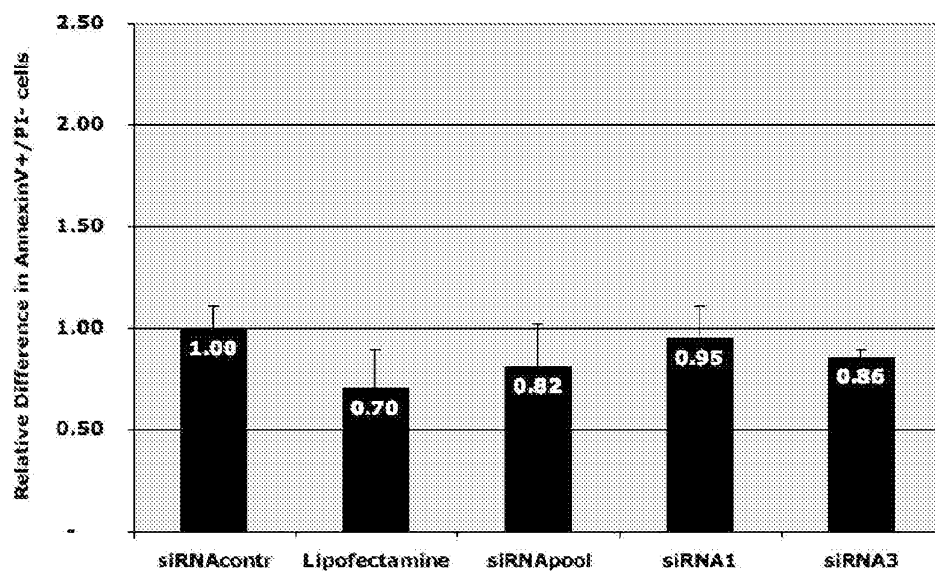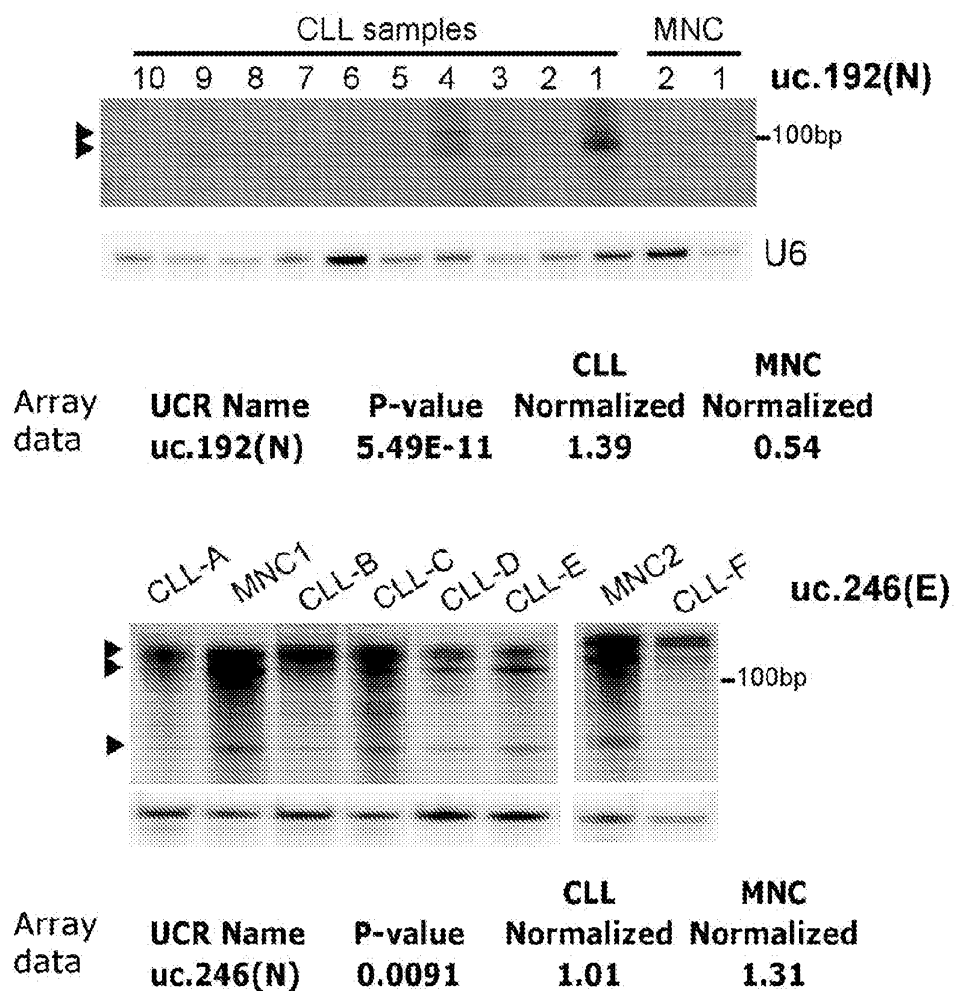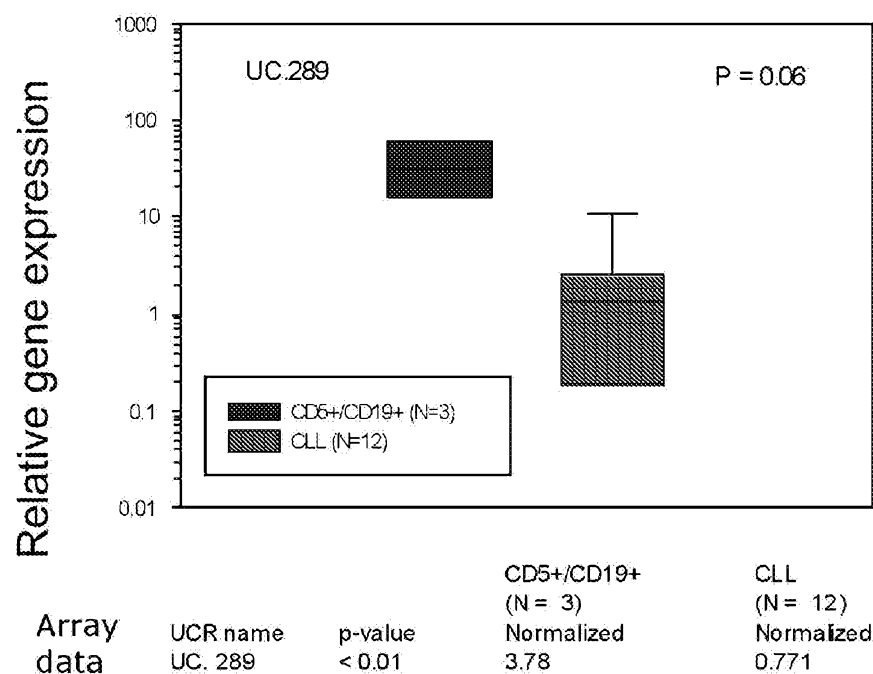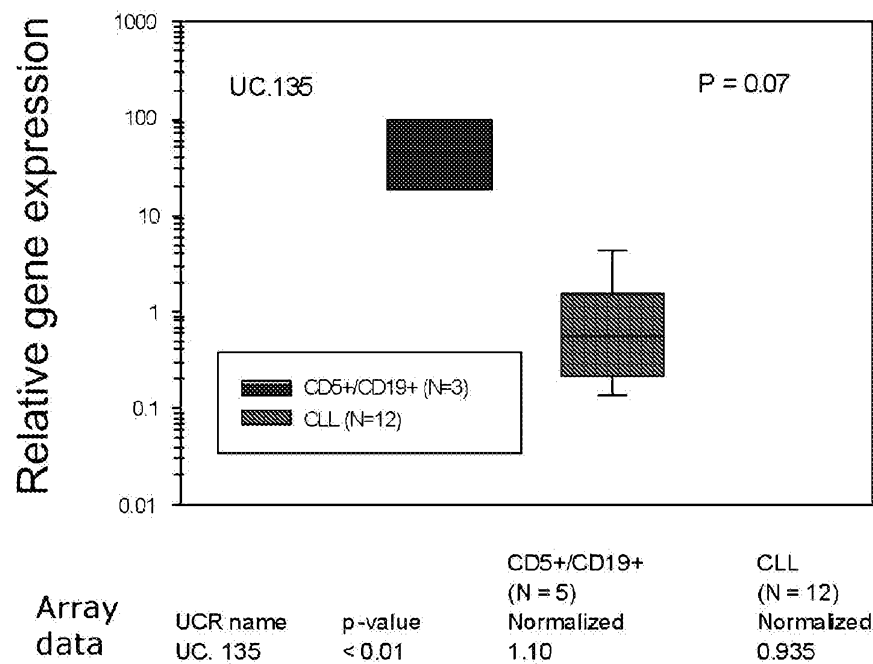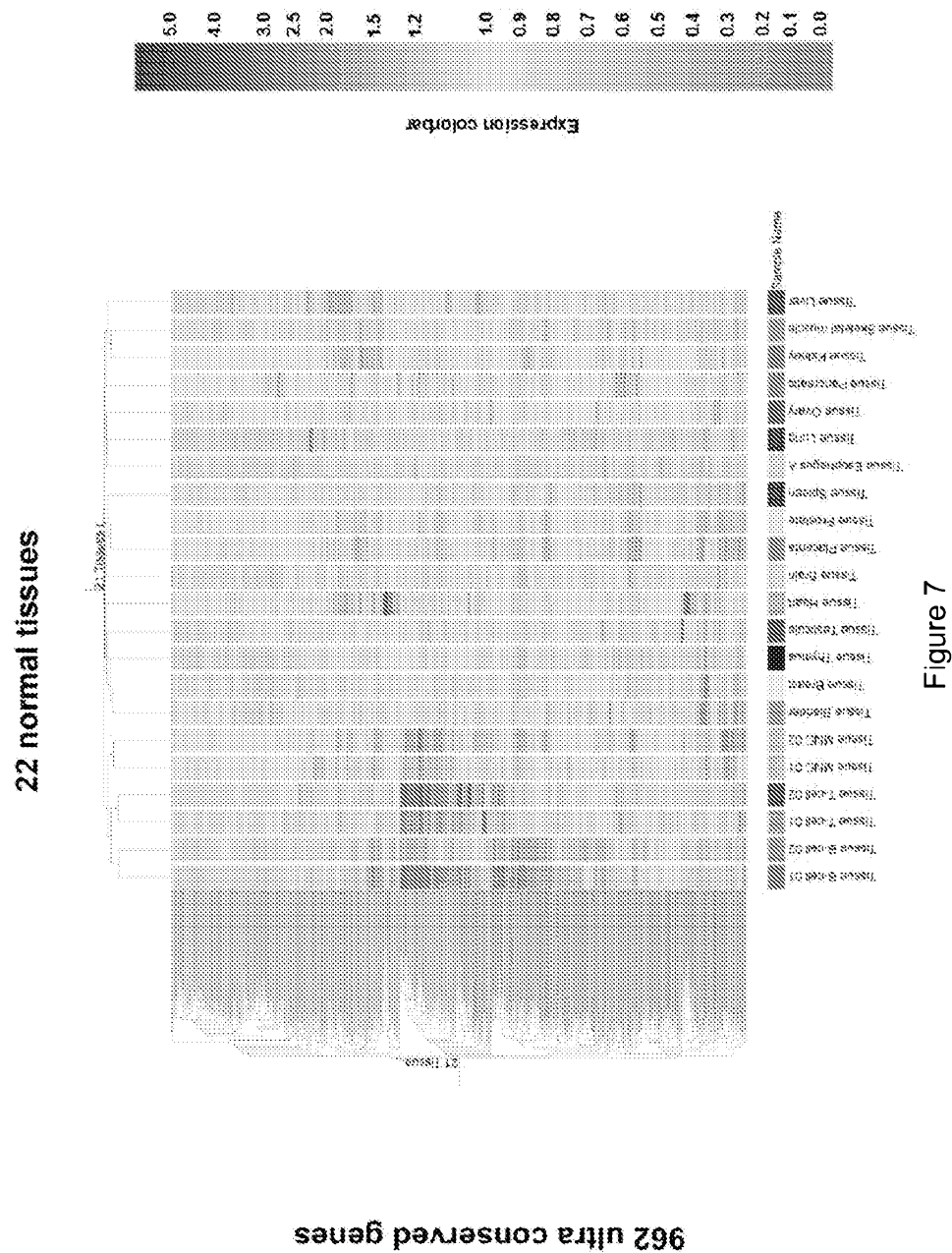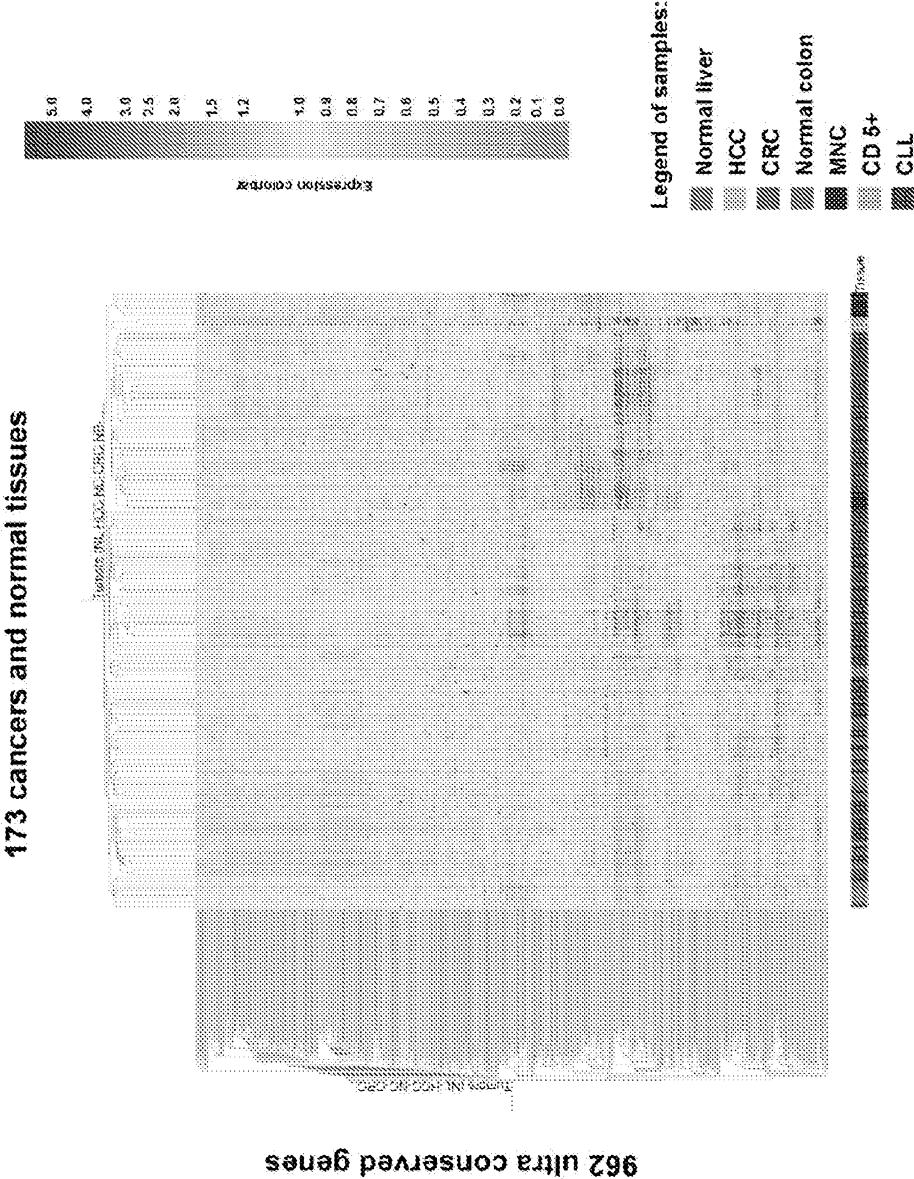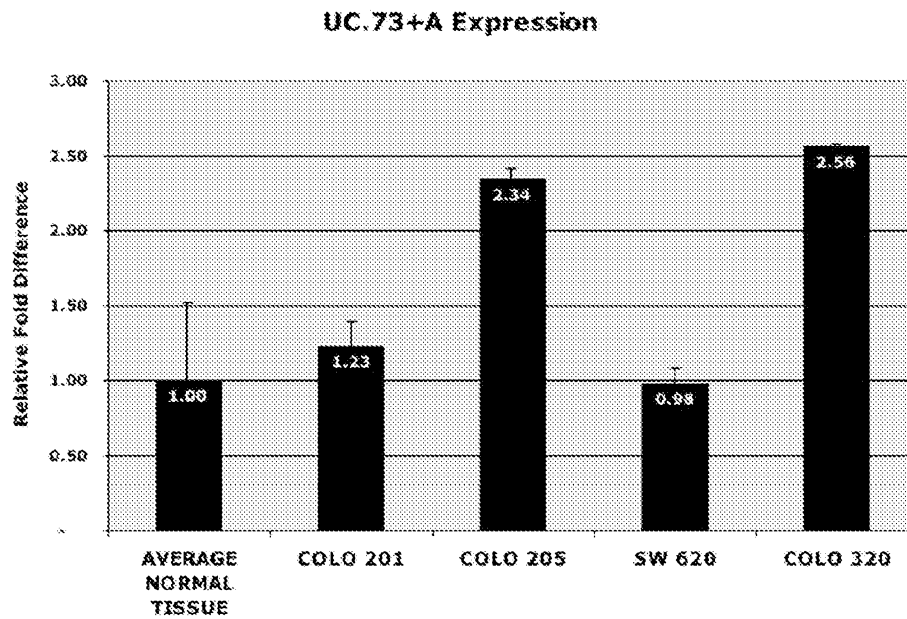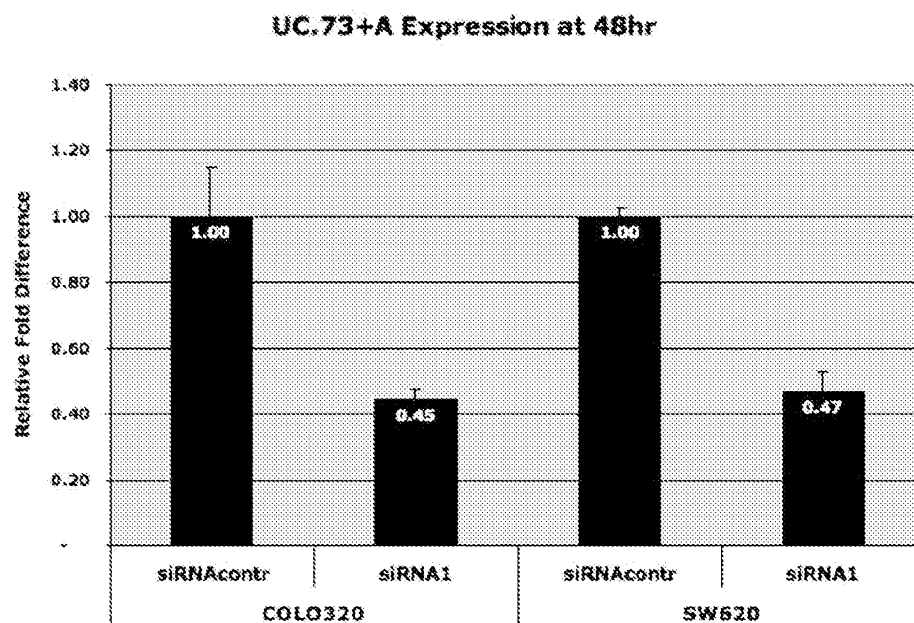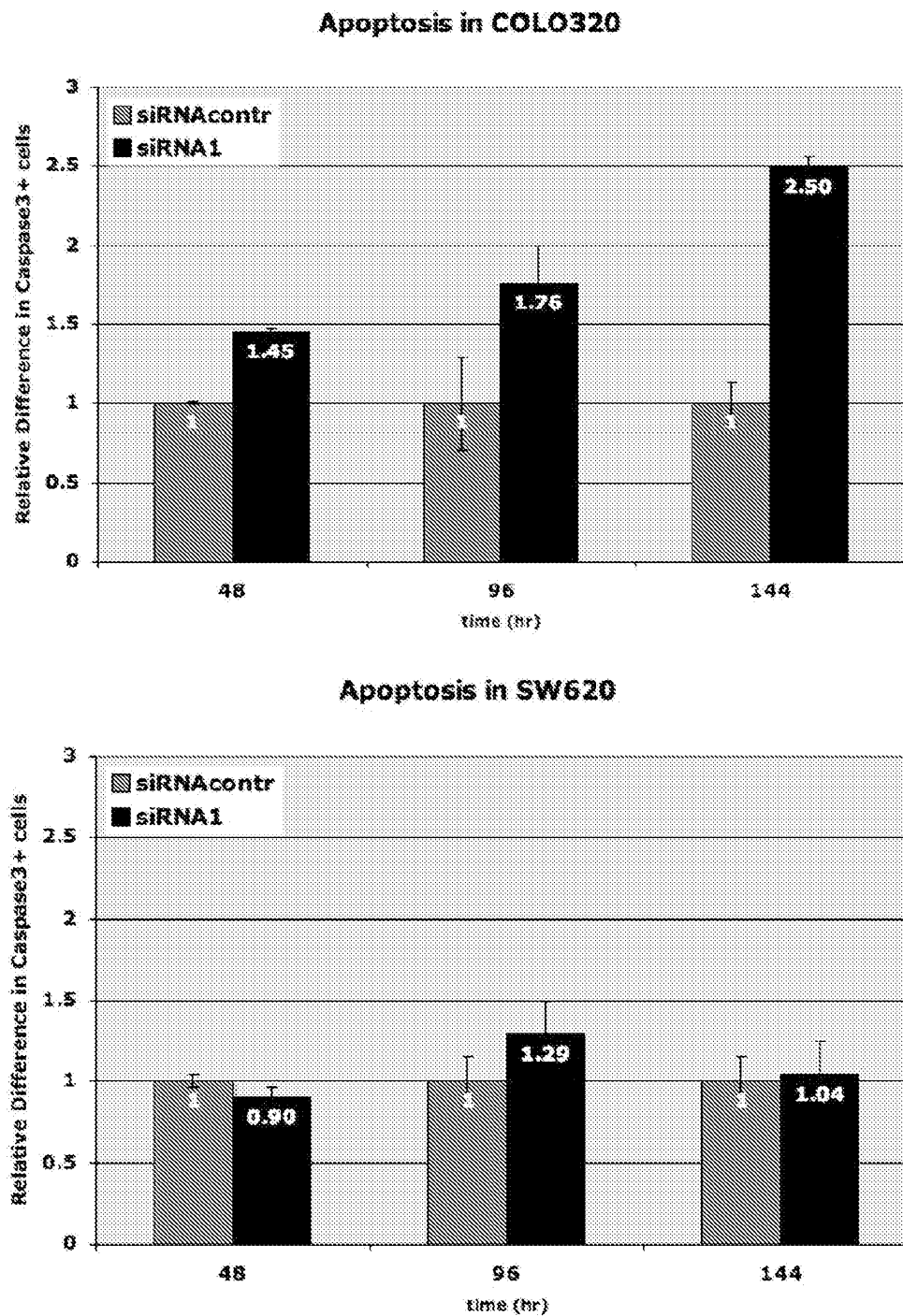
Figure 10

Figure 11

Table 1. Most significant differentially expressed UCRs in leukemias and carcinomas*.

UCR name	Probe (T-UCR)	Type and location	Significance	Upstream, host and downstream genes	CAGR location and host gene cancer connection
uc.29	uc.29+A	Non-exonic	high CRC vs norm	LMO4, N AF118089	
uc.73	uc.73+A	Possibly Exonic	low CLL vs CD5, high CRC vs norm	AK126774, BC017741 ZHX1B	
uc.111	uc.111+	Possibly Exonic	high CRC vs norm	AK128398, N AB051544	yes
uc.112	uc.112+	Non-exonic	high CRC vs norm	TBC1D5, N SATB1	
uc.134	uc.134+A	Possibly Exonic	high CRC vs norm	AF257098, MGC12197, MLF1	
uc.135	uc.135+	Exonic	low CLL vs CD5	GOLPH4, EVI1 ARPM1	yes, in antisense with EVI-1 oncogene overexpressed by t(3;21)(q26;q22)
uc.206	uc.206+	Non-exonic	high CRC vs norm	SP8, N SP4	
uc.230	uc.230+	Possibly Exonic	high CRC vs norm	AK096400, N TFEC	
uc.233	uc.233+	Exonic	low CLL vs CD5	C7orf21, CENTG3 ASB10	in sense with CENTG3
uc.291	uc.291+	Possibly Exonic	low CLL vs CD5	AK024492, C10orf11 KCNMA1	

Figure 12

uc.292	uc.292+	Exonic	high CRC vs norm	AF338191, MLR2 C18orf12	in sense with MLR2
uc.339	uc.339+	Possibly Exonic	high CRC vs norm	ATP2G2, N KIAA1536	yes
uc.341	uc.341+	Exonic	high CRC vs norm	HOXC11, HOXC10 HOXC9	yes in sense with HOXC10
uc.388	uc.388+	Non-exonic	high CRC vs norm	BX641000, TCF12 FLJ14957	
uc.399	uc.399+A	Non-exonic	high CRC vs norm	CYLD, N SALL1	
uc.420	uc.420+A	Exonic	high CRC vs norm	POLG2, DDX5 LOC90799	in sense with DDX5, downregulated in colon

Figure 12 continued

*Note. Only UCRs at P<0.0001 were selected. For full list of UCRs, see Supplementary Table 3. CAGR – cancer associated genomic regions as reported by (Calin et al., 2004b). \N – intronic location. Name of the genes as at www.ncbi.nlm.nih.gov/.

Table 2. Mixed effect Poisson regression results of association of UCRs with regions of interest *.

Region of interest	Ultraconserved regions			microRNAs			Zinc finger proteins		
	IRR	95% CI IRR	p	IRR	95% CI IRR	p	IRR	95% CI IRR	p
Fragile sites vs. non-fragile sites	2.98	1.69, 5.07	<0.001	9.12	6.22, 13.38	<0.001	1.36	0.76, 2.44	0.29
HPV16 insertion vs. all other	5.07	3.37, 7.64	<0.001	3.22	1.55, 6.68	0.002	0.50	0.07, 3.60	0.49
Homeobox genes vs. all other	2.39	1.69, 3.39	<0.001	2.95	1.63, 5.34	<0.001	0.16	0.02, 1.14	0.07
HOX Cluster vs. all other	7.09	3.61, 13.93	<0.001	15.77	7.39, 33.62	<0.001	-†	-	-
Amplified region vs. Non-amplified	3.05	1.99, 4.67	<0.001	3.97	2.31, 6.83	<0.001	0.39	0.12, 1.23	0.11
LOH vs. Other	2.02	1.62, 2.53	<0.001	4.08	2.99, 5.56	<0.001	0.54	0.14, 2.10	0.37

* The comparison with a "positive" and a "negative" control class of genes each, microRNAs and Zinc Finger Proteins respectively, is presented. IRR = Incident Rate Ratio.
† Too few events; likelihood-based models are numerically unstable.

Figure 13

Table 3. T-UCRs whose expression inversely correlates with complementary miRNA differentially expressed in CLL patients*.

TUCR name	Type and location	TUCR expression in ZAP-70 pos vs. neg	Complementary miRNAs	MiRNA expression in ZAP-70 pos vs. neg	Upstream host, downstream genes
uc.269A	Non-exonic, chr 9	downregulated	No complementary sites		AK123000, KIAA1608 LHX2
uc.160	Non-exonic, chr 5	downregulated	miR-155, miR-146a, miR-24 and miR-223	upregulated downregulated	AK128395, N AP3B1
uc.215	Non-exonic, chr 7	upregulated	No complementary sites		INHBA GLI3 C7orf25
uc.346A	Possibly exonic, chr 12	downregulated	miR-155	upregulated	RPC2 N REX1
uc.348	Non-exonic, chr 13	upregulated	miR-29b, miR-29a, miR-29c, and miR-155, miR-24	downregulated upregulated	KLHL1 DACH FLJ22624 gene desert

*Among the UCRs differentially expressed between the 70-kD zeta-associated protein (ZAP-70) positive and negative CLLs we selected only the UCRs identified by three different algorithms -GeneSpring ANOVA, PAM (Prediction Analysis for Microarrays) and SAM (Significance Analysis of Microarrays)- and that had a complementary site for microRNAs differentially expressed among the same groups of CLLs.

Figure 14

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Supplementary Table 1. List of T-UCRs expressed over the background in 19 human
normal tissues (3 tissues are in two copies from different individuals). The filter was
calculated using the average of blank spots + 2 standard deviations. Expression values
were normalized by Lowess and on-chip median centered.

Sample	Number of tissues in which the UCR pass the filter	B-cell 01	B-cell 02	Bladder	Brain	Breast	Esophagus A	Heart	Kidney	Liver	Lung	MNC 01
uc.188+A	19	3.299	2.322	1.020	1.111	0.945	1.322	0.981	0.942	1.041	1.294	1.402
uc.177+A	19	5.091	4.313	1.480	2.045	2.251	1.556	1.691	2.002	2.132	2.414	1.700
uc.245+A	19	1.719	1.043	1.006	1.058	1.140	1.141	1.379	0.944	1.008	1.060	0.996
uc.426+	19	2.020	1.708	1.000	1.031	1.231	1.196	1.067	0.968	1.241	1.286	1.248
uc.335+A	19	2.179	1.898	1.740	1.156	1.116	1.568	1.097	1.289	1.053	1.637	1.241
uc.97+A	19	1.333	1.539	1.154	1.166	1.073	1.273	1.522	1.154	1.099	1.326	1.010
uc.234+A	19	1.709	1.246	0.945	1.041	1.038	1.043	0.953	0.907	0.985	1.039	1.152
uc.422+	19	1.541	1.322	1.146	1.179	1.066	1.264	0.998	1.084	1.264	1.248	1.222
uc.317+	19	0.903	0.969	1.193	1.319	1.224	1.177	1.080	1.001	1.025	1.292	1.255
uc.206+	19	1.699	1.300	0.936	1.037	0.961	0.988	0.914	0.926	1.045	1.009	1.023
uc.411+A	19	3.420	1.943	1.010	1.098	1.011	1.051	0.995	0.944	1.079	1.080	1.135
uc.400+A	19	2.745	2.603	1.415	1.751	1.212	1.821	1.370	1.519	1.206	2.385	1.585
uc.192+	19	0.967	0.925	1.178	1.106	1.228	1.252	1.021	0.964	0.994	1.202	1.038
uc.343+A	19	1.043	1.046	0.962	0.934	0.987	1.029	1.061	1.004	0.999	1.039	1.009
uc.196+A	19	2.443	1.227	0.953	1.024	0.961	0.950	0.938	0.906	0.927	0.999	1.236
uc.346+A	19	4.279	4.936	4.121	3.290	3.567	2.873	2.635	1.976	3.259	4.939	3.304
uc.427+	19	3.093	3.142	2.218	2.363	1.878	1.879	2.129	2.315	2.871	2.662	2.370
uc.50+A	19	1.297	1.516	1.110	1.060	1.124	1.131	0.985	1.111	1.018	1.304	1.372
uc.73+	19	0.893	0.914	1.245	1.086	1.333	0.997	1.162	1.004	1.027	1.114	1.124
uc.321+A	19	1.097	0.984	1.161	1.006	1.063	0.996	1.036	0.960	0.973	0.971	0.932
uc.238+	19	0.927	0.909	1.001	1.026	1.020	0.978	1.688	1.434	1.743	1.278	1.182
uc.310+	19	1.930	1.089	1.402	1.152	1.378	1.112	1.128	1.112	1.184	1.188	1.216
uc.133+A	19	2.558	2.571	1.074	1.258	1.130	1.202	1.445	1.249	1.521	1.352	1.273
uc.456+	19	3.653	1.644	1.437	1.705	1.891	1.311	1.326	1.806	2.074	1.488	2.444
uc.338+A	19	2.900	2.304	0.982	1.459	1.068	1.346	0.974	1.059	0.972	1.533	1.487
uc.128+	19	1.450	1.043	1.065	1.033	1.106	1.098	1.093	0.978	1.079	1.222	1.086
uc.345+	19	1.207	0.981	1.035	1.025	1.073	1.013	0.982	0.936	0.967	1.038	1.126
uc.248+A	19	1.763	1.635	1.318	1.291	1.550	1.140	2.024	1.803	2.469	1.512	1.547
uc.347+	19	0.898	0.917	1.089	0.954	1.086	1.122	1.024	0.958	1.007	1.050	0.993
uc.346+	19	24.635	33.548	11.343	12.676	21.023	24.865	13.634	6.536	15.675	35.282	15.595
uc.204+	19	1.825	2.176	2.900	1.616	2.385	2.462	2.284	1.888	1.612	2.510	2.145
uc.391+A	19	2.105	1.979	1.106	1.227	1.161	1.337	1.015	0.959	1.307	1.308	1.329
uc.457+	19	2.156	1.853	1.413	1.706	1.438	1.422	1.765	1.857	2.215	2.149	1.824
uc.310+A	19	1.458	1.639	1.497	1.659	1.435	1.669	1.220	1.651	1.306	1.722	1.410
uc.470+A	19	6.550	6.053	6.978	11.972	8.041	7.532	6.759	3.437	5.064	15.702	5.101
uc.417+A	19	0.937	0.939	1.050	0.992	0.967	0.960	0.968	0.957	0.966	0.920	0.924
uc.420+	19	6.201	5.773	2.604	3.135	2.480	3.992	2.900	2.713	3.062	7.049	4.700
uc.327+A	19	2.291	3.278	3.256	2.719	3.406	3.451	3.332	1.900	3.060	5.580	3.194
uc.349+	19	1.771	2.209	1.802	1.457	1.494	1.527	1.328	1.440	1.426	3.688	1.784
uc.223+A	19	1.782	1.729	1.219	1.314	1.071	1.284	1.048	1.365	1.090	1.143	1.199
uc.348+	19	1.104	1.337	1.641	1.675	2.082	2.004	1.623	1.267	1.902	1.859	1.239
uc.10+	19	2.455	1.386	1.400	1.386	1.276	1.402	1.314	1.126	1.364	1.520	1.469
uc.46+	19	1.245	1.134	0.951	1.021	0.978	0.973	0.949	0.978	0.920	1.006	0.996
uc.275+	19	2.832	1.291	1.021	1.080	1.161	1.078	1.079	0.938	1.219	1.113	1.808
uc.362+A	19	3.420	2.761	1.723	2.045	2.044	2.062	2.658	1.846	3.457	3.562	2.318
uc.131+	19	1.050	1.111	1.178	1.033	1.097	1.088	1.130	0.994	0.942	1.207	1.173
uc.309+A	19	2.576	2.460	3.077	3.334	4.134	2.815	3.026	1.906	2.487	3.122	3.066
uc.383+	19	3.465	4.800	2.459	2.819	2.494	3.776	2.535	2.736	3.364	7.434	3.232
uc.398+A	19	1.462	1.454	2.613	2.183	2.364	2.182	2.337	1.204	1.476	2.950	2.025
uc.167+	19	11.447	13.139	24.697	16.005	30.161	52.178	21.496	6.796	13.735	71.374	18.629
uc.283+A	19	24.122	23.244	12.128	10.635	17.655	21.088	12.781	5.804	8.923	46.720	14.112
uc.21+A	19	1.292	1.303	0.986	1.053	0.964	1.148	0.958	1.058	1.115	1.121	1.157
uc.133+	19	1.629	1.045	0.981	1.051	1.026	1.048	0.941	0.901	0.993	1.083	0.997
uc.48+	19	2.968	1.881	1.467	2.046	2.675	1.677	1.522	1.190	1.466	1.596	2.076
uc.190+A	19	3.073	3.881	1.745	2.444	1.974	2.161	2.471	2.442	3.109	3.237	3.196
uc.134+	19	2.967	2.350	2.071	2.014	1.713	1.842	1.504	1.426	1.755	2.412	2.048
uc.47+	19	2.281	2.351	1.744	1.964	1.552	1.585	1.911	1.639	2.187	2.147	1.735
uc.10+A	19	1.887	1.921	1.156	1.998	1.114	1.601	1.218	1.616	1.652	1.586	1.450
uc.477+A	19	9.461	8.824	2.869	4.081	3.248	3.748	4.869	3.374	6.340	6.680	5.001
uc.278+	19	5.020	5.384	2.968	3.294	2.751	7.359	2.634	2.270	3.033	10.904	6.726
uc.350+	19	2.495	2.491	1.137	1.531	1.057	1.214	1.294	1.513	1.660	1.597	1.281
uc.118+A	19	1.065	1.066	1.011	1.166	1.072	1.466	1.192	1.113	1.100	1.177	1.192
uc.196+	19	1.050	1.084	1.074	1.068	1.277	1.031	1.265	1.392	1.239	1.200	1.140

Figure 15

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Sample	Number of tissues in which the UCR pass the filter	B-cell 01	B-cell 02	Bladder	Brain	Breast	Esophagus A	Heart	Kidney	Liver	Lung	MNC 01
uc.75+	19	1.378	1.691	0.977	1.177	1.002	1.064	0.945	0.979	1.177	1.025	0.979
uc.297+A	19	1.315	1.272	1.007	0.988	1.001	1.002	1.115	0.961	0.940	1.018	1.015
uc.161+	19	1.379	1.223	1.034	1.252	1.475	1.149	1.206	1.016	1.312	1.557	1.291
uc.195+	19	1.256	1.199	1.235	1.531	1.443	1.021	1.975	1.399	2.458	1.644	1.225
uc.275+A	19	1.167	1.137	1.141	1.127	1.152	1.056	1.333	1.429	1.555	1.202	1.098
uc.469+A	19	1.394	1.535	1.294	1.757	1.790	1.256	2.256	1.833	2.939	2.034	1.683
uc.160+	19	0.921	0.912	2.876	2.724	4.630	2.594	2.820	0.973	1.123	4.875	5.155
uc.354+A	19	2.216	1.932	1.807	1.829	1.872	1.920	2.081	1.746	3.044	2.528	1.902
uc.43+	19	2.729	2.529	1.957	2.177	1.525	2.257	2.009	1.996	2.224	2.573	1.998
uc.78+	19	2.967	3.917	1.678	1.567	1.901	2.435	1.688	1.695	2.423	3.432	2.083
uc.182+A	19	1.670	1.448	1.107	1.082	1.144	1.129	0.987	1.035	1.043	1.210	1.084
uc.373+A	19	1.081	1.176	0.979	0.954	0.922	1.050	0.996	1.074	0.934	0.998	0.977
uc.44+	19	0.992	0.954	2.195	1.098	2.266	1.352	1.648	1.051	1.032	1.084	1.047
uc.77+	19	5.741	7.437	2.978	4.447	3.316	5.462	2.823	3.354	4.181	7.342	3.715
uc.13+A	19	1.237	1.141	0.995	0.993	0.963	0.960	1.056	0.969	1.004	1.101	0.998
uc.422+A	19	2.846	1.710	1.117	1.161	1.017	0.954	0.981	0.919	0.984	1.276	1.210
uc.382+	19	1.655	2.144	1.162	1.366	1.321	1.669	1.197	1.106	1.532	1.845	1.430
uc.162+	19	1.422	1.026	0.947	0.986	0.907	0.939	1.013	1.027	0.990	1.079	1.047
uc.117+A	19	3.317	2.659	3.748	2.641	3.811	4.049	3.042	1.763	2.523	5.085	3.694
uc.186+	19	1.311	1.137	0.932	1.121	0.926	0.965	0.927	1.123	0.994	1.029	1.097
uc.48+A	19	3.796	4.735	3.401	4.793	3.433	4.505	3.510	2.686	4.799	8.173	4.530
uc.151+	19	2.230	1.345	1.068	0.989	1.076	1.046	1.023	0.965	1.073	1.086	1.381
uc.295+	19	1.132	1.037	0.965	0.966	0.947	0.991	0.935	0.935	0.990	0.943	1.074
uc.106+A	19	1.608	1.432	1.205	1.294	1.646	1.008	1.457	1.302	1.801	1.677	1.644
uc.63+	19	6.406	5.658	1.362	1.575	1.401	1.536	1.405	1.192	2.004	1.544	1.729
uc.389+A	19	0.994	0.915	1.089	0.976	0.997	1.004	1.015	0.938	0.969	1.015	1.047
uc.285+A	19	2.101	1.439	1.172	1.284	1.066	1.083	1.157	1.034	1.097	1.333	1.255
uc.185+	19	1.319	1.257	1.226	1.145	0.960	1.264	1.079	1.210	1.113	1.143	1.174
uc.181+A	19	2.596	2.714	2.265	1.418	1.508	1.501	1.535	1.600	1.624	2.113	1.786
uc.207+A	19	1.294	1.215	0.908	1.136	0.909	1.017	0.960	1.057	0.961	0.928	0.977
uc.443+A	19	1.295	1.355	0.965	1.113	1.016	1.150	0.993	1.131	1.086	1.089	1.119
uc.371+	19	1.397	1.594	1.681	1.217	1.339	1.334	1.239	1.038	1.057	1.376	1.458
uc.153+	19	3.933	2.398	1.116	1.465	1.414	1.898	1.164	1.162	1.568	1.674	2.817
uc.170+A	19	2.296	1.539	0.918	1.010	0.902	1.196	0.944	1.022	1.137	1.133	1.282
uc.128+A	19	7.916	10.716	2.611	3.473	2.814	3.505	1.942	1.842	3.592	4.833	4.116
uc.468+A	19	3.113	1.443	1.010	1.207	1.007	1.033	0.975	0.944	1.082	1.224	1.517
uc.189+	19	2.409	2.395	3.340	3.323	3.290	2.953	2.768	1.722	2.841	5.286	3.384
uc.188+	19	1.381	1.369	1.157	1.138	1.074	1.011	1.156	1.142	1.481	1.460	1.277
uc.95+	19	7.874	8.014	2.567	3.761	2.059	4.648	2.264	2.390	3.429	4.134	3.960
uc.309+	19	2.063	1.161	1.166	1.136	1.118	1.068	1.114	0.935	1.096	1.085	1.337
uc.277+A	19	1.166	1.047	0.974	1.001	1.000	1.056	0.965	1.054	0.981	0.992	1.019
uc.96+	19	1.309	1.450	1.278	1.755	1.558	1.458	1.686	1.575	2.293	1.705	1.581
uc.241+A	19	1.137	1.122	1.514	1.149	1.267	1.159	1.110	1.199	1.408	1.111	1.198
uc.266+A	19	5.431	8.578	2.521	2.901	1.884	3.411	2.081	2.821	2.192	3.495	2.858
uc.334+A	19	1.289	1.224	1.044	1.052	1.027	0.978	0.984	1.133	1.142	1.315	1.107
uc.92+	19	1.455	1.309	1.016	1.079	1.013	1.139	1.017	0.961	0.973	1.057	1.155
uc.288+A	19	1.312	1.313	1.036	1.243	1.027	1.017	1.255	1.316	1.286	1.131	1.058
uc.151+A	19	1.407	1.487	1.130	1.550	1.363	1.105	1.398	1.390	1.807	1.354	1.503
uc.183+	19	1.955	1.655	1.378	1.261	1.183	1.606	1.321	1.044	1.134	1.526	1.257
uc.378+A	19	5.805	5.682	3.190	6.598	4.521	6.591	5.666	5.232	9.471	13.484	6.133
uc.291+	19	1.178	1.304	0.995	1.009	0.989	1.071	0.937	0.981	1.036	1.025	1.014
uc.31+	19	1.487	2.106	1.559	1.331	1.852	1.823	1.460	1.613	1.841	1.391	1.531
uc.263+A	19	1.620	1.824	2.093	2.552	2.345	1.339	2.559	2.373	4.174	3.280	2.269
uc.299+A	19	5.938	7.807	3.976	5.207	5.001	5.415	3.687	3.588	5.083	13.260	5.531
uc.181+	19	1.035	1.064	1.044	1.025	1.091	0.974	1.090	1.063	1.115	0.984	1.059
uc.345+A	19	1.045	1.121	1.248	1.016	1.121	1.208	1.316	1.193	1.412	1.256	1.114
uc.331+A	19	3.955	2.266	2.691	1.875	1.990	1.747	1.934	1.328	2.012	2.456	2.027
uc.252+A	19	1.138	1.189	1.308	1.077	1.067	1.105	1.137	1.104	1.163	1.178	1.168
uc.182+	19	4.215	1.794	1.282	1.194	1.465	1.428	1.299	1.106	1.229	1.604	1.931
uc.378+	19	2.975	1.968	1.701	2.523	1.722	1.572	1.466	1.429	1.903	2.224	2.457
uc.462+A	19	8.768	8.357	4.006	7.407	4.339	6.853	6.064	4.677	7.351	10.334	6.308
uc.233+	19	0.942	1.007	1.166	1.774	1.266	1.047	2.289	2.070	1.185	1.197	1.023
uc.158+A	19	1.224	1.487	1.199	1.188	1.219	1.067	1.210	1.218	1.334	1.573	1.301
uc.234+	19	2.728	2.617	1.574	2.068	1.551	1.826	2.712	2.365	3.415	2.467	2.304
uc.215+A	19	1.105	1.037	0.993	1.085	0.977	1.046	1.168	1.026	1.482	1.046	1.010
uc.268+	19	3.141	3.086	1.440	2.376	1.288	1.744	1.888	1.784	2.323	1.769	1.762
uc.20+A	19	2.654	1.304	0.957	1.085	1.093	1.161	1.058	1.023	1.032	1.102	1.974
uc.342+	19	1.264	1.234	1.058	1.252	1.296	1.308	1.376	1.299	1.463	1.349	1.256
uc.450+	19	1.302	1.339	1.095	1.686	1.196	1.097	1.203	1.252	1.611	1.482	1.197
uc.453+	19	2.184	1.357	1.633	1.359	1.526	1.071	1.226	1.027	1.204	1.292	1.350
uc.237+A	19	1.423	1.451	0.940	1.003	0.963	0.964	1.004	1.090	1.026	0.995	0.946

Figure 15

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Sample	Number of tissues in which the UCR pass the filter	B-cell 01	B-cell 02	Bladder	Brain	Breast	Esophagus A	Heart	Kidney	Liver	Lung	MNC 01
uc.452+	19	1.439	1.394	1.019	1.160	1.013	1.260	1.021	1.265	1.071	1.118	1.018
uc.41+	19	1.227	1.330	1.150	1.287	1.161	1.248	1.171	1.312	1.388	1.195	1.104
uc.200+	19	6.017	4.815	2.040	3.308	2.252	3.152	2.342	2.922	2.729	2.817	2.877
uc.305+A	19	2.910	2.410	1.531	2.232	1.327	1.725	1.385	1.689	1.694	1.720	1.774
uc.343+	19	1.165	1.159	0.966	0.967	0.989	1.063	0.994	1.014	1.012	1.028	1.040
uc.383+A	19	1.418	1.141	0.994	0.992	0.926	0.977	1.060	0.953	1.000	0.974	1.083
uc.122+A	19	1.623	1.273	0.968	0.987	0.962	1.113	1.032	1.136	0.996	1.083	1.101
uc.473+A	19	6.485	4.115	4.231	5.594	5.543	4.109	7.036	3.836	10.952	16.614	4.492
uc.229+A	19	1.724	1.767	1.821	2.065	1.859	1.544	2.207	1.883	2.623	1.865	2.040
uc.372+	19	2.034	1.900	1.090	1.370	1.172	1.364	1.120	1.280	1.296	1.277	1.336
uc.465+A	19	9.943	14.994	5.270	7.080	5.869	7.967	5.044	4.957	7.991	11.358	6.270
uc.282+A	19	9.618	17.358	7.878	9.769	13.558	18.494	8.609	5.974	15.622	57.165	8.412
uc.476+A	19	3.785	3.532	1.954	2.908	1.647	2.681	1.604	1.801	1.795	3.137	2.632
uc.299+	19	3.573	2.948	2.824	3.696	3.582	2.843	2.038	1.731	2.663	3.681	3.972
uc.192+A	19	1.340	1.531	1.482	1.107	1.011	1.261	1.239	1.196	1.035	1.268	1.077
uc.33+	19	2.159	1.957	1.813	2.172	1.934	1.795	2.205	2.600	2.825	2.009	2.433
uc.34+	19	1.529	1.159	0.983	1.016	0.981	0.961	0.968	1.016	1.155	1.020	1.458
uc.34+A	19	1.662	1.762	1.272	1.193	1.473	1.249	1.533	1.617	2.117	1.682	1.535
uc.158+	19	2.032	1.211	1.167	1.181	1.139	1.151	1.029	0.995	1.222	1.327	1.261
uc.440+A	19	1.242	1.237	0.971	1.066	1.050	1.008	1.066	1.039	1.176	1.089	1.207
uc.37+	19	1.312	1.239	1.075	1.173	1.041	1.095	1.758	1.152	1.026	1.088	1.127
uc.42+A	19	1.427	1.724	1.054	1.114	0.976	1.092	0.984	1.162	1.053	1.316	1.096
uc.340+	19	2.921	2.797	1.683	2.141	1.913	2.363	1.684	1.723	2.103	2.160	1.977
uc.319+A	19	0.951	0.941	1.147	1.137	1.045	1.155	1.080	1.263	1.051	1.099	1.002
uc.483+	19	1.097	1.360	1.511	1.444	1.614	1.501	1.489	1.545	1.938	2.770	1.623
uc.263+	19	2.926	1.592	1.054	1.261	1.267	1.297	0.909	1.016	1.187	1.419	1.643
uc.204+A	19	2.523	2.777	2.162	1.696	1.907	2.582	1.964	1.456	1.747	2.702	2.088
uc.230+	19	1.291	1.655	3.488	11.308	5.278	4.831	5.044	3.187	5.279	5.932	1.999
uc.292+A	19	1.543	1.604	1.101	1.111	0.997	1.125	0.939	1.415	0.975	1.300	1.053
uc.220+	19	0.959	1.004	0.956	1.071	1.094	0.906	1.011	1.182	1.351	1.032	1.083
uc.473+	19	5.476	5.222	1.170	2.177	1.293	2.111	1.128	1.713	2.043	1.739	1.903
uc.329+A	19	2.042	2.067	1.390	1.392	1.281	1.514	1.256	1.512	1.280	1.461	1.329
uc.203+A	19	1.077	0.973	0.934	0.935	0.930	0.947	1.154	0.929	0.946	0.985	0.925
uc.472+	19	1.408	1.273	1.119	1.308	1.193	1.439	1.150	1.089	1.247	1.522	1.281
uc.475+A	19	3.919	2.136	2.083	2.354	2.275	1.860	1.765	1.179	1.860	2.431	2.447
uc.146+	19	1.027	1.186	1.059	1.250	1.072	1.104	1.302	1.222	1.264	1.226	1.203
uc.27+	19	0.879	0.929	1.031	1.024	1.011	1.066	0.994	1.080	1.044	1.054	0.967
uc.111+	19	1.389	1.263	1.216	1.138	1.176	1.231	1.152	1.086	1.049	1.327	1.186
uc.382+A	19	2.287	1.662	1.422	1.267	1.221	1.248	1.164	1.094	1.505	1.230	1.625
uc.331+	19	2.161	2.163	1.597	2.434	1.446	1.906	1.779	1.689	1.865	1.670	1.554
uc.450+A	19	1.930	1.160	1.202	1.073	0.986	0.991	1.001	0.988	1.049	1.105	1.151
uc.476+	19	1.599	1.216	1.365	1.138	1.247	1.189	1.134	0.992	1.147	1.403	1.225
uc.29+	19	0.993	1.042	1.003	0.989	0.987	1.030	0.982	1.120	1.008	1.054	0.953
uc.28+	19	1.187	1.399	1.259	1.482	1.309	1.239	1.342	1.385	1.617	1.569	1.421
uc.330+	19	1.410	1.366	1.234	1.510	1.020	1.509	1.178	1.245	1.439	1.166	1.195
uc.281+A	19	4.319	5.805	2.535	3.939	2.456	5.342	2.566	4.029	3.090	6.196	4.496
uc.77+A	19	2.153	1.241	1.162	0.995	1.086	1.061	1.120	1.116	1.041	1.164	1.233
uc.475+	19	8.803	11.423	4.463	6.384	5.046	8.229	5.408	4.406	6.394	12.810	8.528
uc.396+	19	0.939	0.963	1.160	1.220	1.071	1.262	1.135	1.176	1.054	1.091	1.074
uc.374+A	19	1.073	0.985	0.954	0.983	1.019	0.958	1.133	1.057	1.280	1.007	1.020
uc.206+A	19	2.480	1.295	1.314	1.252	1.160	1.182	1.350	1.117	1.878	1.367	1.456
uc.22+A	19	2.349	2.260	1.053	1.184	1.036	1.536	1.016	1.141	1.047	1.437	1.364
uc.180+A	19	1.074	1.065	1.007	0.986	0.959	0.964	0.986	0.929	1.677	1.159	1.024
uc.250+	19	1.264	1.343	0.973	1.000	0.966	0.978	1.044	1.124	1.078	1.089	0.973
uc.363+A	19	3.628	2.940	1.311	1.233	1.215	1.266	1.568	1.619	1.693	1.513	1.530
uc.20+	19	3.417	2.994	2.046	2.978	2.322	1.905	2.768	2.118	3.727	2.718	2.848
uc.138+A	19	1.198	1.045	0.906	0.933	0.920	0.958	0.909	0.972	0.997	0.933	1.080
uc.142+	19	1.642	1.464	1.091	1.045	1.055	1.058	1.092	0.962	0.938	1.018	1.324
uc.228+A	19	1.124	0.961	1.024	1.017	1.007	1.049	1.020	0.973	0.948	1.020	0.947
uc.398+	19	23.405	27.414	19.585	19.964	21.304	48.460	19.979	8.140	11.515	56.962	30.263
uc.464+A	19	2.021	2.235	1.236	1.483	1.193	1.635	1.147	1.189	1.546	1.605	1.655
uc.149+	19	1.062	1.145	1.023	1.021	1.037	1.047	1.054	1.065	1.229	1.035	0.987
uc.44+A	19	4.251	4.877	2.815	3.948	2.602	4.374	2.776	2.393	3.207	7.170	4.768
uc.217+A	19	3.240	2.287	2.147	2.432	2.237	2.234	2.712	1.836	4.090	3.238	2.588
uc.453+A	19	8.414	9.429	2.130	5.289	2.032	5.673	2.265	2.855	3.004	5.203	5.102
uc.295+A	19	1.204	1.091	1.012	1.047	1.067	1.034	1.038	1.091	1.020	1.103	1.084
uc.145+	19	1.168	0.978	1.007	1.063	1.103	1.035	1.107	0.966	0.960	1.062	1.091
uc.33+A	19	2.557	1.570	1.438	1.108	1.436	1.279	1.329	0.993	1.166	1.580	2.116
uc.144+	19	1.318	1.132	1.110	1.028	1.054	0.995	1.097	1.029	0.966	1.057	1.100
uc.447+	19	1.665	1.549	1.036	1.087	0.995	1.069	1.006	1.083	1.112	1.304	1.093
uc.338+	19	4.418	4.023	3.565	3.277	3.098	3.288	2.372	2.101	5.761	5.742	3.613

Figure 15

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Sample	Number of tissues in which the UCR pass the filter	B-cell 01	B-cell 02	Bladder	Brain	Breast	Esophagus A	Heart	Kidney	Liver	Lung	MNC 01
uc.269+A	19	1.743	2.019	5.273	3.715	4.911	5.814	4.741	2.206	3.115	10.031	7.560
uc.301+A	19	0.967	0.983	0.967	1.007	1.043	1.056	1.142	1.014	0.952	1.033	0.993
uc.339+	19	15.107	22.611	7.585	40.022	8.322	23.904	8.153	8.047	15.017	75.435	9.369
uc.5+	19	2.001	1.050	1.222	0.989	1.189	1.126	1.116	1.240	1.052	0.928	1.087
uc.445+	19	1.979	1.781	1.774	1.193	1.345	1.694	1.026	1.139	1.425	1.438	1.449
uc.132+A	19	0.915	0.931	1.053	1.044	1.067	0.993	1.134	1.060	1.063	1.067	1.026
uc.411+	19	2.155	1.921	1.417	1.320	1.347	1.324	1.221	1.509	1.197	1.284	1.423
uc.446+	19	1.477	1.602	1.115	1.168	1.179	1.212	1.161	1.262	1.307	1.259	1.303
uc.312+A	19	1.115	1.129	0.994	0.963	0.949	1.205	0.939	1.116	1.098	1.063	1.097
uc.413+	19	1.081	0.972	1.006	0.984	0.985	1.018	1.205	0.923	0.914	0.943	0.987
uc.359+A	19	0.967	1.018	1.002	1.206	1.344	0.948	1.012	0.901	0.945	1.019	0.895
uc.402+A	19	2.434	1.431	0.982	0.922	0.966	1.029	0.925	0.920	1.044	0.986	1.059
uc.91+	19	1.768	1.551	0.978	1.080	0.961	1.027	1.018	0.945	0.987	1.060	1.143
uc.412+	19	3.427	2.069	1.868	1.592	2.229	2.197	1.518	1.336	1.517	2.458	2.215
uc.448+	19	2.450	1.229	1.288	1.370	1.344	1.212	1.119	1.013	1.152	1.523	1.921
uc.9+A	19	1.001	0.989	1.041	1.010	1.069	1.050	0.992	1.169	1.060	1.145	1.093
uc.305+	19	2.359	1.354	1.169	1.256	1.455	1.081	1.172	1.060	1.233	1.268	1.525
uc.233+A	19	2.795	2.009	1.124	1.855	1.495	1.488	0.977	1.112	1.538	1.955	1.787
uc.304+A	19	1.512	1.671	1.022	1.013	1.030	1.086	0.961	1.083	0.950	1.042	1.081
uc.369+	19	3.938	4.798	4.691	2.681	4.221	4.141	3.301	2.075	2.274	4.028	4.047
uc.88+A	19	11.292	12.414	1.898	4.652	1.925	6.634	2.206	2.516	3.390	4.627	4.434
uc.2+	19	0.936	0.955	1.020	0.974	1.013	0.930	1.025	1.270	0.922	0.935	0.985
uc.110+A	19	3.631	5.255	4.457	4.067	4.018	5.847	3.794	1.774	2.708	4.292	4.268
uc.461+A	19	1.004	1.076	1.261	1.266	1.190	1.139	1.174	1.355	1.062	1.127	1.223
uc.419+A	19	1.006	1.047	2.182	1.676	1.836	1.674	1.644	1.315	1.383	2.195	1.643
uc.440+	19	1.149	1.028	1.018	1.013	0.951	0.928	0.931	0.942	0.933	0.953	1.021
uc.478+	19	1.518	1.296	1.844	1.789	1.717	1.824	1.268	1.051	1.202	1.850	1.429
uc.1+	19	3.470	3.835	3.574	2.570	3.012	2.862	3.719	2.840	2.311	2.445	2.353
uc.4+	19	1.839	1.290	1.188	1.246	1.280	1.080	1.471	1.462	1.619	1.217	1.276
uc.335+	19	1.362	1.459	1.135	1.465	1.103	1.373	1.045	1.074	1.031	1.260	1.250
uc.483+A	19	1.594	1.840	2.676	3.099	2.774	3.535	2.635	2.009	2.875	5.520	2.646
uc.8+	19	2.169	3.013	9.916	10.562	5.625	12.980	8.160	2.464	9.704	2.855	5.425
uc.63+A	19	2.937	3.482	1.057	1.316	1.198	1.606	0.976	1.223	1.086	1.437	1.535
uc.443+	19	1.252	1.142	1.021	0.967	0.992	1.008	1.086	0.931	0.936	0.990	0.983
uc.117+	19	5.433	6.885	5.401	5.382	6.179	6.823	5.232	4.995	4.688	8.902	5.933
uc.477+	19	2.604	1.353	0.998	1.737	0.995	1.045	0.933	0.953	1.092	1.144	1.421
uc.200+A	19	2.895	1.682	1.413	1.309	1.292	1.710	1.524	1.016	1.242	1.899	1.598
uc.3+	19	1.053	0.965	1.242	1.257	1.248	1.175	1.797	1.354	1.713	1.202	1.211
uc.322+	19	1.224	1.259	0.935	1.090	1.034	0.959	0.978	0.987	0.992	1.032	1.220
uc.213+	19	10.045	15.102	6.177	5.492	7.526	6.915	5.834	3.246	6.768	9.875	5.788
uc.249+	19	1.994	1.567	2.087	2.545	2.133	1.931	2.288	1.680	2.047	2.013	1.358
uc.303+A	19	1.139	1.195	1.168	1.276	1.291	1.256	1.202	1.267	1.532	1.353	1.163
uc.323+	19	1.320	1.365	1.016	1.173	1.056	1.056	1.161	1.097	1.305	1.220	1.158
uc.248+	19	2.110	1.283	0.937	0.962	0.978	0.984	0.960	1.001	1.044	1.046	1.228
uc.465+	19	1.459	1.089	1.077	1.026	1.185	0.955	1.616	0.903	1.010	1.010	0.982
uc.139+	19	2.470	2.089	2.654	3.207	2.084	4.690	2.562	2.987	1.607	4.478	4.248
uc.214+	19	1.189	1.286	1.111	1.146	1.109	1.360	1.201	1.153	1.548	1.430	1.236
uc.145+A	19	2.067	3.014	11.933	10.163	15.697	15.905	10.732	3.298	7.588	22.091	17.102
uc.325+A	19	1.156	0.966	1.162	1.044	1.161	1.014	1.525	1.175	1.527	1.242	1.106
uc.217+	19	5.017	4.299	1.550	2.139	1.630	2.735	1.311	1.303	2.558	2.893	2.793
uc.325+	19	13.837	20.922	10.216	9.218	10.185	10.609	8.718	5.053	9.949	13.644	9.529
uc.435+	19	1.552	1.601	1.335	1.473	1.342	1.235	1.576	1.377	1.884	1.458	1.380
uc.326+	19	2.817	3.230	1.754	1.741	1.641	3.019	1.303	1.912	1.562	2.767	2.590
uc.106+	19	4.035	1.443	0.985	1.045	1.072	1.127	0.924	0.958	1.029	1.420	2.445
uc.468+	19	1.408	1.171	1.385	1.846	1.528	1.610	1.904	1.560	2.165	1.494	1.933
uc.213+A	19	1.490	1.604	2.324	2.477	2.591	1.935	2.617	2.040	3.249	3.618	2.286
uc.62+A	19	1.178	1.078	0.979	0.988	1.014	1.042	0.909	0.934	0.933	1.011	1.027
uc.246+A	19	1.922	1.374	1.361	1.236	1.335	1.459	1.140	1.132	1.230	1.348	1.434
uc.43+A	19	1.665	1.165	0.950	1.066	1.033	1.034	0.983	0.950	1.002	1.005	1.369
uc.389+	19	1.332	1.299	1.228	1.203	1.237	1.419	1.600	1.166	1.419	1.634	1.215
uc.159+A	19	3.485	3.462	3.926	4.120	3.696	3.593	1.586	2.256	3.162	4.488	4.764
uc.100+	19	1.575	1.769	1.354	1.278	1.638	1.784	1.206	1.168	1.792	1.626	1.410
uc.462+	19	2.441	1.802	2.094	1.775	1.869	1.531	1.455	1.312	1.402	1.830	1.953
uc.352+	19	5.661	5.806	2.825	2.453	3.361	3.686	2.784	1.741	2.804	5.951	3.903
uc.388+	19	4.497	1.918	1.191	1.492	1.407	1.636	1.114	1.068	1.993	1.653	2.461
uc.125+A	19	1.066	0.964	0.994	1.051	1.042	0.992	0.986	0.993	1.519	1.084	1.035
uc.136+	19	1.688	2.509	1.535	1.245	1.232	1.602	1.219	1.321	1.039	1.504	1.640
uc.244+	19	1.179	1.296	0.969	1.006	1.036	0.972	0.966	0.983	1.069	1.092	1.023
uc.138+	19	1.451	1.352	0.992	1.092	0.987	1.180	1.015	1.300	1.047	1.147	1.312
uc.291+A	19	1.219	1.031	1.531	1.257	2.102	1.128	1.686	1.051	1.275	2.536	1.076
uc.249+A	19	2.356	1.484	1.122	1.151	1.154	1.137	1.038	0.982	1.161	1.230	1.322

Figure 15

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Sample	Number of tissues in which the UCR pass the filter	B-cell 01	B-cell 02	Bladder	Brain	Breast	Esophagus A	Heart	Kidney	Liver	Lung	MNC 01
uc.469+	19	1.160	0.994	0.968	0.983	0.961	0.975	0.930	0.961	0.933	0.981	1.051
uc.18+	19	5.129	6.741	2.912	4.286	4.056	5.620	3.577	2.919	6.117	5.531	3.189
uc.245+	19	1.153	1.162	0.955	1.449	1.090	1.100	1.333	1.177	1.026	1.084	1.074
uc.280+A	19	1.490	1.415	1.078	1.118	0.962	1.172	0.993	1.065	1.049	1.079	1.193
uc.14+	19	0.969	1.180	1.059	1.164	1.011	1.117	1.003	1.111	1.082	1.136	1.020
uc.134+A	19	4.401	5.256	2.803	2.033	2.004	2.437	1.875	1.472	1.698	1.962	2.025
uc.246+	19	5.160	5.479	3.346	6.561	3.495	5.679	3.786	4.593	5.518	4.774	3.610
uc.16+	19	2.675	2.369	1.438	1.914	1.316	1.698	1.490	1.739	1.717	1.594	1.658
uc.391+	19	1.060	1.191	1.207	1.238	1.242	1.306	1.136	1.131	1.119	1.296	1.267
uc.262+A	19	3.912	3.639	3.198	3.937	2.364	4.984	2.868	5.025	2.621	5.453	5.133
uc.456+A	19	4.226	5.263	2.251	3.260	2.006	2.899	2.647	2.866	3.611	6.068	3.096
uc.53+	19	0.883	1.046	1.317	1.031	1.230	1.018	1.615	1.208	1.164	0.942	1.119
uc.89+	19	1.175	0.983	1.014	1.050	1.036	1.003	1.270	1.171	1.667	1.353	1.156
uc.390+	19	2.266	2.188	1.194	1.342	1.089	1.506	1.071	1.092	1.208	1.729	1.454
uc.183+A	19	4.222	3.333	1.423	1.597	1.242	1.738	1.367	1.769	1.529	1.814	1.581
uc.377+A	19	1.638	1.230	1.117	1.192	1.100	1.157	1.337	1.011	1.054	1.245	1.095
uc.388+A	19	1.868	1.660	1.734	2.172	1.700	1.393	1.827	1.356	2.525	2.175	1.984
uc.173+	19	1.914	1.388	1.002	1.040	1.007	1.090	0.961	0.925	0.972	1.093	1.168
uc.478+A	19	4.673	4.251	3.632	6.523	4.011	5.537	3.849	4.033	5.148	10.182	5.340
uc.47+A	19	2.507	1.934	1.102	1.212	1.191	1.357	1.197	1.134	1.346	1.400	1.416
uc.393+	19	1.023	1.309	1.220	1.179	1.434	1.126	1.266	1.123	1.245	1.106	1.103
uc.315+A	19	1.382	1.390	1.052	1.037	1.168	1.037	1.017	1.132	1.022	1.032	1.104
uc.177+	19	3.037	2.810	2.021	2.032	2.137	1.981	1.666	1.539	2.052	2.264	2.313
uc.392+	19	1.447	1.187	0.944	0.989	1.005	1.046	0.921	0.969	0.946	1.075	1.024
uc.341+A	19	1.158	1.095	1.036	1.007	1.011	0.958	0.995	0.996	0.942	0.944	0.981
uc.88+	19	3.506	1.594	2.521	2.275	2.226	1.955	2.133	1.489	2.138	3.369	2.367
uc.285+	19	2.164	2.424	2.603	2.393	2.312	3.085	2.128	1.801	3.209	5.887	2.786
uc.420+A	19	2.046	1.671	1.103	1.317	1.079	1.219	0.980	0.945	1.054	1.340	1.315
uc.164+A	19	1.253	1.360	1.027	1.036	0.948	1.030	1.061	1.107	1.041	1.280	1.144
uc.300+A	19	19.467	25.679	6.912	9.169	6.818	16.240	6.685	5.466	6.485	17.350	11.124
uc.153+A	19	1.854	1.736	1.855	2.320	2.180	1.439	2.633	1.961	4.238	2.789	2.369
uc.448+A	19	8.965	10.577	2.801	4.849	2.938	3.573	4.106	3.254	5.187	7.430	3.942
uc.17+A	19	1.028	1.161	1.047	1.304	1.056	1.061	1.034	1.083	1.218	2.016	1.166
uc.436+	19	1.262	1.544	1.099	1.175	1.089	1.191	1.080	1.064	1.096	1.207	1.087
uc.142+A	19	4.770	7.363	2.914	4.927	2.807	3.560	3.168	3.271	5.981	4.971	4.119
uc.73+A	19	3.522	5.222	2.880	3.811	2.964	3.665	2.947	3.081	4.295	5.430	3.600
uc.404+	19	1.039	1.065	0.975	1.140	1.032	0.963	1.327	1.187	1.366	1.220	1.105
uc.84+A	19	2.818	2.794	8.722	5.866	6.605	9.429	4.983	2.851	4.429	12.692	4.198
uc.280+	19	1.773	1.353	1.041	1.038	1.054	1.108	1.043	1.033	1.119	1.068	1.177
uc.172+A	19	10.788	16.805	4.384	6.111	4.931	11.485	5.924	6.007	15.230	26.972	5.607
uc.287+A	19	3.880	3.866	2.522	3.700	2.857	3.232	4.413	3.350	6.476	5.313	3.575
uc.54+	19	0.905	0.915	1.029	0.985	0.969	0.958	0.983	1.004	0.945	1.000	0.993
uc.445+A	19	1.989	1.499	1.307	1.601	1.681	1.268	2.409	1.678	2.961	1.698	1.771
uc.407+	19	1.525	1.422	1.192	1.336	1.141	1.174	1.202	1.233	1.418	1.788	1.428
uc.412+A	19	3.861	4.442	2.470	2.995	2.430	2.991	3.362	2.850	3.831	3.906	3.033
uc.347+A	19	1.167	1.440	1.316	1.095	1.396	1.336	1.305	1.559	1.516	1.416	1.352
uc.87+	19	1.148	1.325	1.011	1.211	0.962	1.136	1.157	1.114	1.139	1.078	1.144
uc.170+	19	4.728	2.962	2.106	2.840	2.466	2.423	1.874	1.746	2.687	2.482	2.613
uc.161+A	19	3.885	4.183	2.241	2.023	1.908	2.308	1.780	1.905	1.841	2.602	2.565

Figure 15

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Sample	Number of tissues in which the UCR pass the filter	MNC 02	Ovary	Pancreatic	Placenta	Prostate	Skeletal muscle	Spleen	T-cell 01	T-cell 02	Testicule	Thymus
uc.188+A	19	1.523	1.056	1.059	1.215	1.195	1.109	1.071	1.961	3.386	1.116	1.150
uc.177+A	19	1.959	1.689	2.833	2.269	1.924	2.574	1.852	1.970	2.344	2.119	2.187
uc.245+A	19	1.107	0.971	1.128	1.049	1.082	1.054	1.063	2.095	4.229	1.060	1.054
uc.426+	19	1.509	1.043	0.956	1.095	1.170	0.973	1.564	1.672	4.504	1.176	1.124
uc.335+A	19	1.516	1.050	0.965	1.443	1.441	1.432	1.115	1.079	1.370	1.171	1.072
uc.97+A	19	1.206	1.132	1.322	1.272	1.397	1.329	1.095	1.019	0.962	1.254	1.152
uc.234+A	19	1.368	0.915	0.980	1.028	0.975	0.933	0.962	1.585	1.752	0.962	0.941
uc.422+	19	1.277	1.044	0.998	1.256	1.246	1.136	1.329	1.219	1.072	1.223	1.138
uc.317+	19	1.104	1.137	0.969	1.003	1.042	1.084	0.961	1.056	0.998	0.971	1.002
uc.206+	19	0.995	0.980	0.917	0.904	0.963	0.998	0.905	1.236	1.445	1.005	1.012
uc.411+A	19	1.090	1.047	1.051	0.978	1.022	1.055	1.015	2.136	3.238	1.017	1.053
uc.400+A	19	2.185	1.196	1.275	1.658	1.711	2.121	1.453	1.580	1.511	1.284	1.121
uc.192+	19	0.989	1.093	1.300	2.037	1.554	1.080	1.637	3.054	1.183	1.279	1.537
uc.343+A	19	1.016	0.917	0.972	0.957	0.950	1.025	0.931	0.926	0.980	0.954	0.971
uc.196+A	19	1.193	0.914	0.973	1.052	1.021	0.976	1.056	1.879	2.715	1.116	0.952
uc.346+A	19	3.839	3.284	9.153	3.219	2.985	3.118	4.932	9.129	6.721	4.381	4.538
uc.427+	19	2.355	1.715	1.571	1.736	2.196	2.566	1.639	1.612	1.717	2.050	2.073
uc.50+A	19	1.203	1.019	0.930	1.177	1.244	1.233	1.155	0.933	0.903	1.086	1.144
uc.73+	19	1.315	1.211	1.311	1.645	1.222	1.129	1.351	1.277	1.055	1.235	1.378
uc.321+A	19	0.931	0.964	1.022	0.967	0.955	1.027	1.018	0.997	1.055	0.988	0.969
uc.238+	19	1.203	1.156	1.161	1.073	1.140	1.219	0.967	0.936	0.945	1.028	1.129
uc.310+	19	1.174	1.094	1.114	0.942	0.981	1.233	1.105	1.624	1.804	1.155	1.098
uc.133+A	19	1.337	1.249	1.082	1.058	1.229	1.466	1.127	1.170	1.246	1.130	1.067
uc.456+	19	2.252	1.301	2.051	1.765	1.675	1.450	1.841	2.841	3.798	1.405	2.004
uc.338+A	19	1.790	0.953	1.033	1.213	1.226	1.691	1.624	1.547	1.592	1.093	1.135
uc.128+	19	0.949	0.931	1.091	1.042	0.927	1.011	0.953	1.299	1.779	0.997	1.099
uc.345+	19	1.027	1.068	0.982	0.966	0.948	0.933	0.949	1.364	1.449	0.961	1.124
uc.248+A	19	1.584	1.363	1.632	1.230	1.619	1.677	1.633	1.224	1.096	1.642	1.646
uc.347+	19	1.030	0.983	1.015	1.035	0.979	0.973	0.952	1.056	0.988	0.983	0.999
uc.346+	19	14.384	8.615	17.507	9.276	8.670	9.897	8.334	12.290	14.745	11.466	14.697
uc.204+	19	2.516	2.101	2.231	4.205	2.075	2.326	1.941	3.723	2.478	2.266	2.894
uc.391+A	19	1.557	1.089	1.107	1.165	1.134	1.058	1.103	1.782	2.149	1.028	1.147
uc.457+	19	1.828	1.514	1.387	1.500	1.809	2.146	1.817	1.614	1.462	1.792	1.453
uc.310+A	19	1.538	1.743	1.365	1.486	1.572	1.707	1.415	1.511	1.434	1.317	1.769
uc.470+A	19	3.994	12.430	5.221	5.656	8.459	5.114	5.014	4.462	3.776	9.171	6.962
uc.417+A	19	0.957	0.944	1.005	1.024	1.036	0.985	1.304	1.024	1.008	1.148	1.085
uc.420+	19	4.071	2.130	2.760	3.404	3.448	3.500	2.183	2.516	2.319	2.730	2.514
uc.327+A	19	3.260	2.825	5.073	4.119	3.684	3.341	3.093	3.728	3.064	4.084	4.606
uc.349+	19	1.423	1.415	1.183	1.477	1.543	1.820	1.533	1.132	1.142	1.236	1.645
uc.223+A	19	1.184	1.152	1.189	1.018	1.119	1.209	1.194	1.290	1.256	1.139	1.035
uc.348+	19	1.268	1.508	2.097	1.549	1.581	1.457	1.637	1.263	1.147	1.793	2.074
uc.10+	19	1.728	1.100	1.213	1.613	1.798	1.268	1.467	2.209	2.307	1.546	1.372
uc.46+	19	1.021	0.991	0.905	1.300	0.986	0.989	0.986	1.032	1.017	0.935	0.935
uc.275+	19	2.528	1.184	1.218	0.963	1.088	1.114	1.134	2.609	3.100	1.048	1.031
uc.362+A	19	2.467	1.667	2.263	1.705	2.203	2.720	1.361	2.326	3.273	2.684	2.277
uc.131+	19	0.980	0.929	1.359	1.056	0.971	1.025	1.018	1.010	0.961	1.170	1.068
uc.309+A	19	3.136	2.360	2.831	3.819	2.886	1.682	1.664	1.630	1.526	2.104	3.169
uc.383+	19	3.180	3.775	3.916	3.286	2.910	3.993	2.962	3.493	2.326	3.368	3.568
uc.398+A	19	2.083	1.480	1.297	1.934	2.156	1.244	1.884	1.498	2.022	1.880	
uc.167+	19	14.211	12.406	15.961	20.443	13.270	8.197	8.118	8.518	5.069	11.896	12.398
uc.283+A	19	12.275	7.926	21.491	9.841	13.435	14.103	7.481	20.563	13.651	13.268	14.464
uc.21+A	19	0.906	0.934	0.970	1.027	1.129	1.085	0.994	0.931	0.943	0.930	1.010
uc.133+	19	1.000	0.946	1.039	0.924	0.903	0.983	0.912	1.500	2.325	0.978	0.983
uc.48+	19	2.323	1.253	1.663	1.783	1.526	1.487	1.654	3.224	2.800	2.097	1.562
uc.190+A	19	2.974	1.989	2.338	1.767	2.224	3.928	1.901	1.502	1.754	2.192	2.055
uc.134+	19	2.082	1.209	1.544	2.188	1.976	1.726	1.308	2.056	2.399	2.962	1.969
uc.47+	19	1.770	1.239	1.516	1.522	1.741	1.727	1.407	1.540	1.736	1.720	1.608
uc.10+A	19	1.354	0.985	1.313	1.120	1.154	1.345	1.360	1.193	1.269	1.048	1.266
uc.477+A	19	4.958	3.046	4.192	3.073	3.390	5.724	2.936	3.595	4.156	3.460	3.446
uc.278+	19	8.195	2.624	2.278	4.226	3.745	2.859	5.817	2.933	2.039	2.626	2.691
uc.350+	19	1.429	1.231	1.335	1.132	1.357	1.995	1.385	1.188	1.154	1.341	1.195
uc.118+A	19	1.375	1.149	1.215	1.426	1.165	1.155	1.183	1.118	0.966	1.001	1.028
uc.196+	19	1.120	1.293	1.191	1.391	1.081	1.373	1.143	1.037	0.942	1.113	1.115

Figure 15

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Sample	Number of tissues in which the UCR pass the filter	MNC 02	Ovary	Pancreatic	Placenta	Prostate	Skeletal muscle	Spleen	T-cell 01	T-cell 02	Testicule	Thymus
uc.75+	19	0.991	0.980	1.074	0.976	1.027	1.019	1.064	0.981	0.938	1.049	1.076
uc.297+A	19	1.059	0.900	1.068	1.002	1.037	1.075	1.078	1.031	1.026	0.956	0.975
uc.161+	19	1.643	1.181	1.105	1.315	1.369	1.043	1.164	1.376	1.500	1.072	1.108
uc.195+	19	1.131	1.207	1.238	1.213	1.294	1.677	1.136	0.971	0.972	1.390	1.260
uc.275+A	19	1.207	1.191	1.224	1.031	1.225	1.268	1.066	1.154	1.072	1.197	1.144
uc.469+A	19	1.479	1.401	2.019	1.083	1.646	2.033	1.426	1.043	1.169	1.211	1.608
uc.160+	19	3.202	2.081	1.227	2.193	2.190	1.463	1.268	0.983	0.828	2.669	4.124
uc.354+A	19	1.930	1.444	1.846	1.583	1.661	1.888	1.643	1.694	1.987	2.109	1.642
uc.43+	19	2.066	1.657	1.539	1.505	1.773	2.122	1.555	1.683	1.819	1.627	1.381
uc.78+	19	2.200	1.514	2.435	1.863	2.534	2.202	2.078	2.220	1.960	1.902	2.035
uc.182+A	19	1.214	1.050	1.210	0.977	1.074	1.232	1.167	1.259	1.063	1.078	1.093
uc.373+A	19	1.032	0.944	1.007	0.944	0.907	1.105	1.017	0.972	0.927	2.733	1.044
uc.44+	19	1.027	1.162	0.958	1.219	1.444	1.094	1.059	1.041	1.021	1.095	2.087
uc.77+	19	3.258	3.027	4.665	2.527	2.663	4.280	3.763	4.250	3.634	3.473	3.492
uc.13+A	19	0.945	0.905	0.996	1.075	0.980	1.020	0.912	0.974	0.975	0.970	1.028
uc.422+A	19	1.054	0.980	0.916	1.048	1.011	0.996	1.065	1.297	1.683	1.117	1.064
uc.382+	19	1.541	1.646	1.417	1.281	1.269	1.510	1.668	1.155	1.542	1.032	1.301
uc.162+	19	0.933	1.010	0.927	0.977	1.400	0.988	0.912	0.989	1.474	0.999	1.043
uc.117+A	19	3.880	2.349	2.690	2.466	2.657	1.950	2.986	3.953	3.201	2.574	3.184
uc.186+	19	0.920	0.996	1.045	1.024	1.098	1.281	1.047	0.925	1.096	1.040	1.008
uc.48+A	19	5.022	3.304	4.970	3.896	3.803	3.872	2.982	4.174	2.806	3.324	3.036
uc.151+	19	1.466	0.936	1.050	0.969	1.004	0.977	1.023	1.619	2.811	1.078	1.012
uc.295+	19	0.959	0.990	0.960	0.989	0.963	1.054	0.928	0.960	0.960	0.936	0.943
uc.106+A	19	1.679	1.099	1.224	1.027	1.146	1.512	1.098	1.130	1.286	1.133	1.207
uc.63+	19	1.855	1.302	1.504	1.768	1.705	1.682	1.425	2.403	3.762	2.247	1.722
uc.389+A	19	0.998	1.069	0.977	0.973	0.974	0.923	0.946	0.996	1.110	0.927	0.996
uc.285+A	19	1.638	1.115	1.135	1.202	1.397	1.249	1.363	1.514	1.596	1.311	1.164
uc.185+	19	1.239	1.039	1.013	1.494	1.150	1.230	1.098	0.995	1.030	1.036	1.047
uc.181+A	19	2.200	1.763	1.405	1.921	2.034	2.171	1.921	2.273	1.911	2.041	1.867
uc.207+A	19	1.102	1.010	1.039	0.997	1.028	1.113	1.080	0.972	1.006	1.815	0.961
uc.443+A	19	1.021	1.080	1.022	1.033	1.006	1.048	1.000	0.960	1.014	1.013	1.024
uc.371+	19	1.015	1.059	1.048	1.014	1.010	1.109	1.010	1.019	0.927	0.985	1.133
uc.153+	19	3.037	1.269	1.490	1.115	1.403	1.305	1.354	3.277	5.077	1.375	1.223
uc.170+A	19	1.401	1.083	1.100	1.030	1.036	1.020	1.003	2.358	3.051	1.061	0.944
uc.128+A	19	3.363	3.299	4.714	3.077	2.852	2.985	4.776	3.126	3.017	3.746	4.194
uc.468+A	19	1.594	1.072	1.090	0.980	1.003	1.114	1.032	3.034	4.007	1.145	1.084
uc.189+	19	4.013	1.808	2.051	3.346	3.133	1.966	2.006	1.750	1.845	3.053	2.489
uc.188+	19	1.145	1.005	1.055	1.131	1.301	1.172	1.100	1.008	1.502	1.139	1.338
uc.95+	19	3.364	2.629	2.615	2.447	2.853	2.602	2.272	2.599	2.439	2.591	2.441
uc.309+	19	1.579	1.136	0.956	1.071	1.097	1.042	0.997	1.720	1.952	1.015	1.081
uc.277+A	19	1.061	0.998	1.083	1.060	1.019	1.135	1.152	1.048	1.135	1.085	1.108
uc.96+	19	1.828	1.441	1.378	1.467	1.491	1.701	1.600	1.111	1.046	1.107	1.481
uc.241+A	19	1.621	1.300	1.024	1.239	1.422	1.318	1.221	1.163	0.961	1.237	1.121
uc.266+A	19	3.149	2.815	2.324	2.966	2.806	4.445	2.868	2.339	2.209	2.813	2.237
uc.334+A	19	0.987	0.938	0.959	1.056	1.070	1.134	1.050	0.961	0.946	1.193	1.077
uc.92+	19	1.101	1.027	1.018	1.104	1.039	1.029	1.018	1.251	1.533	1.031	1.032
uc.288+A	19	1.124	1.104	1.107	1.160	1.082	1.240	1.115	1.054	0.990	1.053	1.119
uc.151+A	19	1.207	1.257	1.353	1.331	1.135	1.431	1.313	1.119	1.235	1.217	1.169
uc.183+	19	1.383	1.272	1.257	1.171	1.439	1.326	1.219	1.252	1.484	1.104	1.082
uc.378+A	19	5.523	1.773	4.463	4.456	4.337	7.869	3.038	2.945	2.509	4.554	4.272
uc.291+	19	1.026	0.980	0.957	0.937	0.978	1.078	0.961	0.978	0.996	0.936	0.949
uc.31+	19	1.277	1.479	2.385	1.834	1.457	1.650	1.781	2.337	1.397	1.781	1.716
uc.263+A	19	2.181	1.881	2.161	1.775	2.074	2.542	2.019	1.138	1.335	1.960	2.544
uc.299+A	19	5.265	3.433	4.842	3.324	4.320	4.771	2.672	3.178	2.495	3.548	3.557
uc.181+	19	0.976	0.971	1.116	0.979	0.939	1.004	1.023	1.220	1.049	1.006	1.013
uc.345+A	19	1.069	1.050	1.104	1.165	1.031	1.188	1.089	1.053	0.962	1.137	1.163
uc.331+A	19	2.045	1.406	1.684	1.869	1.973	1.816	1.722	2.684	3.311	1.988	1.951
uc.252+A	19	1.144	1.025	1.069	1.385	1.440	1.486	1.221	1.093	0.958	1.245	1.260
uc.182+	19	1.960	1.101	1.349	1.609	1.468	1.763	1.417	4.179	4.780	2.611	1.483
uc.378+	19	3.180	1.597	1.769	1.789	1.936	1.760	1.859	2.986	2.997	2.015	1.510
uc.462+A	19	5.458	3.300	3.913	3.389	3.795	6.992	3.464	3.737	3.600	3.503	3.287
uc.233+	19	1.035	1.015	1.134	1.088	1.290	2.514	0.918	1.026	0.987	1.090	1.371
uc.158+A	19	1.522	1.146	1.115	1.407	1.276	1.486	1.330	1.130	0.996	1.295	1.184
uc.234+	19	2.571	1.488	3.977	1.880	1.683	1.741	1.615	1.458	1.566	1.774	1.437
uc.215+A	19	1.060	1.051	0.946	1.073	1.070	1.164	1.030	1.009	0.982	1.084	0.982
uc.268+	19	2.080	1.571	2.574	0.948	1.650	2.615	1.696	1.955	1.763	1.436	1.265
uc.20+A	19	2.386	1.065	1.400	1.037	1.174	1.081	1.059	2.298	2.742	1.052	1.079
uc.342+	19	1.020	1.128	1.249	0.975	0.933	1.397	1.025	0.988	0.983	1.101	1.046
uc.450+	19	1.319	1.142	1.164	1.080	1.091	1.194	1.093	1.312	1.174	1.164	1.181
uc.453+	19	1.705	1.059	1.045	1.141	1.418	1.173	1.240	1.744	1.925	1.323	1.205
uc.237+A	19	1.124	1.000	0.964	1.055	1.233	1.061	1.030	1.037	1.021	1.308	1.091

Figure 15

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Sample	Number of tissues in which the UCR pass the filter	MNC 02	Ovary	Pancreatic	Placenta	Prostate	Skeletal muscle	Spleen	T-cell 01	T-cell 02	Testicule	Thymus
uc.452+	19	1.205	1.171	0.996	1.117	1.024	1.403	1.155	1.176	1.325	0.998	1.142
uc.41+	19	1.269	1.278	1.133	1.142	1.110	1.227	1.143	1.282	0.918	1.144	1.131
uc.200+	19	3.237	2.051	2.652	2.664	2.513	3.066	2.578	2.629	3.037	2.429	2.267
uc.305+A	19	1.776	1.513	1.263	1.611	1.562	1.830	1.344	1.280	1.442	1.090	1.167
uc.343+	19	1.006	0.977	0.939	1.191	1.013	1.016	0.938	1.010	0.982	0.968	0.980
uc.383+A	19	1.190	1.027	1.025	1.031	1.118	1.098	1.010	0.974	1.254	1.053	1.000
uc.122+A	19	1.073	1.037	1.038	1.119	1.054	1.150	0.957	1.158	1.096	0.955	0.957
uc.473+A	19	4.289	3.154	4.532	3.629	4.163	5.880	2.983	4.842	6.286	4.375	3.911
uc.229+A	19	1.733	1.267	2.003	1.209	1.559	1.938	1.444	1.294	1.293	1.822	1.667
uc.372+	19	1.293	1.046	1.070	1.225	1.222	1.414	1.153	1.143	1.337	1.097	1.011
uc.465+A	19	5.119	5.262	6.826	5.094	5.482	8.347	4.420	5.633	5.290	5.650	5.375
uc.282+A	19	10.295	9.517	27.695	9.776	9.015	11.141	9.206	18.238	12.357	13.227	14.084
uc.476+A	19	2.673	1.803	1.653	1.715	1.968	2.481	1.690	2.319	2.136	1.764	1.133
uc.299+	19	3.453	2.601	3.325	2.724	2.860	2.347	2.904	3.309	3.461	3.295	3.264
uc.192+A	19	1.562	1.095	1.128	1.342	1.402	1.828	1.286	1.086	0.988	1.050	1.214
uc.33+	19	1.920	1.677	2.069	1.712	1.925	2.290	1.691	1.517	1.652	1.829	1.789
uc.34+	19	1.236	0.919	1.000	0.998	0.964	0.957	1.066	1.340	1.707	1.020	0.950
uc.34+A	19	1.398	1.371	1.403	1.142	1.323	1.565	1.378	1.387	0.958	1.274	1.380
uc.158+	19	1.041	0.982	1.211	1.242	1.263	1.087	1.505	1.226	1.594	1.142	1.275
uc.440+A	19	0.979	1.072	1.019	0.963	0.970	0.972	0.940	0.995	1.088	1.033	1.037
uc.37+	19	1.124	0.998	1.153	1.045	1.096	1.178	1.418	1.114	1.040	1.129	1.064
uc.42+A	19	1.175	1.138	0.957	0.997	0.967	1.312	1.058	0.941	0.950	1.007	1.015
uc.340+	19	2.155	1.573	1.832	1.584	1.351	1.886	1.681	1.904	1.545	1.372	1.319
uc.319+A	19	1.030	1.065	1.603	1.607	1.036	1.067	1.956	1.088	1.062	1.061	1.068
uc.483+	19	1.117	1.650	1.819	1.183	1.118	1.334	1.192	1.043	1.197	1.258	1.204
uc.263+	19	2.064	1.143	0.998	1.277	1.047	1.041	1.024	2.311	3.298	1.340	1.099
uc.204+A	19	2.285	1.738	2.294	1.950	2.118	2.572	2.071	3.113	2.006	2.024	1.938
uc.230+	19	2.597	5.286	3.133	3.363	6.241	2.259	5.755	2.292	1.506	4.436	4.043
uc.292+A	19	1.053	1.053	1.371	1.041	1.061	1.451	1.096	1.070	0.956	1.069	1.027
uc.220+	19	1.103	1.171	1.121	0.925	1.041	1.234	1.058	0.953	0.898	1.127	1.125
uc.473+	19	2.203	1.555	1.492	1.419	1.600	2.132	1.953	2.605	3.274	1.514	1.224
uc.329+A	19	1.618	1.280	1.310	1.562	1.354	1.671	1.238	1.178	1.490	1.162	1.157
uc.203+A	19	1.015	0.929	0.997	1.001	0.995	1.034	0.987	1.015	1.029	0.950	1.016
uc.472+	19	1.156	1.416	1.290	1.171	1.118	1.055	1.146	1.240	1.252	1.048	1.302
uc.475+A	19	2.841	1.689	1.374	1.610	2.241	1.820	2.191	3.056	3.024	1.858	1.967
uc.146+	19	0.959	1.038	1.212	1.169	1.231	1.598	1.091	0.962	0.967	1.221	1.181
uc.27+	19	0.986	1.031	1.116	1.050	1.046	1.060	1.079	0.966	0.890	0.941	0.974
uc.111+	19	1.140	1.198	0.972	1.530	1.327	1.218	1.104	1.020	1.108	1.081	0.996
uc.382+A	19	1.477	1.048	1.089	1.290	1.471	1.582	1.044	1.802	2.002	1.711	1.256
uc.331+	19	1.687	1.785	1.833	3.173	1.799	2.205	2.049	1.590	1.550	1.688	1.701
uc.450+A	19	1.132	1.072	0.959	0.920	1.064	1.138	1.048	1.222	1.658	1.031	0.989
uc.476+	19	1.245	1.017	1.051	1.591	1.366	1.055	1.145	1.109	1.305	1.081	1.110
uc.29+	19	0.946	0.913	0.972	0.962	1.298	0.965	1.020	0.947	0.927	1.007	0.960
uc.28+	19	1.520	1.134	1.415	1.284	1.652	1.620	1.272	1.075	1.019	1.284	1.291
uc.330+	19	1.467	1.335	1.273	2.086	1.424	1.382	1.174	1.022	1.040	1.210	1.274
uc.281+A	19	4.443	2.837	2.459	4.318	3.177	4.804	3.487	2.566	1.917	2.146	2.006
uc.77+A	19	1.505	0.999	1.073	0.989	1.031	1.106	0.992	1.819	1.703	1.117	1.091
uc.475+	19	6.941	4.399	5.240	4.769	4.529	5.520	4.472	4.177	3.240	4.767	4.995
uc.396+	19	1.044	1.090	1.089	1.902	1.358	1.136	2.054	1.065	0.939	1.313	1.136
uc.374+A	19	0.914	0.962	1.024	1.339	0.981	1.178	0.986	0.982	0.948	1.035	1.029
uc.206+A	19	1.270	1.027	1.254	1.280	1.315	1.429	1.291	1.767	2.710	1.344	1.478
uc.22+A	19	1.363	1.223	1.130	1.294	1.267	1.261	1.521	1.489	1.343	1.177	1.130
uc.180+A	19	1.058	0.952	1.039	0.979	1.103	1.040	1.021	1.028	1.204	1.006	1.030
uc.250+	19	1.003	1.024	1.061	1.000	0.945	1.206	0.961	1.032	1.038	0.997	1.058
uc.363+A	19	1.216	1.120	1.243	0.964	0.949	1.181	1.086	1.164	1.459	1.080	1.114
uc.20+	19	2.909	1.922	1.997	1.480	1.866	2.212	1.841	1.552	1.872	1.825	2.113
uc.138+A	19	1.342	1.236	0.949	0.952	0.960	0.933	0.923	1.050	1.245	0.957	1.002
uc.142+	19	1.384	0.900	1.070	1.096	0.990	0.963	1.063	1.991	1.599	1.079	1.143
uc.228+A	19	1.016	0.979	1.200	0.965	0.967	0.991	1.094	1.116	1.052	0.998	1.026
uc.398+	19	20.839	10.397	23.531	12.466	12.512	9.475	12.736	17.514	9.002	12.372	14.021
uc.464+A	19	1.547	1.400	1.476	1.798	1.483	1.485	1.678	1.284	1.721	1.421	1.378
uc.149+	19	1.021	1.049	1.073	0.984	0.941	0.972	0.951	0.964	0.975	0.970	0.984
uc.44+A	19	4.564	2.233	2.843	3.383	2.869	2.917	2.832	2.732	2.679	2.841	2.480
uc.217+A	19	2.783	1.954	1.913	2.019	2.390	2.111	2.083	2.261	2.903	2.271	2.531
uc.453+A	19	4.134	3.752	3.131	4.288	2.832	4.706	2.407	3.423	3.236	2.486	2.352
uc.295+A	19	1.071	0.963	1.105	0.985	1.004	1.088	1.029	0.961	1.071	1.068	0.950
uc.145+	19	1.361	1.031	0.988	0.998	1.121	0.944	1.051	1.235	1.273	1.069	0.998
uc.33+A	19	2.344	1.132	1.226	1.048	1.368	1.025	1.201	2.062	3.061	1.185	1.223
uc.144+	19	0.955	0.961	0.927	1.330	1.197	1.055	0.968	0.944	1.001	1.027	1.106
uc.447+	19	1.247	0.974	1.031	1.529	1.301	1.273	1.195	1.088	1.083	1.435	1.102
uc.338+	19	4.241	3.146	2.195	4.692	3.857	3.410	2.586	2.726	2.793	4.111	3.565

Figure 15

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Sample	Number of tissues in which the UCR pass the filter	MNC 02	Ovary	Pancreatic	Placenta	Prostate	Skeletal muscle	Spleen	T-cell 01	T-cell 02	Testicule	Thymus
uc.269+A	19	6.573	2.898	3.533	2.003	3.120	2.069	6.861	2.945	1.834	2.903	3.003
uc.301+A	19	1.029	0.956	1.072	0.919	0.968	1.028	1.004	0.964	1.036	0.941	0.933
uc.339+	19	12.665	7.763	11.640	13.797	17.123	11.131	15.008	16.259	11.467	12.505	10.631
uc.5+	19	1.169	1.079	1.147	1.118	1.046	1.067	1.273	2.066	2.996	1.252	1.248
uc.445+	19	1.647	1.286	1.244	1.118	1.470	1.153	1.592	1.910	2.764	1.466	1.397
uc.132+A	19	1.145	1.003	0.978	0.974	1.077	1.196	1.015	1.025	0.907	1.033	1.081
uc.411+	19	1.381	1.375	1.725	1.564	1.696	2.004	1.790	1.358	1.251	1.823	1.303
uc.446+	19	1.306	1.150	1.079	1.126	1.177	1.240	1.295	1.136	1.025	1.356	1.137
uc.312+A	19	0.890	1.181	0.992	0.985	1.062	1.142	1.047	0.980	0.946	0.957	1.051
uc.413+	19	1.073	0.904	1.040	0.954	0.971	1.023	1.003	1.000	0.987	0.937	0.949
uc.359+A	19	1.008	0.959	1.567	1.617	1.440	1.057	1.054	0.961	1.139	1.048	1.043
uc.402+A	19	1.017	0.971	0.949	0.957	0.966	0.964	0.971	1.802	2.720	1.010	0.995
uc.91+	19	1.168	0.971	0.951	1.145	1.086	1.008	1.054	1.126	1.416	1.303	1.055
uc.412+	19	2.008	1.494	1.581	1.653	1.457	1.459	1.781	2.691	3.006	1.651	1.924
uc.448+	19	2.279	1.275	1.233	1.202	1.387	1.280	1.222	2.586	2.891	1.221	1.281
uc.9+A	19	1.059	1.025	1.086	1.061	0.984	1.253	1.011	0.905	0.951	0.936	1.049
uc.305+	19	1.951	1.062	1.038	1.270	1.317	1.153	1.203	1.939	3.336	1.123	1.246
uc.233+A	19	2.397	1.283	1.263	1.125	1.321	1.297	1.283	1.866	2.504	1.272	1.252
uc.304+A	19	0.965	0.944	0.901	1.029	1.056	1.207	1.007	0.935	0.963	0.963	1.007
uc.369+	19	3.072	2.308	3.662	2.792	2.864	2.664	2.784	3.419	2.485	2.211	2.496
uc.88+A	19	4.283	2.710	2.877	3.448	2.575	3.959	2.770	3.500	4.043	2.716	2.154
uc.2+	19	0.978	0.993	1.006	1.188	1.048	1.071	1.031	0.997	0.920	0.952	0.938
uc.110+A	19	4.142	2.701	3.240	3.795	2.845	2.222	2.861	2.311	1.831	3.107	3.625
uc.461+A	19	1.153	1.132	1.009	1.041	1.039	1.337	1.130	1.212	1.744	1.052	1.256
uc.419+A	19	1.809	1.175	1.092	1.920	1.914	1.113	1.081	1.016	0.943	1.354	1.386
uc.440+	19	1.015	0.925	0.940	0.979	0.957	0.995	1.012	1.010	0.978	0.913	1.030
uc.478+	19	2.399	1.508	1.885	2.880	1.931	1.062	1.346	4.275	1.996	1.614	1.926
uc.1+	19	1.888	2.443	3.644	3.343	3.860	3.191	3.457	3.139	2.046	4.080	2.857
uc.4+	19	1.161	1.080	1.161	1.061	1.144	1.396	1.139	1.217	1.427	1.336	1.350
uc.335+	19	1.517	1.019	1.014	1.637	1.117	1.427	1.237	1.031	0.968	1.102	1.106
uc.483+A	19	2.476	2.419	3.509	1.857	2.114	2.707	2.062	1.871	1.904	2.341	2.587
uc.8+	19	5.871	3.210	6.693	17.981	8.321	7.728	10.597	4.058	2.772	12.067	10.934
uc.63+A	19	1.444	1.193	1.102	1.509	1.389	1.535	1.445	1.572	1.914	1.054	1.050
uc.443+	19	1.024	0.918	1.067	0.954	1.038	1.078	1.031	1.191	1.272	1.004	0.986
uc.117+	19	6.207	3.642	4.607	4.206	4.847	6.134	3.149	4.091	3.576	3.145	3.286
uc.477+	19	1.959	1.134	1.032	1.116	1.050	1.073	1.162	2.319	2.875	1.274	1.049
uc.200+A	19	1.847	1.225	1.191	1.580	1.648	1.142	1.477	2.421	2.638	1.454	1.441
uc.3+	19	1.155	1.396	1.150	1.146	1.185	1.312	1.106	1.062	1.106	1.274	1.239
uc.322+	19	0.939	0.976	0.990	0.944	0.928	0.949	0.943	0.955	1.088	0.999	0.989
uc.213+	19	5.487	4.939	5.080	7.083	3.284	3.856	5.529	5.675	5.520	6.395	7.742
uc.249+	19	1.478	1.919	1.688	1.701	2.103	1.535	1.996	2.016	1.562	2.004	2.139
uc.303+A	19	1.422	1.245	1.347	1.144	1.147	1.120	1.129	0.996	1.038	1.102	1.049
uc.323+	19	0.986	1.150	1.108	0.994	0.999	1.041	0.958	1.009	0.960	0.930	1.023
uc.248+	19	1.509	1.053	1.007	0.924	0.939	0.984	0.987	1.700	1.963	0.945	0.954
uc.465+	19	1.102	0.955	0.982	1.047	1.045	1.006	1.090	1.307	1.492	1.128	1.049
uc.139+	19	5.473	1.949	1.576	2.984	2.659	2.715	2.813	1.848	1.336	1.628	2.006
uc.214+	19	1.394	1.509	1.623	1.472	1.279	1.345	1.228	1.164	1.074	1.214	1.447
uc.145+A	19	7.250	5.579	5.641	15.993	4.461	4.560	7.540	3.766	2.756	10.465	9.467
uc.325+A	19	1.002	0.967	1.291	0.920	1.004	1.193	1.012	0.964	1.148	1.182	1.040
uc.217+	19	2.930	1.575	1.524	2.214	1.190	1.626	2.009	4.305	4.295	2.191	1.919
uc.325+	19	7.184	9.000	12.195	7.353	7.289	5.588	5.881	7.133	6.944	7.447	10.892
uc.435+	19	1.298	1.129	1.620	1.112	1.200	1.554	1.301	1.323	1.662	1.281	1.280
uc.326+	19	2.679	1.756	1.413	1.755	1.881	2.695	2.346	1.719	1.309	1.621	1.462
uc.106+	19	3.375	1.013	1.341	0.987	1.025	1.177	0.998	4.189	6.963	1.208	1.157
uc.468+	19	1.599	1.560	1.409	1.097	1.283	1.325	1.292	1.448	1.253	1.553	1.361
uc.213+A	19	2.222	1.834	2.054	1.982	1.928	2.327	1.911	1.618	1.613	2.136	2.295
uc.62+A	19	0.982	0.922	1.051	1.005	0.995	1.143	1.014	1.017	1.007	1.012	0.937
uc.246+A	19	1.481	1.115	1.391	1.220	1.205	1.095	1.287	2.474	2.031	1.346	1.366
uc.43+A	19	1.499	1.045	1.081	1.025	1.053	1.048	1.043	1.071	1.790	1.039	0.931
uc.389+	19	1.447	1.067	1.796	1.210	1.150	1.419	1.185	2.047	1.024	1.200	1.256
uc.159+A	19	3.358	2.353	2.208	3.616	2.644	2.957	2.511	2.209	2.211	2.632	2.688
uc.100+	19	1.101	1.373	1.623	1.276	1.259	1.312	1.584	1.486	1.069	1.424	1.795
uc.462+	19	2.063	1.385	1.507	1.613	1.745	1.397	1.821	2.569	2.365	1.640	1.788
uc.352+	19	4.345	2.225	3.942	2.334	2.486	3.094	1.860	5.051	3.683	2.394	3.026
uc.388+	19	2.326	1.321	1.296	1.204	1.405	1.256	1.459	3.942	5.143	1.554	1.373
uc.125+A	19	1.484	1.068	1.101	1.020	1.045	1.018	0.990	0.988	1.270	1.050	1.122
uc.136+	19	2.027	1.037	1.573	1.609	1.550	2.018	1.905	2.804	2.828	1.675	1.799
uc.244+	19	1.177	1.056	0.988	0.925	1.074	1.137	1.256	1.029	0.929	0.932	1.033
uc.138+	19	0.925	1.013	0.974	0.982	1.046	1.187	0.968	0.969	1.138	0.959	1.126
uc.291+A	19	0.908	1.176	1.377	1.263	2.262	1.140	1.507	1.055	1.103	2.199	1.743
uc.249+A	19	1.447	1.142	1.286	1.083	1.172	1.050	1.162	2.314	2.122	1.132	1.186

Figure 15

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Sample	Number of tissues in which the UCR pass the filter	MNC 02	Ovary	Pancreatic	Placenta	Prostate	Skeletal muscle	Spleen	T-cell 01	T-cell 02	Testicule	Thymus
uc.469+	19	1.166	0.907	0.989	0.936	0.926	0.935	0.963	1.244	1.458	0.988	0.929
uc.18+	19	3.390	3.614	4.712	2.379	2.944	3.843	3.323	3.911	3.271	5.127	5.072
uc.245+	19	0.966	1.132	1.114	0.986	1.374	1.111	1.053	1.059	1.091	0.980	0.957
uc.280+A	19	1.126	1.096	0.997	1.120	1.121	1.154	1.140	1.288	1.469	1.130	0.991
uc.14+	19	1.102	1.133	1.102	1.325	1.162	1.283	1.221	1.032	0.942	1.147	1.027
uc.134+A	19	2.530	1.679	1.470	2.176	2.492	1.965	3.870	2.203	2.548	2.426	2.572
uc.246+	19	3.279	3.477	3.665	4.015	2.975	5.144	2.441	3.318	2.669	2.711	2.959
uc.16+	19	1.697	1.430	1.296	1.133	1.270	1.425	1.439	1.347	1.623	1.274	1.208
uc.391+	19	1.156	1.032	1.322	1.377	1.216	1.183	1.174	1.077	0.938	1.142	1.141
uc.262+A	19	5.156	3.671	2.332	2.388	2.827	3.992	3.690	2.254	1.668	2.634	2.310
uc.456+A	19	3.191	2.290	2.816	2.374	2.219	4.331	2.206	2.124	2.338	2.345	2.119
uc.53+	19	1.129	1.363	1.178	1.131	1.139	1.077	1.125	1.106	0.971	1.171	1.161
uc.89+	19	1.172	1.057	1.062	1.116	1.137	1.194	1.077	1.177	1.579	1.115	1.127
uc.390+	19	1.556	1.155	1.262	1.265	1.204	1.496	1.604	1.347	1.137	1.262	1.235
uc.183+A	19	1.878	1.509	1.189	1.762	1.117	2.269	1.367	2.675	2.909	1.212	1.263
uc.377+A	19	1.337	1.144	1.059	1.383	1.414	1.109	1.143	1.240	1.463	1.134	1.099
uc.388+A	19	1.853	1.181	1.582	1.202	1.469	1.452	1.197	1.590	1.781	1.473	1.391
uc.173+	19	1.171	0.943	1.036	0.919	0.909	0.971	0.959	1.794	2.257	0.985	0.993
uc.478+A	19	5.702	5.041	7.227	3.697	4.289	6.193	4.162	5.264	3.696	4.023	3.658
uc.47+A	19	1.787	1.355	1.147	1.338	1.295	1.149	1.109	1.944	2.304	0.982	1.100
uc.393+	19	1.159	1.002	1.233	1.141	1.041	1.079	1.158	0.955	0.928	1.138	1.128
uc.315+A	19	1.168	0.962	0.982	1.194	1.039	1.141	1.018	0.996	1.027	1.048	1.077
uc.177+	19	2.075	1.574	2.310	1.484	1.459	1.453	1.832	2.510	2.125	1.988	1.927
uc.392+	19	1.048	0.978	0.922	0.951	0.955	0.938	1.020	1.435	3.546	1.037	0.989
uc.341+A	19	0.965	0.956	1.139	0.996	0.960	1.065	0.978	1.502	1.152	1.041	0.983
uc.88+	19	2.495	1.782	1.825	1.803	2.100	2.176	1.817	3.178	4.193	2.068	2.042
uc.285+	19	3.559	1.753	2.019	2.296	2.232	2.191	1.954	2.129	2.927	2.162	2.171
uc.420+A	19	1.610	1.144	1.103	0.970	1.042	1.023	1.140	1.999	2.100	1.250	1.025
uc.164+A	19	1.248	1.111	0.979	1.344	1.127	1.252	1.039	0.998	0.984	1.005	1.112
uc.300+A	19	11.305	6.271	10.132	8.368	5.453	7.133	6.574	10.090	7.640	4.684	5.212
uc.153+A	19	2.353	1.594	2.235	1.284	1.811	2.085	1.585	1.552	1.985	1.960	1.651
uc.448+A	19	3.772	2.983	4.117	2.371	3.175	4.683	2.819	4.244	4.399	3.509	2.721
uc.17+A	19	1.243	1.118	1.237	1.154	1.637	1.139	0.997	0.923	0.887	1.025	1.491
uc.436+	19	1.117	1.114	1.188	1.159	1.008	1.045	1.217	1.102	0.984	1.110	1.103
uc.142+A	19	4.748	2.818	4.135	2.708	2.427	3.569	2.338	4.830	3.344	2.433	2.828
uc.73+A	19	4.743	2.904	4.313	3.258	3.532	3.692	2.955	2.572	2.781	3.182	2.997
uc.404+	19	1.022	1.012	0.992	0.989	1.024	1.096	0.951	0.963	1.014	0.998	0.997
uc.84+A	19	3.780	4.511	8.488	5.964	4.908	3.053	4.186	5.387	2.647	4.585	4.175
uc.280+	19	1.355	1.067	1.678	1.874	1.293	1.204	1.049	1.135	1.403	1.146	1.211
uc.172+A	19	6.390	7.669	18.509	8.125	6.448	9.018	7.936	6.680	4.294	8.306	7.686
uc.287+A	19	3.526	2.591	2.773	2.302	2.976	4.956	2.617	2.152	2.201	2.832	3.052
uc.54+	19	0.966	0.952	1.040	1.006	1.028	1.069	1.083	1.271	0.900	0.998	0.995
uc.445+A	19	1.844	1.264	1.607	1.490	1.567	2.044	1.196	1.317	2.009	1.283	1.487
uc.407+	19	1.749	1.246	1.195	1.308	1.406	1.441	1.200	1.120	1.119	1.121	1.124
uc.412+A	19	2.949	1.942	1.868	2.179	2.402	3.570	2.145	1.987	1.911	2.426	2.074
uc.347+A	19	1.326	1.317	1.559	1.057	1.081	1.524	1.248	1.422	1.183	1.167	1.166
uc.87+	19	1.119	1.070	1.116	1.428	1.164	1.250	1.182	1.046	0.940	1.264	1.089
uc.170+	19	2.879	1.322	2.229	2.103	2.783	2.699	1.959	4.648	5.083	2.809	3.014
uc.161+A	19	3.148	1.741	1.161	2.979	2.830	4.067	1.895	1.787	1.988	2.126	2.196

Figure 15

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Supplementary table 2. T-UCRs differentially expressed (ANOVA at p<0.005) among each cancer type with the corresponding normal tissues.

Comparison	Probe	P-value	Expression Tumor/Normal	Significance	UCR name	UCR type
CLL vs CD5+	uc.289+	0.00097	0.22	down in tumors	uc.289	N
CLL vs CD5+	uc.285+	0.00021	0.39	down in tumors	uc.285	E
CLL vs CD5+	uc.73+A	1.36E-07	0.58	down in tumors	uc.73	P
CLL vs CD5+	uc.291+	1.12E-06	0.58	down in tumors	uc.291	P
CLL vs CD5+	uc.231+	0.000106	0.58	down in tumors	uc.231	N
CLL vs CD5+	uc.233+	4.42E-05	0.68	down in tumors	uc.233	E
CLL vs CD5+	uc.435+	0.00426	0.69	down in tumors	uc.435	N
CLL vs CD5+	uc.183+	0.00481	0.81	down in tumors	uc.183	E
CLL vs CD5+	uc.135+	8.91E-06	0.85	down in tumors	uc.135	E
CLL vs CD5+	uc.349+A	0.000699	0.88	down in tumors	uc.349	P
CLL vs CD5+	uc.316+	0.00166	0.92	down in tumors	uc.316	N
CLL vs CD5+	uc.122+	0.000553	1.15	up in tumors	uc.122	N
CLL vs CD5+	uc.422+A	8.46E-05	1.20	up in tumors	uc.422	P
CLL vs CD5+	uc.144+	0.000352	1.21	up in tumors	uc.144	E
CLL vs CD5+	uc.377+A	0.000352	1.21	up in tumors	uc.377	E
CLL vs CD5+	uc.262+	0.000847	1.48	up in tumors	uc.262	N
CLL vs CD5+	uc.352+	0.000537	1.61	up in tumors	uc.352	N
CLL vs CD5+	uc.192+	0.000106	2.34	up in tumors	uc.192	N
CLL vs CD5+	uc.160+	0.000115	2.48	up in tumors	uc.160	N
Comparison	Probe	P-value	Tumor/Normal	Tumor/Normal	UCR name	UCR type
CRC vs colon mucosa	uc.43+	0.00342	0.84	down in tumors	uc.43	N
CRC vs colon mucosa	uc.3+	0.00429	0.94	down in tumors	uc.3	P
CRC vs colon mucosa	uc.204+A	0.00353	1.07	up in tumors	uc.204	N
CRC vs colon mucosa	uc.305+A	0.00341	1.08	up in tumors	uc.305	P
CRC vs colon mucosa	uc.9+	0.0044	1.08	up in tumors	uc.9	N
CRC vs colon mucosa	uc.340+A	0.00121	1.09	up in tumors	uc.340	N
CRC vs colon mucosa	uc.198+A	0.000842	1.09	up in tumors	uc.198	N
CRC vs colon mucosa	uc.330+	0.000934	1.09	up in tumors	uc.330	E
CRC vs colon mucosa	uc.249+A	0.000253	1.09	up in tumors	uc.249	N
CRC vs colon mucosa	uc.221+A	0.00191	1.10	up in tumors	uc.221	P
CRC vs colon mucosa	uc.422+A	0.00497	1.10	up in tumors	uc.422	P
CRC vs colon mucosa	uc.427+A	0.000972	1.10	up in tumors	uc.427	P
CRC vs colon mucosa	uc.413+A	0.00176	1.11	up in tumors	uc.413	E
CRC vs colon mucosa	uc.29+A	3.26E-05	1.11	up in tumors	uc.29	N
CRC vs colon mucosa	uc.292+	0.000013	1.11	up in tumors	uc.292	E
CRC vs colon mucosa	uc.92+	0.0039	1.12	up in tumors	uc.92	N
CRC vs colon mucosa	uc.144+	0.000223	1.12	up in tumors	uc.144	E
CRC vs colon mucosa	uc.206+	2.16E-05	1.14	up in tumors	uc.206	N
CRC vs colon mucosa	uc.202+A	0.00441	1.14	up in tumors	uc.202	N
CRC vs colon mucosa	uc.310+	0.0049	1.14	up in tumors	uc.310	N
CRC vs colon mucosa	uc.298+A	7.37E-05	1.14	up in tumors	uc.298	N
CRC vs colon mucosa	uc.249+	0.000208	1.15	up in tumors	uc.249	N
CRC vs colon mucosa	uc.234+A	0.00139	1.16	up in tumors	uc.234	P
CRC vs colon mucosa	uc.91+	0.00424	1.16	up in tumors	uc.91	N
CRC vs colon mucosa	uc.435+A	0.00201	1.17	up in tumors	uc.435	N
CRC vs colon mucosa	uc.338+A	0.000673	1.17	up in tumors	uc.338	E
CRC vs colon mucosa	uc.10+	0.00322	1.18	up in tumors	uc.10	N
CRC vs colon mucosa	uc.457+A	0.00281	1.19	up in tumors	uc.457	E
CRC vs colon mucosa	uc.426+	0.00497	1.19	up in tumors	uc.426	P
CRC vs colon mucosa	uc.281+	0.00237	1.19	up in tumors	uc.281	P
CRC vs colon mucosa	uc.399+A	9.97E-06	1.20	up in tumors	uc.399	N
CRC vs colon mucosa	uc.445+	0.00322	1.20	up in tumors	uc.445	N
CRC vs colon mucosa	uc.1+	0.00429	1.20	up in tumors	uc.1	P

Figure 16

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Comparison	Probe	P-value	Expression Tumor/Normal	Significance	UCR name	UCR type
CRC vs colon mucosa	uc.158+	0.00156	1.20	up in tumors	uc.158	N
CRC vs colon mucosa	uc.326+	0.000355	1.21	up in tumors	uc.326	P
CRC vs colon mucosa	uc.111+	4.04E-05	1.21	up in tumors	uc.111	P
CRC vs colon mucosa	uc.182+	0.000355	1.22	up in tumors	uc.182	P
CRC vs colon mucosa	uc.63+	0.000511	1.22	up in tumors	uc.63	E
CRC vs colon mucosa	uc.468+A	0.000198	1.23	up in tumors	uc.468	P
CRC vs colon mucosa	uc.475+	0.00455	1.24	up in tumors	uc.475	E
CRC vs colon mucosa	uc.200+	0.000763	1.24	up in tumors	uc.200	N
CRC vs colon mucosa	uc.341+	0.000045	1.24	up in tumors	uc.341	E
CRC vs colon mucosa	uc.420+A	0.000013	1.27	up in tumors	uc.420	E
CRC vs colon mucosa	uc.106+	0.00137	1.28	up in tumors	uc.106	P
CRC vs colon mucosa	uc.246+	0.000511	1.28	up in tumors	uc.246	E
CRC vs colon mucosa	uc.470+A	0.000253	1.29	up in tumors	uc.470	N
CRC vs colon mucosa	uc.362+	0.000603	1.29	up in tumors	uc.362	P
CRC vs colon mucosa	uc.383+	0.000308	1.31	up in tumors	uc.383	N
CRC vs colon mucosa	uc.73+A	0.000972	1.31	up in tumors	uc.73	P
CRC vs colon mucosa	uc.412+	0.000105	1.31	up in tumors	uc.412	N
CRC vs colon mucosa	uc.266+A	0.00081	1.36	up in tumors	uc.266	P
CRC vs colon mucosa	uc.63+A	0.00305	1.36	up in tumors	uc.63	E
CRC vs colon mucosa	uc.388+	3.05E-06	1.37	up in tumors	uc.388	N
CRC vs colon mucosa	uc.300+A	0.000208	1.37	up in tumors	uc.300	N
CRC vs colon mucosa	uc.230+	3.16E-06	1.40	up in tumors	uc.230	P
CRC vs colon mucosa	uc.18+	0.000536	1.50	up in tumors	uc.18	N
CRC vs colon mucosa	uc.134+A	2.92E-08	1.53	up in tumors	uc.134	P
CRC vs colon mucosa	uc.398+	0.000777	1.54	up in tumors	uc.398	P
CRC vs colon mucosa	uc.112+	1.88E-14	1.71	up in tumors	uc.112	N
CRC vs colon mucosa	uc.145+A	0.000253	1.79	up in tumors	uc.145	N
CRC vs colon mucosa	uc.339+	2.33E-09	2.17	up in tumors	uc.339	P
Comparison	Probe	P-value*	Tumor/Normal	Tumor/Normal	UCR name	UCR type
HCC vs Normal liver	uc.198+	0.000477	0.89	down in tumors	uc.198	N
HCC vs Normal liver	uc.23+	0.00221	0.90	down in tumors	uc.23	N
HCC vs Normal liver	uc.27+	0.00175	0.93	down in tumors	uc.27	N
HCC vs Normal liver	uc.274+	0.00367	0.93	down in tumors	uc.274	P
HCC vs Normal liver	uc.396+	0.00105	0.95	down in tumors	uc.396	N
HCC vs Normal liver	uc.252+A	0.00152	1.17	up in tumors	uc.252	N
HCC vs Normal liver	uc.20+A	0.00372	1.38	up in tumors	uc.20	P
HCC vs Normal liver	uc.402+A	0.00141	1.38	up in tumors	uc.402	P

*Statistical comparison was performed without Benjamini and Hochberg correction.

Figure 16

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Supplemental Table 3. Genomic location of UCRs is correlated with CAGR (Cancer Associated Genomic Regions)
(databases as in Bejerano G et al, Science 2004; Calin GA et al, PNAS 2004)

ultra conserved element name	type	Build 34 coords	LOH exact	FRA <2Mb	AMPLIF exact	HPV 16 <2.5Mb	HOX clusters	HOX genes
uc.1	p	chr1:10307243-10307449	X					
uc.2	n	chr1:10442089-10442295	X					
uc.3	p	chr1:10460711-10460935	X					
uc.4	n	chr1:10467795-10468153	X					
uc.5	n	chr1:10490897-10491110	X					
uc.6	p	chr1:10504667-10504967	X					
uc.7	p	chr1:10545679-10545934	X					
uc.8	n	chr1:10561364-10561579	X					
uc.9	n	chr1:10634956-10635157	X					
uc.10	n	chr1:10675120-10675394	X					
uc.12	p	chr1:35077889-35078089						
uc.13	e	chr1:35786852-35787088						
uc.14	p	chr1:37908298-37908510						
uc.15	n	chr1:37974370-37974602						
uc.16	p	chr1:38041493-38041703						
uc.17	n	chr1:38215445-38215681						
uc.18	n	chr1:44128955-44129192						
uc.19	n	chr1:44403606-44403861						
uc.20	p	chr1:44415666-44415934						
uc.21	n	chr1:48482903-48483137	X					
uc.22	n	chr1:50376149-50376456	X					
uc.23	n	chr1:50405695-50405923	X					
uc.24	n	chr1:50469063-50469398	X					
uc.25	n	chr1:50535952-50536186	X					
uc.26	n	chr1:62739563-62739774	X					
uc.27	n	chr1:62739797-62740086	X					
uc.28	e	chr1:70066629-70066983		X				
uc.29	n	chr1:87244976-87245194						
uc.30	n	chr1:87451593-87451835						
uc.31	n	chr1:88395168-88395420						
uc.33	e	chr1:96743538-96743849						
uc.34	e	chr1:96751973-96752180						
uc.35	p	chr1:97465205-97465409	X					
uc.36	p	chr1:108587040-108587303						
uc.37	e	chr1:114578780-114578981						
uc.38	n	chr1:161127332-161127555		X				
uc.39	n	chr1:161210912-161211267		X				
uc.40	p	chr1:161825339-161825585		X				
uc.41	n	chr1:210655265-210655480						
uc.42	n	chr1:212945530-212945795						
uc.43	n	chr1:240842759-240843015						
uc.44	e	chr1:241164431-241164660						
uc.45	e	chr1:241963410-241963612						
uc.46	e	chr1:241964327-241964543						
uc.47	n	chr2:7796390-7796616						
uc.48	e	chr2:20462845-20463142						
uc.49	e	chr2:33787944-33788150						
uc.50	e	chr2:38950836-38951057						

Figure 17

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ultra conserved element name	type	Build 34 coords	LOH exact	FRA <2Mb	AMPLIF exact	HPV 16 <2.5Mb	HOX clusters	HOX genes
uc.51	n	chr2:57947093-57947299						
uc.52	n	chr2:59082720-59082993						
uc.53	n	chr2:59107845-59108076						
uc.54	n	chr2:59173937-59174145						
uc.55	n	chr2:59721112-59721351						
uc.56	n	chr2:59922365-59922566						
uc.57	n	chr2:60113774-60114019						
uc.58	n	chr2:60272497-60272699						
uc.59	n	chr2:60272917-60273136						
uc.60	n	chr2:60416094-60416310						
uc.61	e	chr2:60662107-60662432						
uc.62	e	chr2:60755216-60755449				▨		
uc.63	e	chr2:61727035-61727312				▨		
uc.64	p	chr2:63168625-63168869						
uc.65	n	chr2:66273125-66273336						
uc.66	n	chr2:73149541-73149787						▨
uc.67	n	chr2:104358126-104358342						
uc.68	n	chr2:144125491-144125745						
uc.69	n	chr2:144322879-144323179						
uc.70	p	chr2:144648108-144648344						
uc.71	n	chr2:144923625-144923872						
uc.72	n	chr2:144925741-144926147						
uc.73	p	chr2:144973082-144973282						
uc.74	p	chr2:145036732-145037269						
uc.75	e	chr2:145356619-145356854						
uc.76	n	chr2:145371902-145372236						
uc.77	e	chr2:145396534-145396829						
uc.78	n	chr2:145399123-145399370						
uc.79	p	chr2:145407946-145408240						
uc.80	n	chr2:145411621-145411914						
uc.81	n	chr2:147344834-147345044						
uc.82	n	chr2:156929644-156929853						
uc.83	n	chr2:157194172-157194467						
uc.84	p	chr2:157397251-157397459						
uc.85	n	chr2:157753959-157754206						
uc.86	n	chr2:157862655-157862994						
uc.87	n	chr2:158102814-158103103						
uc.88	n	chr2:162297586-162297897						
uc.89	p	chr2:162441217-162441523						
uc.90	e	chr2:162475571-162475776						
uc.91	n	chr2:163247566-163247772						
uc.92	n	chr2:164653223-164653531						
uc.93	n	chr2:164864451-164864713						
uc.94	n	chr2:165046714-165046913						
uc.95	p	chr2:171774074-171774324		▨				
uc.96	p	chr2:173023218-173023478						▨
uc.97	e	chr2:173025175-173025616						▨
uc.98	n	chr2:173159062-173159299						
uc.99	n	chr2:173160925-173161322						▨
uc.100	n	chr2:174317324-174317530						
uc.101	e	chr2:174977025-174977278						
uc.102	e	chr2:175148953-175149290						
uc.103	p	chr2:175172216-175172448						
uc.104	n	chr2:175189478-175189693						
uc.105	n	chr2:175192331-175192553						
uc.106	p	chr2:175227967-175228172						
uc.107	n	chr2:175410152-175410388						
uc.108	n	chr2:177142901-177143274					▨	
uc.109	n	chr2:177705882-177706105					▨	
uc.110	n	chr2:237358132-237358374						▨
uc.111	p	chr3:9446461-9446756	▨					
uc.483	p	chr3:17567733-17568134						

Figure 17

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ultra conserved element name	type	Build 34 coords	LOH exact	FRA <2Mb	AMPLIF exact	HPV 16 <2.5Mb	HOX clusters	HOX genes
			1	2	3	4	5	6
uc.112	n	chr3:18144568-18144913						
uc.113	p	chr3:18651408-18651654						
uc.114	n	chr3:18819454-18819747						
uc.115	n	chr3:19009162-19009380						
uc.116	n	chr3:70499494-70499699	X					
uc.117	n	chr3:70792683-70792933	X					
uc.118	n	chr3:70792935-70793153	X					
uc.119	n	chr3:115754368-115754668						
uc.120	p	chr3:115755940-115756209						
uc.121	n	chr3:115896375-115896667						
uc.122	n	chr3:115932792-115933006						
uc.123	n	chr3:138304453-138304944						
uc.124	n	chr3:138369353-138369639						
uc.125	n	chr3:138389226-138389490						
uc.126	n	chr3:138446557-138446827						
uc.127	n	chr3:148351617-148351888						
uc.128	p	chr3:148370547-148370845						
uc.129	e	chr3:153485296-153485507						
uc.130	p	chr3:159097487-159097710						
uc.131	n	chr3:159310953-159311159						
uc.132	n	chr3:159347072-159347279						
uc.133	n	chr3:159347391-159347667						
uc.134	p	chr3:159566817-159567027						
uc.135	e	chr3:170155196-170155396	X					
uc.136	p	chr3:170514865-170515211						
uc.137	n	chr3:181757770-181758154			X			
uc.138	e	chr3:186970209-186970627						
uc.139	p	chr4:4587982-4588319						X
uc.140	n	chr4:12760753-12760975						X
uc.141	e	chr4:24280045-24280339	X					
uc.142	p	chr4:41665611-41665869	X					
uc.143	e	chr4:77037519-77037736						
uc.144	e	chr4:83805060-83805264						
uc.145	n	chr4:105805133-105805380	X					X
uc.146	n	chr4:112375296-112375509						X
uc.147	p	chr4:151814010-151814317						
uc.148	p	chr4:152071579-152071818						
uc.149	p	chr4:152071820-152072023						
uc.150	n	chr5:3565359-3565620			X			X
uc.151	e	chr5:32425638-32425851			X			X
uc.152	n	chr5:50351523-50351723		X				
uc.153	e	chr5:72279759-72279998						
uc.154	p	chr5:72294088-72294290						
uc.155	p	chr5:77018437-77018643						
uc.156	p	chr5:77019492-77019704						
uc.157	n	chr5:77025234-77025440						
uc.158	n	chr5:77224326-77224549						
uc.159	n	chr5:77232005-77232476						
uc.160	n	chr5:77352917-77353238						
uc.161	p	chr5:77442602-77442879						
uc.162	p	chr5:81231434-81231651						
uc.163	n	chr5:87252696-87253071						
uc.164	n	chr5:87324478-87324680						
uc.165	n	chr5:87777006-87777229						
uc.166	p	chr5:88045878-88046187						
uc.167	n	chr5:88263697-88263897						
uc.168	n	chr5:91012866-91013085						
uc.169	e	chr5:92995090-92995293						
uc.170	n	chr5:93301743-93302052						
uc.171	n	chr5:93649920-93650127						
uc.172	n	chr5:93724792-93725009						
uc.173	e	chr5:133802376-133802651		X		X		

Figure 17

Calin GA et al   4

ultra conserved element name	type	Build 34 coords	LOH exact	FRA <2Mb	AMPLIF exact	HPV 16 <2.5Mb	HOX clusters	HOX genes
uc.174	e	chr5:138719870-138720129						
uc.175	n	chr5:158322733-158322982						
uc.176	n	chr5:167313590-167313835						
uc.177	n	chr5:170398551-170398807				▓		
uc.178	n	chr5:170398920-170399168				▓		
uc.179	n	chr5:170609134-170609352				▓		
uc.180	n	chr5:170609411-170609635				▓		
uc.181	n	chr5:170610401-170610678				▓		
uc.182	p	chr5:170684001-170684239				▓		
uc.183	e	chr5:171365442-171365677						▓
uc.184	e	chr5:173366215-173366444						
uc.185	e	chr5:178157908-178158318						
uc.186	e	chr5:179155889-179156193						
uc.187	n	chr6:10502663-10502874						
uc.188	e	chr6:16407363-16407577						
uc.189	e	chr6:36614372-36614944						
uc.190	n	chr6:41570295-41570494						
uc.191	n	chr6:51123630-51123837						
uc.192	n	chr6:51195833-51196076						
uc.193	e	chr6:86317282-86317600	▓					
uc.194	e	chr6:93964662-93964862	▓					
uc.195	p	chr6:97708954-97709226						
uc.196	n	chr6:98162138-98162358						
uc.197	n	chr6:98408397-98408620						
uc.198	n	chr6:98765487-98765793						
uc.199	n	chr6:98859453-98859708						
uc.200	n	chr6:99041131-99041384						
uc.201	n	chr6:100097582-100097821						
uc.202	n	chr6:101019581-101019810						
uc.203	e	chr6:163900992-163901194	▓					
uc.204	n	chr7:1010242-1010443						
uc.205	n	chr7:20574105-20574356						
uc.206	n	chr7:20748081-20748579						
uc.207	n	chr7:21555809-21556038						
uc.208	e	chr7:23303942-23304159						
uc.209	e	chr7:23304160-23304409						
uc.210	p	chr7:26439350-26439606					▓	▓
uc.211	n	chr7:26471744-26472034					▓	▓
uc.212	p	chr7:26884210-26884414					▓	▓
uc.213	e	chr7:26925404-26925604					▓	▓
uc.214	n	chr7:31144670-31144912						
uc.215	n	chr7:41933365-41933626						
uc.216	p	chr7:50102955-50103266						
uc.217	p	chr7:54378405-54378625						
uc.218	p	chr7:69215092-69215377						
uc.219	p	chr7:69392897-69393106						
uc.220	n	chr7:96245647-96245903						▓
uc.221	p	chr7:96253032-96253380						▓
uc.222	n	chr7:113611674-113611874		▓				
uc.223	n	chr7:113612688-113612955		▓				
uc.224	n	chr7:113617522-113617816		▓				
uc.225	n	chr7:113627358-113627558		▓				
uc.226	n	chr7:113763821-113764025		▓				
uc.227	n	chr7:113849819-113850049		▓				
uc.228	n	chr7:114671200-114671464	▓	▓				
uc.229	n	chr7:114689148-114689443	▓	▓				
uc.230	p	chr7:114873964-114874201	▓	▓				
uc.231	n	chr7:115136620-115136843	▓	▓				
uc.232	p	chr7:121499109-121499355						
uc.233	e	chr7:150220055-150220320						
uc.234	p	chr7:156229240-156229511						
uc.235	n	chr8:25797831-25798057	▓					

Figure 17

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ultra conserved element name	type	Build 34 coords	LOH exact	FRA <2Mb	AMPLIF exact	HPV 16 <2.5Mb	HOX clusters	HOX genes
			1	2	3	4	5	6
uc.236	n	chr8:37307753-37308019						
uc.237	p	chr8:53187862-53188329						
uc.238	p	chr8:53217077-53217434						
uc.239	p	chr8:59992334-59992633						
uc.240	p	chr8:65542500-65542705						
uc.241	n	chr8:65547091-65547292						
uc.242	n	chr8:66199258-66199522						
uc.243	p	chr8:77740924-77741139				▨		
uc.244	n	chr8:105918932-105919252						
uc.245	n	chr8:106290415-106290753						
uc.246	e	chr8:119079806-119080089			▨	▨		
uc.247	p	chr9:959154-959514						
uc.248	n	chr9:964189-964410						
uc.249	n	chr9:8085728-8085987						
uc.250	n	chr9:13929910-13930118						
uc.251	n	chr9:15864309-15864521						
uc.252	n	chr9:16700753-16700983						
uc.253	n	chr9:17322212-17322433						
uc.254	n	chr9:23486725-23487003						
uc.255	e	chr9:23681768-23681999						
uc.256	e	chr9:23682234-23682439						
uc.257	n	chr9:37205204-37205467						
uc.258	p	chr9:37314424-37314624						
uc.259	p	chr9:75084998-75085305						
uc.260	n	chr9:76929543-76929773						
uc.261	n	chr9:77328693-77329003						
uc.262	n	chr9:79184841-79185095						
uc.263	e	chr9:82047403-82047609						
uc.264	e	chr9:82047611-82047877						
uc.265	e	chr9:103498309-103498525	▨					
uc.266	p	chr9:104758130-104758372	▨					
uc.267	e	chr9:120429935-120430137	▨					
uc.268	p	chr9:120982873-120983123	▨					
uc.269	n	chr9:121913982-121914198	▨					
uc.270	p	chr9:123680114-123680391	▨					
uc.271	p	chr9:123680397-123680607	▨					
uc.272	n	chr9:123808633-123808845	▨					
uc.273	p	chr9:123893643-123893963	▨					
uc.274	p	chr9:123897916-123898242	▨					
uc.275	n	chr9:123960161-123960415	▨					
uc.276	p	chr9:123981857-123982288	▨					
uc.277	p	chr9:123983755-123984030	▨					
uc.278	p	chr9:124022210-124022446	▨					
uc.279	n	chr9:124048604-124048939	▨					
uc.280	e	chr9:124054051-124054270	▨					
uc.281	p	chr9:130771570-130771807						
uc.282	e	chr9:135399783-135399989				▨		
uc.283	n	chr10:49949360-49949636						
uc.284	p	chr10:49951459-49951667						
uc.285	e	chr10:69860594-69860825						
uc.286	n	chr10:76483627-76483878						
uc.287	p	chr10:76840546-76840802						
uc.288	n	chr10:77071786-77072008						
uc.289	n	chr10:77335142-77335395						
uc.290	e	chr10:77386885-77387090						
uc.291	p	chr10:77628227-77628457						
uc.292	e	chr10:98380042-98380258						
uc.293	n	chr10:102037256-102037498	▨					▨
uc.294	n	chr10:102038204-102038647	▨					▨
uc.295	n	chr10:102039687-102039895	▨					▨
uc.296	n	chr10:102079693-102080153	▨					▨
uc.297	n	chr10:102083807-102084170	▨					▨

Figure 17

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ultra conserved element name	type	Build 34 coords	LOH exact	FRA <2Mb	AMPLIF exact	HPV 16 <2.5Mb	HOX clusters	HOX genes
			1	2	3	4	5	6
uc.298	n	chr10:102112245-102112603	▨					▨
uc.299	e	chr10:102174022-102174231	▨					▨
uc.300	n	chr10:102211705-102211912	▨					▨
uc.301	p	chr10:102232378-102232661	▨					▨
uc.302	n	chr10:102643767-102644107	▨					▨
uc.303	n	chr10:102717014-102717285	▨					▨
uc.304	p	chr10:102747091-102747362	▨					▨
uc.305	p	chr10:102876022-102876326	▨					▨
uc.306	p	chr10:102876626-102876849	▨					▨
uc.307	p	chr10:102908570-102908801	▨					▨
uc.308	p	chr10:102910399-102910675	▨					▨
uc.309	n	chr10:102931618-102931885	▨					▨
uc.310	n	chr10:114068810-114069038	▨	■				
uc.311	p	chr10:119738989-119739207						▨
uc.312	p	chr10:119741124-119741445						▨
uc.313	e	chr10:121004761-121004991						
uc.314	n	chr10:124392535-124392736						
uc.315	n	chr10:124392947-124393181						
uc.316	n	chr10:126479965-126480204						
uc.317	n	chr10:130920738-130920955	▨					
uc.318	p	chr10:131165986-131166306	▨					
uc.319	n	chr11:8269004-8269319						
uc.320	n	chr11:8282143-8282477						
uc.321	n	chr11:15588733-15588936						
uc.322	n	chr11:16280660-16280882						
uc.323	p	chr11:16439645-16439844						
uc.324	e	chr11:30521830-30522054						
uc.325	n	chr11:31649953-31650187						
uc.326	p	chr11:31749989-31750303						
uc.327	n	chr11:31750593-31750860						
uc.328	p	chr11:31789972-31790202						
uc.329	n	chr11:32162301-32162607						
uc.330	e	chr11:66169256-66169462		■				
uc.331	e	chr11:82921467-82921684						
uc.332	n	chr11:115770342-115770678						
uc.333	e	chr11:124182299-124182568	▨					
uc.334	n	chr11:131405597-131405818						
uc.335	n	chr12:16606681-16606894						
uc.336	n	chr12:24183273-24183523						
uc.337	n	chr12:40035446-40035663						
uc.338	e	chr12:52144756-52144978		■				
uc.339	p	chr12:52357363-52357614		■				
uc.340	n	chr12:52377099-52377357		■				
uc.341	e	chr12:52669185-52669498		■				
uc.342	e	chr12:52696761-52696987		■				
uc.343	e	chr12:52708708-52709095		■				
uc.344	e	chr12:52713153-52713406		■				
uc.345	e	chr12:52733867-52734167		■				
uc.346	p	chr12:105478977-105479178						
uc.347	n	chr13:69591989-69592197						
uc.348	n	chr13:69861358-69861597						
uc.349	p	chr13:69919303-69919505						
uc.350	n	chr13:70054101-70054340		■		■		
uc.351	n	chr13:70466901-70467155		■		■		
uc.352	n	chr13:70492166-70492365		■		■		
uc.353	n	chr13:70569554-70569876		■		■		
uc.354	p	chr13:76774830-76775064						
uc.355	n	chr13:93316883-93317110	▨			▨		
uc.356	e	chr13:95706821-95707071	▨			▨		
uc.357	p	chr13:110664338-110664579	▨					
uc.358	n	chr14:24368162-24368387						
uc.359	e	chr14:24905096-24905419						

Figure 17

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ultra conserved element name	type	Build 34 coords	LOH exact	FRA <2Mb	AMPLIF exact	HPV 16 <2.5Mb	HOX clusters	HOX genes
uc.360	e	chr14:24905510-24905796						
uc.361	p	chr14:27223174-27223440	▨					
uc.362	p	chr14:27338791-27339029	▨					
uc.363	n	chr14:27851358-27851622	▨					
uc.364	n	chr14:28702798-28703004	▨					
uc.365	n	chr14:28732401-28732678	▨					
uc.366	e	chr14:29372746-29372947	▨					
uc.367	p	chr14:31834502-31834799	▨					
uc.368	n	chr14:32058615-32058842	▨	▨				
uc.369	n	chr14:32112656-32112868	▨	▨				
uc.370	n	chr14:32192610-32193002	▨	▨				
uc.371	n	chr14:34010228-34010523	▨	▨				
uc.372	n	chr14:34033074-34033350	▨	▨				
uc.373	n	chr14:34571846-34572239	▨	▨				
uc.374	p	chr14:35705952-35706175	▨	▨				
uc.375	e	chr14:35767259-35767558	▨	▨				
uc.376	e	chr14:43555788-43556077						
uc.377	e	chr14:43569061-43569277						
uc.378	e	chr14:78317518-78317768						
uc.379	n	chr14:95421409-95421660	▨					
uc.380	n	chr14:95752635-95752866	▨					
uc.381	n	chr14:95869331-95869568	▨					
uc.382	n	chr15:33634968-33635167	▨					
uc.383	n	chr15:34535983-34536251	▨					
uc.384	p	chr15:34681449-34681714	▨					
uc.385	p	chr15:34901726-34901934	▨					
uc.386	n	chr15:35238065-35238267	▨					
uc.387	e	chr15:39748110-39748347						
uc.388	n	chr15:55141581-55141878						
uc.389	n	chr15:65381203-65381473						
uc.390	e	chr15:65593988-65594192						
uc.391	e	chr15:65756122-65756432						
uc.392	n	chr15:68107952-68108207						
uc.393	e	chr15:72630059-72630333						
uc.394	n	chr15:94965868-94966069						
uc.395	e	chr16:24545554-24545802						
uc.396	n	chr16:48872692-48872899						
uc.397	p	chr16:49513876-49514186						
uc.398	p	chr16:49668919-49669240						
uc.399	n	chr16:50627024-50627237						
uc.400	n	chr16:51450088-51450293						
uc.401	p	chr16:52273300-52273549						
uc.402	p	chr16:53432987-53433231						
uc.403	p	chr16:54102457-54102662						
uc.404	p	chr16:55001959-55002193						
uc.405	n	chr16:59350792-59351001						
uc.406	e	chr16:69456552-69456762						
uc.407	e	chr16:69457343-69457668						
uc.408	e	chr16:72597321-72597572						
uc.409	e	chr16:72869147-72869390						
uc.410	n	chr17:35207780-35207998						
uc.411	n	chr17:35525169-35525397						
uc.412	n	chr17:35532036-35532303						
uc.413	e	chr17:37941482-37941753			▨			
uc.414	e	chr17:38624137-38624382						
uc.415	n	chr17:47138544-47138750					▨	▨
uc.416	e	chr17:47145525-47145810					▨	▨
uc.417	e	chr17:47156950-47157171					▨	▨
uc.418	e	chr17:56556866-56557082		▮		▮		
uc.419	e	chr17:56557353-56557641		▮		▮		
uc.420	e	chr17:63046872-63047104						
uc.421	n	chr18:20945142-20945486						

Figure 17

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ultra conserved element name	type	Build 34 coords	LOH exact	FRA <2Mb	AMPLIF exact	HPV 16 <2.5Mb	HOX clusters	HOX genes
uc.422	p	chr18:21000175-21000400	▨	▨	▨	▨	▨	▨
uc.423	n	chr18:21008342-21008564						
uc.424	p	chr18:21019766-21019980						
uc.425	n	chr18:21117194-21117518						
uc.426	p	chr18:22167579-22167840						
uc.427	p	chr18:22489186-22489400						
uc.428	p	chr18:28605196-28605434						
uc.429	n	chr18:32732528-32732765						
uc.430	n	chr18:33315637-33315849						
uc.431	n	chr18:33430587-33430816						
uc.432	n	chr18:33816919-33817129						
uc.433	n	chr18:34315619-34315824						
uc.434	n	chr18:43022775-43023023						
uc.435	n	chr18:51238918-51239144						
uc.436	e	chr18:51403228-51403437						
uc.437	n	chr18:70484635-70484849						
uc.438	n	chr18:70484851-70485091						
uc.439	n	chr18:70490008-70490270						
uc.440	n	chr18:70490342-70490670						
uc.441	p	chr18:70695569-70695816						
uc.442	n	chr18:70719689-70719937						
uc.443	e	chr19:8433269-8433507						
uc.444	n	chr19:35186619-35187006				▨		
uc.445	n	chr19:35258275-35258584				▨		
uc.446	p	chr19:35439694-35439965				▨		
uc.447	n	chr19:35459621-35459893				▨		
uc.448	n	chr19:35533370-35533601						
uc.449	n	chr19:35695381-35695670						
uc.450	n	chr19:36279466-36279676						
uc.451	n	chr19:36498460-36498684						
uc.452	e	chr19:36519787-36519990						
uc.453	n	chr19:47129157-47129481						
uc.454	e	chr20:4861440-4861647						
uc.455	e	chr20:35043808-35044052						
uc.456	e	chr20:42773185-42773504						
uc.457	e	chr22:17770463-17770673						
uc.458	e	chr22:34420305-34420508	▨	▨				
uc.459	e	chrX:20895986-20896240						
uc.460	p	chrX:24184937-24185211						
uc.461	n	chrX:24226223-24226619						
uc.462	p	chrX:24256252-24257030						
uc.463	n	chrX:24277308-24277582						
uc.464	n	chrX:24277584-24278353						
uc.465	n	chrX:24278907-24279216						
uc.466	n	chrX:24307884-24308232						
uc.467	n	chrX:24369780-24370510						
uc.468	p	chrX:24378989-24379477						
uc.469	p	chrX:24379479-24379700						
uc.470	n	chrX:24762642-24762982						
uc.471	e	chrX:40239309-40239547						
uc.472	e	chrX:40410244-40410445						
uc.473	e	chrX:69240015-69240236						
uc.474	e	chrX:69335634-69335843						
uc.475	e	chrX:69632846-69633242						
uc.476	n	chrX:80545473-80545710						
uc.477	e	chrX:101813348-101813556						
uc.478	e	chrX:121297212-121297463						
uc.479	e	chrX:121311506-121311807						
uc.480	e	chrX:121933027-121933228						
uc.481	e	chrX:121933230-121933433						
uc.482	n	chrX:137876095-137876389						

Figure 17

Calin GA　　　　　　　　　　　　　　　　　　　1

Supplementary Table 4. Negative correlations between the expression of miRNAs and T-UCRs in CLL patients. All validated negative correlations by FDR method at 0.01 treshold , or 1%false positive results, and with an R correlation lower as -0.040 were considered.

The probe complementary to the genomic orientation is named "+", while the probe to the complementary sequence is named "A+".

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-let-7a-1-prec	uc.420+	-0.7315	hsa-let-7a
hsa-let-7a-2-precNo2	uc.73+A	-0.7284	hsa-let-7a
hsa-let-7a-1-prec	uc.189+	-0.6855	hsa-let-7a
hsa-let-7a-1-prec	uc.285+	-0.6832	hsa-let-7a
hsa-let-7a-1-prec	uc.299+A	-0.6717	hsa-let-7a
hsa-let-7a-2-precNo2	uc.462+A	-0.6683	hsa-let-7a
hsa-let-7a-1-prec	uc.73+A	-0.6596	hsa-let-7a
hsa-let-7a-2-precNo2	uc.477+A	-0.6589	hsa-let-7a
hsa-let-7a-2-precNo2	uc.456+A	-0.6518	hsa-let-7a
hsa-let-7a-2-precNo2	uc.200+	-0.6496	hsa-let-7a
hsa-let-7a-2-precNo2	uc.448+A	-0.6475	hsa-let-7a
hsa-let-7a-2-precNo2	uc.287+A	-0.6465	hsa-let-7a
hsa-let-7a-2-precNo2	uc.190+A	-0.6443	hsa-let-7a
hsa-let-7a-1-prec	uc.388+A	-0.6224	hsa-let-7a
hsa-let-7a-1-prec	uc.462+A	-0.6077	hsa-let-7a
hsa-let-7a-1-prec	uc.153+A	-0.6059	hsa-let-7a
hsa-let-7a-2-precNo2	uc.217+	-0.6049	hsa-let-7a
hsa-let-7a-3-prec	uc.420+	-0.603	hsa-let-7a
hsa-let-7a-1-prec	uc.33+	-0.598	hsa-let-7a
hsa-let-7a-2-precNo2	uc.378+A	-0.594	hsa-let-7a
hsa-let-7a-1-prec	uc.412+A	-0.5928	hsa-let-7a
hsa-let-7a-2-precNo2	uc.161+A	-0.5926	hsa-let-7a
hsa-let-7a-3-prec	uc.262+A	-0.5889	hsa-let-7a
hsa-let-7a-1-prec	uc.354+A	-0.5867	hsa-let-7a
hsa-let-7a-1-prec	uc.8+	-0.5855	hsa-let-7a
hsa-let-7a-2-precNo2	uc.88+A	-0.583	hsa-let-7a
hsa-let-7a-2-precNo2	uc.412+	-0.5829	hsa-let-7a
hsa-let-7a-1-prec	uc.234+	-0.5827	hsa-let-7a
hsa-let-7a-2-precNo2	uc.378+	-0.5826	hsa-let-7a
hsa-let-7a-2-precNo2	uc.338+	-0.5807	hsa-let-7a
hsa-let-7a-3-prec	uc.8+	-0.5782	hsa-let-7a
hsa-let-7a-3-prec	uc.161+A	-0.577	hsa-let-7a
hsa-let-7a-2-precNo2	uc.145+A	-0.5761	hsa-let-7a
hsa-let-7a-1-prec	uc.151+A	-0.5756	hsa-let-7a
hsa-let-7a-3-prec	uc.145+A	-0.5745	hsa-let-7a
hsa-let-7a-1-prec	uc.456+A	-0.5716	hsa-let-7a
hsa-let-7a-1-prec	uc.33+A	-0.5702	hsa-let-7a
hsa-let-7a-2-precNo2	uc.427+	-0.5685	hsa-let-7a
hsa-let-7a-1-prec	uc.468+	-0.5659	hsa-let-7a
hsa-let-7a-3-prec	uc.160+	-0.5658	hsa-let-7a
hsa-let-7a-2-precNo2	uc.412+A	-0.5634	hsa-let-7a
hsa-let-7a-3-prec	uc.134+	-0.5563	hsa-let-7a
hsa-let-7a-1-prec	uc.134+	-0.554	hsa-let-7a
hsa-let-7a-1-prec	uc.338+	-0.5524	hsa-let-7a
hsa-let-7a-2-precNo2	uc.420+	-0.5507	hsa-let-7a
hsa-let-7a-2-precNo2	uc.189+	-0.5502	hsa-let-7a
hsa-let-7a-2-precNo2	uc.95+	-0.5486	hsa-let-7a
hsa-let-7a-3-prec	uc.117+	-0.5479	hsa-let-7a
hsa-let-7a-1-prec	uc.44+A	-0.5461	hsa-let-7a
hsa-let-7a-2-precNo2	uc.281+A	-0.5384	hsa-let-7a
hsa-let-7a-1-prec	uc.190+A	-0.5302	hsa-let-7a
hsa-let-7a-3-prec	uc.478+A	-0.5285	hsa-let-7a
hsa-let-7a-3-prec	uc.183+	-0.5275	hsa-let-7a
hsa-let-7a-3-prec	uc.299+A	-0.5255	hsa-let-7a
hsa-let-7a-1-prec	uc.445+A	-0.5253	hsa-let-7a
hsa-let-7a-2-precNo2	uc.234+	-0.5203	hsa-let-7a
hsa-let-7a-1-prec	uc.420+A	-0.5185	hsa-let-7a
hsa-let-7a-1-prec	uc.183+	-0.5149	hsa-let-7a
hsa-let-7a-1-prec	uc.378+A	-0.5138	hsa-let-7a
hsa-let-7a-3-prec	uc.352+	-0.5131	hsa-let-7a
hsa-let-7a-1-prec	uc.262+A	-0.5101	hsa-let-7a
hsa-let-7a-1-prec	uc.43+	-0.5074	hsa-let-7a
hsa-let-7a-1-prec	uc.217+A	-0.5033	hsa-let-7a
hsa-let-7a-2-precNo2	uc.44+A	-0.5027	hsa-let-7a
hsa-let-7a-2-precNo2	uc.354+A	-0.5016	hsa-let-7a
hsa-let-7a-1-prec	uc.275+	-0.4998	hsa-let-7a
hsa-let-7a-2-precNo2	uc.159+A	-0.4975	hsa-let-7a
hsa-let-7a-3-prec	uc.338+	-0.4951	hsa-let-7a
hsa-let-7a-1-prec	uc.388+	-0.495	hsa-let-7a
hsa-let-7a-2-precNo2	uc.456+	-0.4948	hsa-let-7a
hsa-let-7a-3-prec	uc.189+	-0.4939	hsa-let-7a
hsa-let-7a-2-precNo2	uc.285+	-0.4917	hsa-let-7a
hsa-let-7a-2-precNo2	uc.275+	-0.4882	hsa-let-7a
hsa-let-7a-3-prec	uc.462+A	-0.4878	hsa-let-7a
hsa-let-7a-3-prec	uc.285+	-0.4856	hsa-let-7a
hsa-let-7a-2-precNo2	uc.299+A	-0.4848	hsa-let-7a
hsa-let-7a-2-precNo2	uc.153+A	-0.484	hsa-let-7a
hsa-let-7a-3-prec	uc.234+	-0.4836	hsa-let-7a

Figure 18

Calin GA   2

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-let-7a-2-precNo2	uc.190+	-0.4768	hsa-let-7a
hsa-let-7a-2-precNo2	uc.78+	-0.4758	hsa-let-7a
hsa-let-7a-3-prec	uc.73+A	-0.4754	hsa-let-7a
hsa-let-7a-1-prec	uc.173+	-0.4738	hsa-let-7a
hsa-let-7a-1-prec	uc.117+	-0.4697	hsa-let-7a
hsa-let-7a-1-prec	uc.477+A	-0.466	hsa-let-7a
hsa-let-7a-3-prec	uc.78+	-0.4656	hsa-let-7a
hsa-let-7a-2-precNo2	uc.473+A	-0.4646	hsa-let-7a
hsa-let-7a-1-prec	uc.331+A	-0.4591	hsa-let-7a
hsa-let-7a-1-prec	uc.190+	-0.4586	hsa-let-7a
hsa-let-7a-1-prec	uc.233+A	-0.4572	hsa-let-7a
hsa-let-7a-1-prec	uc.106+	-0.4547	hsa-let-7a
hsa-let-7a-3-prec	uc.268+	-0.4545	hsa-let-7a
hsa-let-7a-1-prec	uc.287+A	-0.4538	hsa-let-7a
hsa-let-7a-2-precNo2	uc.170+	-0.4518	hsa-let-7a
hsa-let-7a-1-prec	uc.427+	-0.4493	hsa-let-7a
hsa-let-7a-2-precNo2	uc.388+	-0.4484	hsa-let-7a
hsa-let-7c-prec	uc.145+A	-0.5297	hsa-let-7c
hsa-let-7c-prec	uc.352+	-0.5169	hsa-let-7c
hsa-let-7c-prec	uc.281+A	-0.4844	hsa-let-7c
hsa-let-7c-prec	uc.262+A	-0.4484	hsa-let-7c
hsa-let-7d-prec	uc.352+	-0.6191	hsa-let-7d
hsa-let-7d-prec	uc.145+A	-0.5737	hsa-let-7d
hsa-let-7d-prec	uc.269+A	-0.5569	hsa-let-7d
hsa-let-7d-prec	uc.262+A	-0.5485	hsa-let-7d
hsa-let-7d-prec	uc.478+A	-0.5376	hsa-let-7d
hsa-let-7d-prec	uc.262+	-0.5259	hsa-let-7d
hsa-let-7d-prec	uc.160+	-0.4846	hsa-let-7d
hsa-let-7d-prec	uc.78+	-0.484	hsa-let-7d
hsa-let-7d-prec	uc.283+A	-0.4636	hsa-let-7d
hsa-let-7d-prec	uc.161+A	-0.458	hsa-let-7d
hsa-let-7d-prec	uc.398+	-0.4513	hsa-let-7d
hsa-let-7d-prec	uc.339+	-0.4495	hsa-let-7d
hsa-let-7e-prec	uc.473+	-0.6242	hsa-let-7e
hsa-let-7e-prec	uc.95+	-0.5034	hsa-let-7e
hsa-let-7e-prec	uc.453+A	-0.4872	hsa-let-7e
hsa-let-7e-prec	uc.88+A	-0.4812	hsa-let-7e
hsa-let-7f-2-prec2	uc.420+	-0.7661	hsa-let-7f
hsa-let-7f-2-prec2	uc.299+A	-0.7152	hsa-let-7f
hsa-let-7f-1-precNo2	uc.352+	-0.6966	hsa-let-7f
hsa-let-7f-2-prec2	uc.189+	-0.6916	hsa-let-7f
hsa-let-7f-2-prec2	uc.285+	-0.6809	hsa-let-7f
hsa-let-7f-2-prec2	uc.78+	-0.6496	hsa-let-7f
hsa-let-7f-2-prec2	uc.8+	-0.6458	hsa-let-7f
hsa-let-7f-2-prec2	uc.462+A	-0.6427	hsa-let-7f
hsa-let-7f-2-prec2	uc.151+	-0.631	hsa-let-7f
hsa-let-7f-2-prec2	uc.33+A	-0.6246	hsa-let-7f
hsa-let-7f-2-prec2	uc.33+	-0.581	hsa-let-7f
hsa-let-7f-2-prec2	uc.44+A	-0.5784	hsa-let-7f
hsa-let-7f-2-prec2	uc.73+A	-0.5747	hsa-let-7f
hsa-let-7f-1-precNo2	uc.283+A	-0.5705	hsa-let-7f
hsa-let-7f-2-prec2	uc.327+A	-0.5608	hsa-let-7f
hsa-let-7f-1-precNo2	uc.262+	-0.5535	hsa-let-7f
hsa-let-7f-2-prec2	uc.177+	-0.5533	hsa-let-7f
hsa-let-7f-2-prec2	uc.153+	-0.5486	hsa-let-7f
hsa-let-7f-2-prec2	uc.412+	-0.5483	hsa-let-7f
hsa-let-7f-2-prec2	uc.234+	-0.5421	hsa-let-7f
hsa-let-7f-2-prec2	uc.134+	-0.5385	hsa-let-7f
hsa-let-7f-2-prec2	uc.412+A	-0.5381	hsa-let-7f
hsa-let-7f-2-prec2	uc.338+	-0.5376	hsa-let-7f
hsa-let-7f-2-prec2	uc.153+A	-0.5346	hsa-let-7f
hsa-let-7f-2-prec2	uc.183+	-0.532	hsa-let-7f
hsa-let-7f-2-prec2	uc.88+	-0.5177	hsa-let-7f
hsa-let-7f-2-prec2	uc.106+	-0.5168	hsa-let-7f
hsa-let-7f-2-prec2	uc.378+	-0.5128	hsa-let-7f
hsa-let-7f-2-prec2	uc.151+A	-0.4967	hsa-let-7f
hsa-let-7f-2-prec2	uc.388+A	-0.4962	hsa-let-7f
hsa-let-7f-2-prec2	uc.173+	-0.4842	hsa-let-7f
hsa-let-7f-2-prec2	uc.477+A	-0.4775	hsa-let-7f
hsa-let-7f-2-prec2	uc.331+A	-0.4771	hsa-let-7f
hsa-let-7f-2-prec2	uc.167+	-0.4762	hsa-let-7f
hsa-let-7f-2-prec2	uc.190+A	-0.4672	hsa-let-7f
hsa-let-7f-2-prec2	uc.420+A	-0.465	hsa-let-7f
hsa-let-7f-1-precNo2	uc.269+A	-0.4627	hsa-let-7f
hsa-let-7f-2-prec2	uc.354+A	-0.4595	hsa-let-7f
hsa-let-7f-2-prec2	uc.378+A	-0.4592	hsa-let-7f
hsa-let-7f-2-prec2	uc.10+	-0.4591	hsa-let-7f
hsa-let-7f-2-prec2	uc.456+A	-0.4518	hsa-let-7f
hsa-let-7f-2-prec2	uc.43+	-0.4493	hsa-let-7f
hsa-let-7g-precNo1	uc.420+	-0.7906	hsa-let-7g
hsa-let-7g-precNo1	uc.234+	-0.7436	hsa-let-7g
hsa-let-7g-precNo1	uc.412+A	-0.7325	hsa-let-7g
hsa-let-7g-precNo1	uc.73+A	-0.7293	hsa-let-7g
hsa-let-7g-precNo1	uc.354+A	-0.7201	hsa-let-7g

Figure 18

Calin GA

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-let-7g-precNo1	uc.190+A	-0.7168	hsa-let-7g
hsa-let-7g-precNo1	uc.153+A	-0.7122	hsa-let-7g
hsa-let-7g-precNo1	uc.189+	-0.7059	hsa-let-7g
hsa-let-7g-precNo1	uc.285+	-0.6955	hsa-let-7g
hsa-let-7g-precNo1	uc.456+A	-0.6835	hsa-let-7g
hsa-let-7g-precNo1	uc.33+A	-0.6647	hsa-let-7g
hsa-let-7g-precNo1	uc.427+	-0.6627	hsa-let-7g
hsa-let-7g-precNo1	uc.106+	-0.6607	hsa-let-7g
hsa-let-7g-precNo1	uc.43+	-0.6584	hsa-let-7g
hsa-let-7g-precNo1	uc.462+A	-0.6574	hsa-let-7g
hsa-let-7g-precNo1	uc.299+A	-0.6537	hsa-let-7g
hsa-let-7g-precNo1	uc.33+	-0.6498	hsa-let-7g
hsa-let-7g-precNo1	uc.8+	-0.6443	hsa-let-7g
hsa-let-7g-precNo1	uc.378+A	-0.6308	hsa-let-7g
hsa-let-7g-precNo1	uc.388+A	-0.6239	hsa-let-7g
hsa-let-7g-precNo1	uc.477+A	-0.6184	hsa-let-7g
hsa-let-7g-precNo1	uc.468+	-0.6122	hsa-let-7g
hsa-let-7g-precNo1	uc.287+A	-0.6008	hsa-let-7g
hsa-let-7g-precNo1	uc.153+	-0.5961	hsa-let-7g
hsa-let-7g-precNo1	uc.445+A	-0.5906	hsa-let-7g
hsa-let-7g-precNo1	uc.217+A	-0.5796	hsa-let-7g
hsa-let-7g-precNo1	uc.378+	-0.5785	hsa-let-7g
hsa-let-7g-precNo1	uc.44+A	-0.572	hsa-let-7g
hsa-let-7g-precNo1	uc.200+	-0.5646	hsa-let-7g
hsa-let-7g-precNo1	uc.233+A	-0.5626	hsa-let-7g
hsa-let-7g-precNo1	uc.473+A	-0.5575	hsa-let-7g
hsa-let-7g-precNo1	uc.327+A	-0.5546	hsa-let-7g
hsa-let-7g-precNo1	uc.18+	-0.5523	hsa-let-7g
hsa-let-7g-precNo1	uc.190+	-0.546	hsa-let-7g
hsa-let-7g-precNo1	uc.388+	-0.5406	hsa-let-7g
hsa-let-7g-precNo1	uc.420+A	-0.5365	hsa-let-7g
hsa-let-7g-precNo1	uc.20+	-0.5357	hsa-let-7g
hsa-let-7g-precNo1	uc.448+A	-0.5327	hsa-let-7g
hsa-let-7g-precNo1	uc.78+	-0.5237	hsa-let-7g
hsa-let-7g-precNo1	uc.275+	-0.5215	hsa-let-7g
hsa-let-7g-precNo1	uc.468+A	-0.5211	hsa-let-7g
hsa-let-7g-precNo1	uc.213+	-0.5193	hsa-let-7g
hsa-let-7g-precNo1	uc.161+A	-0.5192	hsa-let-7g
hsa-let-7g-precNo1	uc.383+	-0.5128	hsa-let-7g
hsa-let-7g-precNo1	uc.412+	-0.5076	hsa-let-7g
hsa-let-7g-precNo1	uc.10+	-0.5064	hsa-let-7g
hsa-let-7g-precNo1	uc.263+	-0.5059	hsa-let-7g
hsa-let-7g-precNo1	uc.151+A	-0.5047	hsa-let-7g
hsa-let-7g-precNo1	uc.88+	-0.5042	hsa-let-7g
hsa-let-7g-precNo1	uc.456+	-0.5034	hsa-let-7g
hsa-let-7g-precNo1	uc.263+A	-0.5023	hsa-let-7g
hsa-let-7g-precNo1	uc.217+	-0.5018	hsa-let-7g
hsa-let-7g-precNo1	uc.134+	-0.499	hsa-let-7g
hsa-let-7g-precNo1	uc.338+	-0.4948	hsa-let-7g
hsa-let-7g-precNo1	uc.173+	-0.4869	hsa-let-7g
hsa-let-7g-precNo1	uc.177+	-0.4836	hsa-let-7g
hsa-let-7g-precNo1	uc.172+A	-0.4752	hsa-let-7g
hsa-let-7g-precNo1	uc.20+A	-0.4696	hsa-let-7g
hsa-let-7g-precNo1	uc.466+A	-0.4696	hsa-let-7g
hsa-let-7g-precNo1	uc.362+A	-0.4632	hsa-let-7g
hsa-let-7g-precNo1	uc.151+	-0.4573	hsa-let-7g
hsa-let-7g-precNo1	uc.262+A	-0.4494	hsa-let-7g
hsa-let-7iNo1	uc.326+	-0.5234	hsa-let-7i
hsa-let-7iNo1	uc.262+A	-0.5231	hsa-let-7i
hsa-let-7iNo1	uc.125+A	-0.4855	hsa-let-7i
hsa-let-7iNo1	uc.136+	-0.4768	hsa-let-7i
hsa-let-7iNo1	uc.345+A	-0.4675	hsa-let-7i
hsa-let-7iNo1	uc.278+	-0.4673	hsa-let-7i
hsa-mir-103-prec-5=103-1	uc.346+A	-0.6765	hsa-miR-103
hsa-mir-103-prec-5=103-1	uc.282+A	-0.6633	hsa-miR-103
hsa-mir-103-prec-5=103-1	uc.325+	-0.6073	hsa-miR-103
hsa-mir-103-prec-5=103-1	uc.34+A	-0.5571	hsa-miR-103
hsa-mir-103-prec-5=103-1	uc.283+A	-0.5373	hsa-miR-103
hsa-mir-103-prec-5=103-1	uc.339+	-0.5287	hsa-miR-103
hsa-mir-103-prec-5=103-1	uc.398+	-0.5028	hsa-miR-103
hsa-mir-103-prec-5=103-1	uc.465+A	-0.5	hsa-miR-103
hsa-mir-103-prec-5=103-1	uc.269+A	-0.482	hsa-miR-103
hsa-mir-103-prec-5=103-1	uc.478+A	-0.4723	hsa-miR-103
hsa-mir-106-prec-X	uc.167+	-0.6399	hsa-miR-106a
hsa-mir-106aNo1	uc.48+A	-0.6329	hsa-miR-106a
hsa-mir-106aNo1	uc.283+A	-0.6323	hsa-miR-106a
hsa-mir-106-prec-X	uc.478+A	-0.6299	hsa-miR-106a
hsa-mir-106aNo1	uc.282+A	-0.6256	hsa-miR-106a
hsa-mir-106aNo1	uc.478+A	-0.6253	hsa-miR-106a
hsa-mir-106-prec-X	uc.48+A	-0.6244	hsa-miR-106a
hsa-mir-106aNo1	uc.160+	-0.6177	hsa-miR-106a
hsa-mir-106aNo1	uc.327+A	-0.6067	hsa-miR-106a
hsa-mir-106aNo1	uc.465+A	-0.6057	hsa-miR-106a
hsa-mir-106aNo1	uc.167+	-0.6024	hsa-miR-106a

Figure 18

Calin GA

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miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-106-prec-X	uc.160+	-0.59	hsa-miR-106a
hsa-mir-106-prec-X	uc.282+A	-0.58	hsa-miR-106a
hsa-mir-106-prec-X	uc.283+A	-0.5735	hsa-miR-106a
hsa-mir-106aNo1	uc.339+	-0.5724	hsa-miR-106a
hsa-mir-106-prec-X	uc.465+A	-0.5685	hsa-miR-106a
hsa-mir-106aNo1	uc.325+	-0.565	hsa-miR-106a
hsa-mir-106aNo1	uc.117+	-0.5566	hsa-miR-106a
hsa-mir-106-prec-X	uc.339+	-0.5533	hsa-miR-106a
hsa-mir-106-prec-X	uc.327+A	-0.5461	hsa-miR-106a
hsa-mir-106-prec-X	uc.325+	-0.5384	hsa-miR-106a
hsa-mir-106aNo1	uc.213+	-0.5257	hsa-miR-106a
hsa-mir-106aNo1	uc.84+A	-0.5242	hsa-miR-106a
hsa-mir-106-prec-X	uc.117+	-0.5217	hsa-miR-106a
hsa-mir-106-prec-X	uc.84+A	-0.5149	hsa-miR-106a
hsa-mir-106-prec-X	uc.170+	-0.5004	hsa-miR-106a
hsa-mir-106-prec-X	uc.213+	-0.4948	hsa-miR-106a
hsa-mir-106aNo1	uc.170+	-0.4931	hsa-miR-106a
hsa-mir-106aNo1	uc.300+A	-0.485	hsa-miR-106a
hsa-mir-106aNo1	uc.263+	-0.4845	hsa-miR-106a
hsa-mir-106-prec-X	uc.299+	-0.4807	hsa-miR-106a
hsa-mir-106aNo1	uc.269+A	-0.4782	hsa-miR-106a
hsa-mir-106-prec-X	uc.200+	-0.4742	hsa-miR-106a
hsa-mir-106aNo1	uc.153+A	-0.4735	hsa-miR-106a
hsa-mir-106aNo1	uc.153+	-0.4728	hsa-miR-106a
hsa-mir-106-prec-X	uc.88+A	-0.4711	hsa-miR-106a
hsa-mir-106-prec-X	uc.427+	-0.4703	hsa-miR-106a
hsa-mir-106aNo1	uc.427+	-0.4654	hsa-miR-106a
hsa-mir-106-prec-X	uc.448+A	-0.4608	hsa-miR-106a
hsa-mir-106-prec-X	uc.263+	-0.4606	hsa-miR-106a
hsa-mir-106-prec-X	uc.300+A	-0.4559	hsa-miR-106a
hsa-mir-106aNo1	uc.285+	-0.454	hsa-miR-106a
hsa-mir-106aNo1	uc.346+A	-0.4533	hsa-miR-106a
hsa-mir-106-prec-X	uc.346+A	-0.452	hsa-miR-106a
hsa-mir-106bNo1	uc.478+A	-0.6573	hsa-miR-106b
hsa-mir-106bNo1	uc.48+A	-0.6432	hsa-miR-106b
hsa-mir-106bNo1	uc.465+A	-0.6366	hsa-miR-106b
hsa-mir-106bNo1	uc.327+A	-0.613	hsa-miR-106b
hsa-mir-106bNo1	uc.167+	-0.6037	hsa-miR-106b
hsa-mir-106bNo1	uc.117+	-0.5939	hsa-miR-106b
hsa-mir-106bNo1	uc.160+	-0.5934	hsa-miR-106b
hsa-mir-106bNo1	uc.325+	-0.5738	hsa-miR-106b
hsa-mir-106bNo1	uc.283+A	-0.569	hsa-miR-106b
hsa-mir-106bNo1	uc.346+	-0.5522	hsa-miR-106b
hsa-mir-106bNo1	uc.282+A	-0.5496	hsa-miR-106b
hsa-mir-106bNo1	uc.84+A	-0.5416	hsa-miR-106b
hsa-mir-106bNo1	uc.339+	-0.5323	hsa-miR-106b
hsa-mir-106bNo1	uc.110+A	-0.5313	hsa-miR-106b
hsa-mir-106bNo1	uc.153+	-0.5296	hsa-miR-106b
hsa-mir-106bNo1	uc.285+	-0.5289	hsa-miR-106b
hsa-mir-106bNo1	uc.151+A	-0.5224	hsa-miR-106b
hsa-mir-106bNo1	uc.213+	-0.522	hsa-miR-106b
hsa-mir-106bNo1	uc.153+A	-0.5214	hsa-miR-106b
hsa-mir-106bNo1	uc.106+	-0.5074	hsa-miR-106b
hsa-mir-106bNo1	uc.217+A	-0.4977	hsa-miR-106b
hsa-mir-106bNo1	uc.300+A	-0.4952	hsa-miR-106b
hsa-mir-106bNo1	uc.18+	-0.4794	hsa-miR-106b
hsa-mir-106bNo1	uc.33+	-0.4706	hsa-miR-106b
hsa-mir-106bNo1	uc.462+A	-0.4705	hsa-miR-106b
hsa-mir-106bNo1	uc.269+A	-0.4634	hsa-miR-106b
hsa-mir-106bNo1	uc.172+A	-0.4623	hsa-miR-106b
hsa-mir-106bNo1	uc.234+	-0.4571	hsa-miR-106b
hsa-mir-106bNo1	uc.33+A	-0.4569	hsa-miR-106b
hsa-mir-106bNo1	uc.388+A	-0.4555	hsa-miR-106b
hsa-mir-106bNo1	uc.263+	-0.4542	hsa-miR-106b
hsa-mir-106bNo1	uc.170+	-0.4532	hsa-miR-106b
hsa-mir-106bNo1	uc.88+	-0.4517	hsa-miR-106b
hsa-mir-106bNo1	uc.352+	-0.4478	hsa-miR-106b
hsa-mir-107No1	uc.282+A	-0.665	hsa-miR-107
hsa-mir-107No1	uc.346+A	-0.6312	hsa-miR-107
hsa-mir-107-prec-10	uc.282+A	-0.6273	hsa-miR-107
hsa-mir-107No1	uc.283+A	-0.616	hsa-miR-107
hsa-mir-107-prec-10	uc.346+A	-0.6094	hsa-miR-107
hsa-mir-107-prec-10	uc.283+A	-0.5694	hsa-miR-107
hsa-mir-107No1	uc.325+	-0.551	hsa-miR-107
hsa-mir-107-prec-10	uc.325+	-0.5381	hsa-miR-107
hsa-mir-107No1	uc.339+	-0.5338	hsa-miR-107
hsa-mir-107-prec-10	uc.142+A	-0.5334	hsa-miR-107
hsa-mir-107No1	uc.34+A	-0.5257	hsa-miR-107
hsa-mir-107-prec-10	uc.339+	-0.5191	hsa-miR-107
hsa-mir-107No1	uc.478+A	-0.5132	hsa-miR-107
hsa-mir-107No1	uc.84+A	-0.5122	hsa-miR-107
hsa-mir-107No1	uc.398+	-0.5097	hsa-miR-107
hsa-mir-107No1	uc.465+A	-0.5005	hsa-miR-107
hsa-mir-107-prec-10	uc.84+A	-0.4869	hsa-miR-107

Figure 18

Calin GA

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-107-prec-10	uc.34+A	-0.4807	hsa-miR-107
hsa-mir-107No1	uc.352+	-0.479	hsa-miR-107
hsa-mir-107-prec-10	uc.478+A	-0.4774	hsa-miR-107
hsa-mir-107-prec-10	uc.204+A	-0.4658	hsa-miR-107
hsa-mir-107No1	uc.142+A	-0.4655	hsa-miR-107
hsa-mir-107No1	uc.269+A	-0.4565	hsa-miR-107
hsa-mir-107-prec-10	uc.48+A	-0.4559	hsa-miR-107
hsa-mir-107No1	uc.48+A	-0.4535	hsa-miR-107
hsa-mir-122a-prec	uc.230+	-0.6636	hsa-miR-122a
hsa-mir-122a-prec	uc.366+	-0.6077	hsa-miR-122a
hsa-mir-122a-prec	uc.192+	-0.6018	hsa-miR-122a
hsa-mir-122a-prec	uc.389+	-0.5285	hsa-miR-122a
hsa-mir-122a-prec	uc.345+A	-0.5157	hsa-miR-122a
hsa-mir-122a-prec	uc.125+A	-0.4675	hsa-miR-122a
hsa-mir-122a-prec	uc.73+	-0.4493	hsa-miR-122a
hsa-mir-122a-prec	uc.181+A	-0.448	hsa-miR-122a
hsa-mir-122a-prec	uc.310+A	-0.448	hsa-miR-122a
hsa-mir-128a-precNo1	uc.420+	-0.5341	hsa-mir-128a
hsa-mir-128a-precNo1	uc.299+A	-0.5232	hsa-mir-128a
hsa-mir-128a-precNo1	uc.134+	-0.5068	hsa-mir-128a
hsa-mir-128a-precNo1	uc.33+A	-0.4685	hsa-mir-128a
hsa-mir-129-precNo1	uc.466+A	-0.479	hsa-mir-129
hsa-mir-130bNo2	uc.8+	-0.6653	hsa-mir-130b
hsa-mir-130bNo2	uc.420+	-0.605	hsa-mir-130b
hsa-mir-130bNo2	uc.189+	-0.5375	hsa-mir-130b
hsa-mir-130bNo2	uc.33+	-0.5232	hsa-mir-130b
hsa-mir-130bNo2	uc.388+A	-0.5015	hsa-mir-130b
hsa-mir-130bNo1	uc.48+A	-0.4947	hsa-miR-130b
hsa-mir-130bNo2	uc.468+	-0.4887	hsa-mir-130b
hsa-mir-130bNo2	uc.229+	-0.4844	hsa-mir-130b
hsa-mir-130bNo2	uc.299+A	-0.4723	hsa-mir-130b
hsa-mir-130bNo2	uc.466+A	-0.4686	hsa-mir-130b
hsa-mir-130bNo1	uc.167+	-0.4682	hsa-miR-130b
hsa-mir-130bNo1	uc.142+A	-0.4661	hsa-miR-130b
hsa-mir-130bNo2	uc.177+	-0.4529	hsa-mir-130b
hsa-mir-130bNo1	uc.84+A	-0.4503	hsa-miR-130b
hsa-mir-130bNo2	uc.134+	-0.4479	hsa-mir-130b
hsa-mir-136-precNo2	uc.378+	-0.4528	hsa-miR-136
hsa-mir-138-2-prec	uc.20+	-0.5607	hsa-miR-138
hsa-mir-138-2-prec	uc.477+	-0.5512	hsa-miR-138
hsa-mir-138-2-prec	uc.20+A	-0.5388	hsa-miR-138
hsa-mir-138-2-prec	uc.362+	-0.4761	hsa-miR-138
hsa-mir-138-2-prec	uc.263+	-0.469	hsa-miR-138
hsa-mir-140No2	uc.465+A	-0.575	hsa-mir-140
hsa-mir-140No2	uc.299+A	-0.5569	hsa-mir-140
hsa-mir-140No2	uc.388+A	-0.5525	hsa-mir-140
hsa-mir-140No2	uc.151+A	-0.5378	hsa-mir-140
hsa-mir-140No2	uc.18+	-0.5346	hsa-mir-140
hsa-mir-140No2	uc.420+	-0.5319	hsa-mir-140
hsa-mir-140No2	uc.213+	-0.5249	hsa-mir-140
hsa-mir-140No2	uc.153+A	-0.5216	hsa-mir-140
hsa-mir-140No2	uc.33+A	-0.519	hsa-mir-140
hsa-mir-140No2	uc.327+A	-0.5149	hsa-mir-140
hsa-mir-140No2	uc.172+A	-0.5107	hsa-mir-140
hsa-mir-140No2	uc.151+	-0.5103	hsa-mir-140
hsa-mir-140No2	uc.325+	-0.5074	hsa-mir-140
hsa-mir-140No2	uc.77+	-0.499	hsa-mir-140
hsa-mir-140No2	uc.173+	-0.4987	hsa-mir-140
hsa-mir-140No2	uc.285+	-0.4973	hsa-mir-140
hsa-mir-140No2	uc.117+	-0.4921	hsa-mir-140
hsa-mir-140No2	uc.128+A	-0.4741	hsa-mir-140
hsa-mir-140No2	uc.468+	-0.4735	hsa-mir-140
hsa-mir-140No2	uc.234+	-0.4726	hsa-mir-140
hsa-mir-140No2	uc.462+A	-0.4707	hsa-mir-140
hsa-mir-140No2	uc.478+A	-0.4692	hsa-mir-140
hsa-mir-140No2	uc.106+	-0.4635	hsa-mir-140
hsa-mir-140No2	uc.354+A	-0.4628	hsa-mir-140
hsa-mir-140No2	uc.346+	-0.4618	hsa-mir-140
hsa-mir-140No2	uc.339+	-0.4597	hsa-mir-140
hsa-mir-140No2	uc.427+	-0.4596	hsa-mir-140
hsa-mir-140No2	uc.44+A	-0.4561	hsa-mir-140
hsa-mir-140No2	uc.8+	-0.4517	hsa-mir-140
hsa-mir-140No2	uc.177+	-0.4477	hsa-mir-140
hsa-mir-142-prec	uc.420+	-0.8325	hsa-miR-142-5p
hsa-mir-142-prec	uc.33+A	-0.8101	hsa-miR-142-5p
hsa-mir-142-prec	uc.462+A	-0.7796	hsa-miR-142-5p
hsa-mir-142-prec	uc.189+	-0.775	hsa-miR-142-5p
hsa-mir-142-prec	uc.106+	-0.7498	hsa-miR-142-5p
hsa-mir-142-prec	uc.383+	-0.7397	hsa-miR-142-5p
hsa-mir-142-prec	uc.456+A	-0.7304	hsa-miR-142-5p
hsa-mir-142-prec	uc.153+A	-0.7288	hsa-miR-142-5p
hsa-mir-142-prec	uc.73+A	-0.7259	hsa-miR-142-5p
hsa-mir-142-prec	uc.468+	-0.7169	hsa-miR-142-5p
hsa-mir-142-prec	uc.275+	-0.7114	hsa-miR-142-5p

Figure 18

Calin GA   6

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-142-prec	uc.354+A	-0.7079	hsa-miR-142-5p
hsa-mir-142-prec	uc.378+A	-0.7073	hsa-miR-142-5p
hsa-mir-142-prec	uc.190+A	-0.7067	hsa-miR-142-5p
hsa-mir-142-prec	uc.33+	-0.701	hsa-miR-142-5p
hsa-mir-142-prec	uc.412+A	-0.6934	hsa-miR-142-5p
hsa-mir-142-prec	uc.234+	-0.688	hsa-miR-142-5p
hsa-mir-142-prec	uc.299+A	-0.6812	hsa-miR-142-5p
hsa-mir-142-prec	uc.88+	-0.6807	hsa-miR-142-5p
hsa-mir-142-prec	uc.473+A	-0.6767	hsa-miR-142-5p
hsa-mir-142-prec	uc.153+	-0.6735	hsa-miR-142-5p
hsa-mir-142-prec	uc.8+	-0.6726	hsa-miR-142-5p
hsa-mir-142-prec	uc.217+A	-0.6688	hsa-miR-142-5p
hsa-mir-142-prec	uc.477+A	-0.6672	hsa-miR-142-5p
hsa-mir-142-prec	uc.18+	-0.6586	hsa-miR-142-5p
hsa-mir-142-prec	uc.388+	-0.6484	hsa-miR-142-5p
hsa-mir-142-prec	uc.44+A	-0.6436	hsa-miR-142-5p
hsa-mir-142-prec	uc.287+A	-0.643	hsa-miR-142-5p
hsa-mir-142-prec	uc.378+	-0.6406	hsa-miR-142-5p
hsa-mir-142-prec	uc.388+A	-0.6403	hsa-miR-142-5p
hsa-mir-142-prec	uc.427+	-0.6392	hsa-miR-142-5p
hsa-mir-142-prec	uc.20+	-0.6283	hsa-miR-142-5p
hsa-mir-142-prec	uc.263+	-0.6193	hsa-miR-142-5p
hsa-mir-142-prec	uc.285+	-0.614	hsa-miR-142-5p
hsa-mir-142-prec	uc.213+	-0.6089	hsa-miR-142-5p
hsa-mir-142-prec	uc.217+	-0.6062	hsa-miR-142-5p
hsa-mir-142-prec	uc.43+	-0.6049	hsa-miR-142-5p
hsa-mir-142-prec	uc.445+A	-0.6041	hsa-miR-142-5p
hsa-mir-142-prec	uc.468+A	-0.5924	hsa-miR-142-5p
hsa-mir-142-prec	uc.20+A	-0.5842	hsa-miR-142-5p
hsa-mir-142-prec	uc.327+A	-0.5712	hsa-miR-142-5p
hsa-mir-142-prec	uc.456+	-0.5614	hsa-miR-142-5p
hsa-mir-142-prec	uc.151+A	-0.5488	hsa-miR-142-5p
hsa-mir-142-prec	uc.170+	-0.5193	hsa-miR-142-5p
hsa-mir-142-prec	uc.448+A	-0.519	hsa-miR-142-5p
hsa-mir-142-prec	uc.412+	-0.5176	hsa-miR-142-5p
hsa-mir-142-prec	uc.10+	-0.5173	hsa-miR-142-5p
hsa-mir-142-prec	uc.331+A	-0.5152	hsa-miR-142-5p
hsa-mir-142-prec	uc.420+A	-0.5145	hsa-miR-142-5p
hsa-mir-142-prec	uc.448+	-0.5103	hsa-miR-142-5p
hsa-mir-142-prec	uc.338+	-0.5096	hsa-miR-142-5p
hsa-mir-142-prec	uc.190+	-0.5058	hsa-miR-142-5p
hsa-mir-142-prec	uc.182+	-0.5	hsa-miR-142-5p
hsa-mir-142-prec	uc.362+A	-0.4983	hsa-miR-142-5p
hsa-mir-142-prec	uc.263+A	-0.4789	hsa-miR-142-5p
hsa-mir-142-prec	uc.200+	-0.4748	hsa-miR-142-5p
hsa-mir-142-prec	uc.177+	-0.4718	hsa-miR-142-5p
hsa-mir-142-prec	uc.173+	-0.4716	hsa-miR-142-5p
hsa-mir-142-prec	uc.183+	-0.4633	hsa-miR-142-5p
hsa-mir-142-prec	uc.134+	-0.4615	hsa-miR-142-5p
hsa-mir-142-prec	uc.128+A	-0.45	hsa-miR-142-5p
hsa-mir-142-prec	uc.151+	-0.4493	hsa-miR-142-5p
hsa-mir-145-prec	uc.223+A	-0.5491	hsa-miR-145
hsa-mir-145-prec	uc.278+A	-0.5047	hsa-miR-145
hsa-mir-145-prec	uc.291+	-0.4904	hsa-miR-145
hsa-mir-145-prec	uc.90+A	-0.4838	hsa-miR-145
hsa-mir-145-prec	uc.298+	-0.4764	hsa-miR-145
hsa-mir-146-prec	uc.478+A	-0.4815	hsa-miR-146a
hsa-mir-146-prec	uc.160+	-0.4667	hsa-miR-146a
hsa-mir-146-prec	uc.325+	-0.4649	hsa-miR-146a
hsa-mir-148-prec	uc.145+A	-0.5377	hsa-miR-148a
hsa-mir-148-prec	uc.478+A	-0.4857	hsa-miR-148a
hsa-mir-148-prec	uc.475+	-0.4619	hsa-miR-148a
hsa-mir-149-prec	uc.8+	-0.5258	hsa-miR-149
hsa-mir-149-prec	uc.299+A	-0.466	hsa-miR-149
hsa-mir-149-prec	uc.420+	-0.4481	hsa-miR-149
hsa-mir-150-prec	uc.8+	-0.7279	hsa-miR-150
hsa-mir-150-prec	uc.466+A	-0.657	hsa-miR-150
hsa-mir-150-prec	uc.189+	-0.6232	hsa-miR-150
hsa-mir-150-prec	uc.420+	-0.577	hsa-miR-150
hsa-mir-150-prec	uc.299+A	-0.5766	hsa-miR-150
hsa-mir-150-prec	uc.468+	-0.5347	hsa-miR-150
hsa-mir-150-prec	uc.134+A	-0.5124	hsa-miR-150
hsa-mir-150-prec	uc.190+A	-0.4915	hsa-miR-150
hsa-mir-150-prec	uc.73+A	-0.4885	hsa-miR-150
hsa-mir-150-prec	uc.412+A	-0.4814	hsa-miR-150
hsa-mir-150-prec	uc.43+	-0.477	hsa-miR-150
hsa-mir-150-prec	uc.412+	-0.4661	hsa-miR-150
hsa-mir-150-prec	uc.177+	-0.4644	hsa-miR-150
hsa-mir-150-prec	uc.229+	-0.4602	hsa-miR-150
hsa-mir-150-prec	uc.462+A	-0.4546	hsa-miR-150
hsa-mir-150-prec	uc.456+A	-0.4474	hsa-miR-150
hsa-mir-151-prec	uc.412+	-0.5811	hsa-miR-151
hsa-mir-151-prec	uc.189+	-0.5673	hsa-miR-151
hsa-mir-151-prec	uc.8+	-0.5411	hsa-miR-151

Figure 18

Calin GA   7

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-151-prec	uc.299+A	-0.5331	hsa-miR-151
hsa-mir-151-prec	uc.338+	-0.4979	hsa-miR-151
hsa-mir-151-prec	uc.73+A	-0.4795	hsa-miR-151
hsa-mir-151-prec	uc.477+A	-0.471	hsa-miR-151
hsa-mir-151-prec	uc.134+A	-0.467	hsa-miR-151
hsa-mir-151-prec	uc.420+	-0.4534	hsa-miR-151
hsa-mir-152-precNo1	uc.229+	-0.7536	hsa-miR-152
hsa-mir-152-precNo1	uc.466+A	-0.734	hsa-miR-152
hsa-mir-152-precNo1	uc.349+	-0.7159	hsa-miR-152
hsa-mir-152-precNo1	uc.177+	-0.7128	hsa-miR-152
hsa-mir-152-precNo1	uc.262+A	-0.6541	hsa-miR-152
hsa-mir-152-precNo1	uc.278+	-0.6345	hsa-miR-152
hsa-mir-152-precNo1	uc.8+	-0.62	hsa-miR-152
hsa-mir-152-precNo1	uc.134+A	-0.6118	hsa-miR-152
hsa-mir-152-precNo2	uc.388+	-0.5947	hsa-mir-152
hsa-mir-152-precNo1	uc.346+	-0.5874	hsa-miR-152
hsa-mir-152-precNo2	uc.468+A	-0.5752	hsa-mir-152
hsa-mir-152-precNo1	uc.128+A	-0.5626	hsa-miR-152
hsa-mir-152-precNo1	uc.426+	-0.5546	hsa-miR-152
hsa-mir-152-precNo1	uc.462+	-0.5515	hsa-miR-152
hsa-mir-152-precNo2	uc.473+A	-0.5506	hsa-mir-152
hsa-mir-152-precNo1	uc.183+	-0.5492	hsa-miR-152
hsa-mir-152-precNo1	uc.172+A	-0.5416	hsa-miR-152
hsa-mir-152-precNo1	uc.151+	-0.5342	hsa-miR-152
hsa-mir-152-precNo2	uc.477+	-0.5269	hsa-mir-152
hsa-mir-152-precNo2	uc.310+	-0.5167	hsa-mir-152
hsa-mir-152-precNo1	uc.77+	-0.5107	hsa-miR-152
hsa-mir-152-precNo1	uc.204+	-0.5101	hsa-miR-152
hsa-mir-152-precNo2	uc.18+	-0.5089	hsa-mir-152
hsa-mir-152-precNo2	uc.20+A	-0.5056	hsa-mir-152
hsa-mir-152-precNo2	uc.20+	-0.5038	hsa-mir-152
hsa-mir-152-precNo2	uc.263+	-0.4976	hsa-mir-152
hsa-mir-152-precNo1	uc.186+A	-0.4883	hsa-miR-152
hsa-mir-152-precNo2	uc.153+	-0.4869	hsa-mir-152
hsa-mir-152-precNo1	uc.136+	-0.485	hsa-miR-152
hsa-mir-152-precNo2	uc.362+	-0.4786	hsa-mir-152
hsa-mir-152-precNo1	uc.165+	-0.4775	hsa-miR-152
hsa-mir-152-precNo1	uc.134+	-0.4751	hsa-miR-152
hsa-mir-152-precNo2	uc.445+A	-0.475	hsa-mir-152
hsa-mir-152-precNo1	uc.73+	-0.4741	hsa-miR-152
hsa-mir-152-precNo2	uc.106+	-0.4678	hsa-mir-152
hsa-mir-152-precNo1	uc.420+A	-0.4643	hsa-miR-152
hsa-mir-152-precNo1	uc.465+A	-0.4641	hsa-miR-152
hsa-mir-152-precNo2	uc.88+	-0.4619	hsa-mir-152
hsa-mir-152-precNo1	uc.139+	-0.4518	hsa-miR-152
hsa-mir-152-precNo2	uc.63+	-0.4495	hsa-mir-152
hsa-mir-153-1-prec1	uc.466+A	-0.7389	hsa-miR-153
hsa-mir-153-1-prec1	uc.229+	-0.7232	hsa-miR-153
hsa-mir-153-1-prec1	uc.349+	-0.7215	hsa-miR-153
hsa-mir-153-1-prec1	uc.177+	-0.6679	hsa-miR-153
hsa-mir-153-1-prec1	uc.262+A	-0.6193	hsa-miR-153
hsa-mir-153-1-prec1	uc.426+	-0.605	hsa-miR-153
hsa-mir-153-1-prec1	uc.278+	-0.5817	hsa-miR-153
hsa-mir-153-1-prec1	uc.8+	-0.5706	hsa-miR-153
hsa-mir-153-1-prec1	uc.73+	-0.5675	hsa-miR-153
hsa-mir-153-1-prec1	uc.346+	-0.5664	hsa-miR-153
hsa-mir-153-1-prec1	uc.136+	-0.5601	hsa-miR-153
hsa-mir-153-1-prec1	uc.204+	-0.5479	hsa-miR-153
hsa-mir-153-1-prec1	uc.134+A	-0.5266	hsa-miR-153
hsa-mir-153-1-prec1	uc.462+	-0.5212	hsa-miR-153
hsa-mir-153-1-prec1	uc.172+A	-0.5128	hsa-miR-153
hsa-mir-153-1-prec1	uc.165+	-0.5083	hsa-miR-153
hsa-mir-153-1-prec1	uc.128+A	-0.4974	hsa-miR-153
hsa-mir-153-1-prec1	uc.77+	-0.4872	hsa-miR-153
hsa-mir-153-1-prec1	uc.483+	-0.4773	hsa-miR-153
hsa-mir-155-prec	uc.282+A	-0.6215	hsa-miR-155
hsa-mir-155-prec	uc.283+A	-0.6176	hsa-miR-155
hsa-mir-155-prec	uc.346+A	-0.528	hsa-miR-155
hsa-mir-155-prec	uc.465+A	-0.525	hsa-miR-155
hsa-mir-155-prec	uc.84+A	-0.4589	hsa-miR-155
hsa-mir-15aNo1	uc.420+	-0.7206	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.420+	-0.7013	hsa-miR-15a
hsa-mir-15aNo1	uc.285+	-0.6703	hsa-miR-15a
hsa-mir-15aNo1	uc.33+A	-0.6354	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.285+	-0.6268	hsa-miR-15a
hsa-mir-15aNo1	uc.151+	-0.6262	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.327+A	-0.612	hsa-miR-15a
hsa-mir-15aNo1	uc.8+	-0.604	hsa-miR-15a
hsa-mir-15aNo1	uc.327+A	-0.6035	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.462+A	-0.601	hsa-miR-15a
hsa-mir-15aNo1	uc.262+A	-0.586	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.78+	-0.5824	hsa-miR-15a
hsa-mir-15aNo1	uc.189+	-0.582	hsa-miR-15a
hsa-mir-15aNo1	uc.177+	-0.5817	hsa-miR-15a

Figure 18

Calin GA   8

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-015a-2-precNo1	uc.8+	-0.58	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.427+	-0.5784	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.73+A	-0.5784	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.44+A	-0.5756	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.33+A	-0.5754	hsa-miR-15a
hsa-mir-15aNo1	uc.465+A	-0.571	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.189+	-0.5684	hsa-miR-15a
hsa-mir-15aNo1	uc.172+A	-0.5602	hsa-miR-15a
hsa-mir-15aNo1	uc.44+A	-0.5494	hsa-miR-15a
hsa-mir-15aNo1	uc.346+	-0.5457	hsa-miR-15a
hsa-mir-15aNo1	uc.160+	-0.5437	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.299+A	-0.5333	hsa-miR-15a
hsa-mir-15aNo1	uc.153+A	-0.5317	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.456+A	-0.529	hsa-miR-15a
hsa-mir-15aNo1	uc.462+A	-0.527	hsa-miR-15a
hsa-mir-15aNo1	uc.78+	-0.5231	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.151+	-0.5195	hsa-miR-15a
hsa-mir-15aNo1	uc.183+	-0.5163	hsa-miR-15a
hsa-mir-15aNo1	uc.388+A	-0.5151	hsa-miR-15a
hsa-mir-15aNo1	uc.299+A	-0.5148	hsa-miR-15a
hsa-mir-15aNo1	uc.420+A	-0.5139	hsa-miR-15a
hsa-mir-15aNo1	uc.427+	-0.5125	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.153+A	-0.5114	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.378+A	-0.5087	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.354+A	-0.5078	hsa-miR-15a
hsa-mir-15aNo1	uc.234+	-0.5078	hsa-miR-15a
hsa-mir-15aNo1	uc.77+	-0.5067	hsa-miR-15a
hsa-mir-15aNo1	uc.354+A	-0.5051	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.161+A	-0.5041	hsa-miR-15a
hsa-mir-15aNo1	uc.33+	-0.5038	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.338+	-0.5031	hsa-miR-15a
hsa-mir-15aNo1	uc.412+A	-0.5026	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.167+	-0.5	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.412+A	-0.4977	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.234+	-0.4949	hsa-miR-15a
hsa-mir-15aNo1	uc.456+A	-0.4865	hsa-miR-15a
hsa-mir-15aNo1	uc.173+	-0.4856	hsa-miR-15a
hsa-mir-15aNo1	uc.128+A	-0.4826	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.456+	-0.4819	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.477+A	-0.477	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.331+A	-0.4758	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.160+	-0.4755	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.190+A	-0.475	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.217+A	-0.4722	hsa-miR-15a
hsa-mir-15aNo1	uc.73+A	-0.4695	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.213+	-0.4641	hsa-miR-15a
hsa-mir-15aNo1	uc.331+A	-0.4633	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.478+A	-0.4612	hsa-miR-15a
hsa-mir-15aNo1	uc.106+	-0.4601	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.262+A	-0.4597	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.465+A	-0.4592	hsa-miR-15a
hsa-mir-15aNo1	uc.134+	-0.4567	hsa-miR-15a
hsa-mir-15aNo1	uc.213+	-0.4553	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.378+	-0.4546	hsa-miR-15a
hsa-mir-15aNo1	uc.151+A	-0.45	hsa-miR-15a
hsa-mir-015a-2-precNo1	uc.33+	-0.4495	hsa-miR-15a
hsa-mir-15aNo1	uc.217+A	-0.4481	hsa-miR-15a
hsa-mir-15aNo1	uc.378+A	-0.4475	hsa-miR-15a
hsa-mir-015b-precNo1	uc.420+	-0.7727	hsa-miR-15b
hsa-mir-015b-precNo1	uc.462+A	-0.7277	hsa-miR-15b
hsa-mir-015b-precNo1	uc.189+	-0.7125	hsa-miR-15b
hsa-mir-015b-precNo1	uc.73+A	-0.6877	hsa-miR-15b
hsa-mir-015b-precNo1	uc.338+	-0.6657	hsa-miR-15b
hsa-mir-015b-precNo1	uc.78+	-0.6637	hsa-miR-15b
hsa-mir-015b-precNo1	uc.44+A	-0.6532	hsa-miR-15b
hsa-mir-015b-precNo1	uc.299+A	-0.646	hsa-miR-15b
hsa-mir-015b-precNo1	uc.285+	-0.6458	hsa-miR-15b
hsa-mir-015b-precNo1	uc.412+	-0.6146	hsa-miR-15b
hsa-mir-015b-precNo1	uc.8+	-0.6097	hsa-miR-15b
hsa-mir-015b-precNo1	uc.331+A	-0.6019	hsa-miR-15b
hsa-mir-015b-precNo1	uc.456+	-0.5974	hsa-miR-15b
hsa-mir-015b-precNo1	uc.477+A	-0.5942	hsa-miR-15b
hsa-mir-015b-precNo1	uc.378+	-0.591	hsa-miR-15b
hsa-mir-015b-precNo1	uc.378+A	-0.5734	hsa-miR-15b
hsa-mir-015b-precNo1	uc.427+	-0.5729	hsa-miR-15b
hsa-mir-015b-precNo1	uc.33+A	-0.5723	hsa-miR-15b
hsa-mir-015b-precNo1	uc.327+A	-0.5714	hsa-miR-15b
hsa-mir-015b-precNo1	uc.217+	-0.5697	hsa-miR-15b
hsa-mir-015b-precNo1	uc.456+A	-0.5693	hsa-miR-15b
hsa-mir-015b-precNo1	uc.412+A	-0.5626	hsa-miR-15b
hsa-mir-015b-precNo1	uc.161+A	-0.5595	hsa-miR-15b
hsa-mir-015b-precNo1	uc.88+	-0.5592	hsa-miR-15b
hsa-mir-015b-precNo1	uc.275+	-0.5508	hsa-miR-15b
hsa-mir-015b-precNo1	uc.153+	-0.5415	hsa-miR-15b

Figure 18

Calin GA

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miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-015b-precNo1	uc.190+A	-0.5337	hsa-miR-15b
hsa-mir-015b-precNo1	uc.234+	-0.5316	hsa-miR-15b
hsa-mir-015b-precNo1	uc.151+	-0.5265	hsa-miR-15b
hsa-mir-015b-precNo1	uc.167+	-0.5187	hsa-miR-15b
hsa-mir-015b-precNo1	uc.263+	-0.5174	hsa-miR-15b
hsa-mir-015b-precNo1	uc.473+A	-0.5071	hsa-miR-15b
hsa-mir-015b-precNo1	uc.354+A	-0.5015	hsa-miR-15b
hsa-mir-015b-precNo1	uc.145+A	-0.4998	hsa-miR-15b
hsa-mir-015b-precNo1	uc.153+A	-0.499	hsa-miR-15b
hsa-mir-015b-precNo1	uc.448+A	-0.4979	hsa-miR-15b
hsa-mir-015b-precNo1	uc.170+	-0.497	hsa-miR-15b
hsa-mir-015b-precNo1	uc.287+A	-0.4894	hsa-miR-15b
hsa-mir-015b-precNo1	uc.448+	-0.482	hsa-miR-15b
hsa-mir-015b-precNo1	uc.106+	-0.4731	hsa-miR-15b
hsa-mir-015b-precNo1	uc.33+	-0.4708	hsa-miR-15b
hsa-mir-015b-precNo1	uc.388+	-0.4693	hsa-miR-15b
hsa-mir-015b-precNo1	uc.217+A	-0.4608	hsa-miR-15b
hsa-mir-015b-precNo1	uc.213+	-0.4576	hsa-miR-15b
hsa-mir-015b-precNo1	uc.134+	-0.4548	hsa-miR-15b
hsa-mir-015b-precNo1	uc.88+A	-0.4513	hsa-miR-15b
hsa-mir-16-2No1	uc.420+	-0.7565	hsa-miR-16
hsa-mir-016b-chr3	uc.420+	-0.741	hsa-miR-16
hsa-mir-16-1No1	uc.420+	-0.7116	hsa-miR-16
hsa-mir-016a-chr13	uc.420+	-0.7036	hsa-miR-16
hsa-mir-16-2No1	uc.8+	-0.6832	hsa-miR-16
hsa-mir-016a-chr13	uc.177+	-0.668	hsa-miR-16
hsa-mir-016b-chr3	uc.8+	-0.6536	hsa-miR-16
hsa-mir-016b-chr3	uc.151+	-0.636	hsa-miR-16
hsa-mir-016a-chr13	uc.8+	-0.6347	hsa-miR-16
hsa-mir-16-1No1	uc.8+	-0.6272	hsa-miR-16
hsa-mir-016b-chr3	uc.33+A	-0.6254	hsa-miR-16
hsa-mir-16-1No1	uc.33+A	-0.6236	hsa-miR-16
hsa-mir-16-2No1	uc.151+	-0.6215	hsa-miR-16
hsa-mir-16-2No1	uc.33+A	-0.6215	hsa-miR-16
hsa-mir-016a-chr13	uc.466+A	-0.6213	hsa-miR-16
hsa-mir-016a-chr13	uc.33+A	-0.613	hsa-miR-16
hsa-mir-16-2No1	uc.189+	-0.6116	hsa-miR-16
hsa-mir-016a-chr13	uc.151+	-0.6068	hsa-miR-16
hsa-mir-16-1No1	uc.189+	-0.6024	hsa-miR-16
hsa-mir-016b-chr3	uc.189+	-0.5978	hsa-miR-16
hsa-mir-16-1No1	uc.151+	-0.5912	hsa-miR-16
hsa-mir-16-1No1	uc.456+	-0.5902	hsa-miR-16
hsa-mir-16-1No1	uc.427+	-0.5896	hsa-miR-16
hsa-mir-16-1No1	uc.462+A	-0.5804	hsa-miR-16
hsa-mir-016a-chr13	uc.172+A	-0.5797	hsa-miR-16
hsa-mir-16-2No1	uc.177+	-0.5791	hsa-miR-16
hsa-mir-16-1No1	uc.456+A	-0.5694	hsa-miR-16
hsa-mir-16-1No1	uc.412+A	-0.5687	hsa-miR-16
hsa-mir-16-2No1	uc.412+A	-0.5627	hsa-miR-16
hsa-mir-16-2No1	uc.299+A	-0.5607	hsa-miR-16
hsa-mir-016a-chr13	uc.346+	-0.5605	hsa-miR-16
hsa-mir-16-2No1	uc.456+A	-0.5557	hsa-miR-16
hsa-mir-016a-chr13	uc.262+A	-0.555	hsa-miR-16
hsa-mir-16-2No1	uc.462+A	-0.5523	hsa-miR-16
hsa-mir-16-1No1	uc.299+A	-0.5521	hsa-miR-16
hsa-mir-016b-chr3	uc.177+	-0.551	hsa-miR-16
hsa-mir-016b-chr3	uc.299+A	-0.5477	hsa-miR-16
hsa-mir-016b-chr3	uc.412+A	-0.5468	hsa-miR-16
hsa-mir-16-1No1	uc.327+A	-0.546	hsa-miR-16
hsa-mir-016a-chr13	uc.285+	-0.5458	hsa-miR-16
hsa-mir-016b-chr3	uc.456+A	-0.5453	hsa-miR-16
hsa-mir-016b-chr3	uc.285+	-0.5431	hsa-miR-16
hsa-mir-16-2No1	uc.466+A	-0.5399	hsa-miR-16
hsa-mir-016b-chr3	uc.462+A	-0.5382	hsa-miR-16
hsa-mir-016a-chr13	uc.128+A	-0.5375	hsa-miR-16
hsa-mir-016a-chr13	uc.189+	-0.5355	hsa-miR-16
hsa-mir-16-2No1	uc.354+A	-0.5236	hsa-miR-16
hsa-mir-16-1No1	uc.190+A	-0.523	hsa-miR-16
hsa-mir-16-1No1	uc.383+	-0.5206	hsa-miR-16
hsa-mir-16-2No1	uc.285+	-0.5192	hsa-miR-16
hsa-mir-016b-chr3	uc.172+A	-0.5183	hsa-miR-16
hsa-mir-16-1No1	uc.378+	-0.5182	hsa-miR-16
hsa-mir-16-1No1	uc.78+	-0.5177	hsa-miR-16
hsa-mir-016a-chr13	uc.77+	-0.5143	hsa-miR-16
hsa-mir-16-2No1	uc.420+A	-0.5135	hsa-miR-16
hsa-mir-16-1No1	uc.234+	-0.5117	hsa-miR-16
hsa-mir-16-2No1	uc.106+	-0.5098	hsa-miR-16
hsa-mir-16-1No1	uc.378+A	-0.5074	hsa-miR-16
hsa-mir-16-2No1	uc.173+	-0.5068	hsa-miR-16
hsa-mir-016b-chr3	uc.173+	-0.5064	hsa-miR-16
hsa-mir-16-2No1	uc.10+	-0.5059	hsa-miR-16
hsa-mir-16-2No1	uc.172+A	-0.5049	hsa-miR-16
hsa-mir-16-2No1	uc.234+	-0.5038	hsa-miR-16
hsa-mir-16-2No1	uc.153+A	-0.5036	hsa-miR-16

Figure 18

Calin GA

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miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-16-2No1	uc.190+A	-0.5022	hsa-miR-16
hsa-mir-16-1No1	uc.44+A	-0.5005	hsa-miR-16
hsa-mir-016b-chr3	uc.466+A	-0.4986	hsa-miR-16
hsa-mir-016b-chr3	uc.78+	-0.4982	hsa-miR-16
hsa-mir-16-1No1	uc.73+A	-0.4975	hsa-miR-16
hsa-mir-16-1No1	uc.20+	-0.4966	hsa-miR-16
hsa-mir-16-1No1	uc.477+A	-0.4958	hsa-miR-16
hsa-mir-16-1No1	uc.106+	-0.495	hsa-miR-16
hsa-mir-016b-chr3	uc.354+A	-0.4944	hsa-miR-16
hsa-mir-016b-chr3	uc.427+	-0.494	hsa-miR-16
hsa-mir-016a-chr13	uc.173+	-0.4929	hsa-miR-16
hsa-mir-016b-chr3	uc.234+	-0.4927	hsa-miR-16
hsa-mir-016b-chr3	uc.456+	-0.4908	hsa-miR-16
hsa-mir-16-1No1	uc.354+A	-0.4897	hsa-miR-16
hsa-mir-016a-chr13	uc.229+	-0.4894	hsa-miR-16
hsa-mir-016a-chr13	uc.420+A	-0.4894	hsa-miR-16
hsa-mir-016b-chr3	uc.420+A	-0.489	hsa-miR-16
hsa-mir-16-1No1	uc.153+A	-0.4884	hsa-miR-16
hsa-mir-016b-chr3	uc.190+A	-0.4881	hsa-miR-16
hsa-mir-16-1No1	uc.285+	-0.4871	hsa-miR-16
hsa-mir-016b-chr3	uc.327+A	-0.4863	hsa-miR-16
hsa-mir-016b-chr3	uc.10+	-0.4856	hsa-miR-16
hsa-mir-016a-chr13	uc.299+A	-0.484	hsa-miR-16
hsa-mir-16-1No1	uc.412+	-0.4833	hsa-miR-16
hsa-mir-16-1No1	uc.153+	-0.4824	hsa-miR-16
hsa-mir-16-2No1	uc.33+	-0.4824	hsa-miR-16
hsa-mir-16-1No1	uc.173+	-0.4805	hsa-miR-16
hsa-mir-16-1No1	uc.263+	-0.4786	hsa-miR-16
hsa-mir-16-1No1	uc.213+	-0.4774	hsa-miR-16
hsa-mir-016b-chr3	uc.106+	-0.4768	hsa-miR-16
hsa-mir-16-2No1	uc.262+A	-0.4756	hsa-miR-16
hsa-mir-16-2No1	uc.427+	-0.4749	hsa-miR-16
hsa-mir-016b-chr3	uc.153+A	-0.4736	hsa-miR-16
hsa-mir-16-2No1	uc.78+	-0.4717	hsa-miR-16
hsa-mir-16-1No1	uc.88+	-0.4711	hsa-miR-16
hsa-mir-16-1No1	uc.473+A	-0.4701	hsa-miR-16
hsa-mir-16-1No1	uc.18+	-0.4699	hsa-miR-16
hsa-mir-16-2No1	uc.128+A	-0.4694	hsa-miR-16
hsa-mir-16-1No1	uc.177+	-0.4686	hsa-miR-16
hsa-mir-16-2No1	uc.134+	-0.465	hsa-miR-16
hsa-mir-016b-chr3	uc.128+A	-0.4648	hsa-miR-16
hsa-mir-016b-chr3	uc.262+A	-0.4645	hsa-miR-16
hsa-mir-16-2No1	uc.378+A	-0.4637	hsa-miR-16
hsa-mir-16-2No1	uc.456+	-0.4627	hsa-miR-16
hsa-mir-16-1No1	uc.172+A	-0.4617	hsa-miR-16
hsa-mir-16-2No1	uc.182+	-0.4612	hsa-miR-16
hsa-mir-016b-chr3	uc.378+A	-0.4608	hsa-miR-16
hsa-mir-16-1No1	uc.275+	-0.4596	hsa-miR-16
hsa-mir-16-2No1	uc.327+A	-0.4587	hsa-miR-16
hsa-mir-16-2No1	uc.388+A	-0.458	hsa-miR-16
hsa-mir-16-2No1	uc.77+	-0.4571	hsa-miR-16
hsa-mir-16-1No1	uc.161+A	-0.4556	hsa-miR-16
hsa-mir-16-2No1	uc.161+A	-0.4556	hsa-miR-16
hsa-mir-016b-chr3	uc.44+A	-0.4512	hsa-miR-16
hsa-mir-016a-chr13	uc.465+A	-0.4509	hsa-miR-16
hsa-mir-16-1No1	uc.331+A	-0.4506	hsa-miR-16
hsa-mir-016a-chr13	uc.134+A	-0.4495	hsa-miR-16
hsa-mir-016a-chr13	uc.327+A	-0.4494	hsa-miR-16
hsa-mir-16-2No1	uc.18+	-0.4493	hsa-miR-16
hsa-mir-017-precNo1	uc.420+	-0.5884	hsa-miR-17-3p
hsa-mir-017-precNo1	uc.299+A	-0.5716	hsa-miR-17-3p
hsa-mir-017-precNo1	uc.462+A	-0.5506	hsa-miR-17-3p
hsa-mir-017-precNo1	uc.338+	-0.5454	hsa-miR-17-3p
hsa-mir-017-precNo1	uc.8+	-0.5347	hsa-miR-17-3p
hsa-mir-017-precNo1	uc.78+	-0.5153	hsa-miR-17-3p
hsa-mir-017-precNo1	uc.145+A	-0.4627	hsa-miR-17-3p
hsa-mir-017-precNo1	uc.412+	-0.4624	hsa-miR-17-3p
hsa-mir-017-precNo1	uc.73+A	-0.4577	hsa-miR-17-3p
hsa-mir-017-precNo1	uc.161+A	-0.451	hsa-miR-17-3p
hsa-mir-017-precNo1	uc.189+	-0.4488	hsa-miR-17-3p
hsa-mir-017-precNo2	uc.160+	-0.6241	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.48+A	-0.6134	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.478+A	-0.5866	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.167+	-0.5711	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.170+	-0.5611	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.448+A	-0.529	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.325+	-0.5271	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.427+	-0.5219	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.117+	-0.5114	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.153+A	-0.5091	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.282+A	-0.506	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.327+A	-0.501	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.283+A	-0.499	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.88+A	-0.4971	hsa-miR-17-5p

Figure 18

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miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-017-precNo2	uc.339+	-0.4912	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.263+	-0.4901	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.84+A	-0.4843	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.473+A	-0.4792	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.465+A	-0.4764	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.217+A	-0.4747	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.106+	-0.4741	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.200+	-0.4718	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.213+	-0.464	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.153+	-0.4632	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.448+	-0.4586	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.234+	-0.4565	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.88+	-0.4548	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.151+A	-0.4526	hsa-miR-17-5p
hsa-mir-017-precNo2	uc.269+A	-0.4498	hsa-miR-17-5p
hsa-mir-181a-precNo1	uc.95+	-0.6264	hsa-miR-181a
hsa-mir-181a-precNo1	uc.281+A	-0.6145	hsa-miR-181a
hsa-mir-181a-precNo1	uc.475+	-0.6131	hsa-miR-181a
hsa-mir-181a-precNo1	uc.142+A	-0.5892	hsa-miR-181a
hsa-mir-181a-precNo1	uc.88+A	-0.5668	hsa-miR-181a
hsa-mir-181a-precNo1	uc.159+A	-0.5604	hsa-miR-181a
hsa-mir-181a-precNo1	uc.299+	-0.5529	hsa-miR-181a
hsa-mir-181a-precNo1	uc.117+	-0.5251	hsa-miR-181a
hsa-mir-181a-precNo1	uc.200+	-0.5103	hsa-miR-181a
hsa-mir-181a-precNo1	uc.84+A	-0.5008	hsa-miR-181a
hsa-mir-181b-precNo1	uc.338+	-0.4732	hsa-miR-181a
hsa-mir-181b-precNo1	uc.427+	-0.4671	hsa-miR-181a
hsa-mir-181a-precNo1	uc.167+	-0.4658	hsa-miR-181a
hsa-mir-181a-precNo1	uc.473+	-0.4656	hsa-miR-181a
hsa-mir-181a-precNo1	uc.73+A	-0.4654	hsa-miR-181a
hsa-mir-181a-precNo1	uc.291+	-0.4629	hsa-miR-181a
hsa-mir-181a-precNo1	uc.448+A	-0.4598	hsa-miR-181a
hsa-mir-181a-precNo1	uc.448+	-0.4555	hsa-miR-181a
hsa-mir-181a-precNo1	uc.145+A	-0.4513	hsa-miR-181a
hsa-mir-181a-precNo1	uc.78+	-0.4495	hsa-miR-181a
hsa-mir-213-precNo1	uc.204+	-0.7109	hsa-miR-181b
hsa-mir-213-precNo1	uc.73+	-0.7034	hsa-miR-181b
hsa-mir-213-precNo1	uc.41+	-0.6853	hsa-miR-181b
hsa-mir-213-precNo1	uc.165+	-0.6522	hsa-miR-181b
hsa-mir-213-precNo1	uc.366+	-0.6408	hsa-miR-181b
hsa-mir-213-precNo1	uc.349+	-0.6308	hsa-miR-181b
hsa-mir-213-precNo1	uc.483+	-0.6172	hsa-miR-181b
hsa-mir-213-precNo1	uc.278+	-0.6149	hsa-miR-181b
hsa-mir-213-precNo1	uc.229+	-0.6035	hsa-miR-181b
hsa-mir-213-precNo1	uc.426+	-0.5906	hsa-miR-181b
hsa-mir-213-precNo1	uc.346+	-0.5627	hsa-miR-181b
hsa-mir-213-precNo1	uc.345+	-0.5573	hsa-miR-181b
hsa-mir-213-precNo1	uc.136+	-0.5534	hsa-miR-181b
hsa-mir-213-precNo1	uc.345+A	-0.5449	hsa-miR-181b
hsa-mir-181b-1No1	uc.44+A	-0.5289	hsa-miR-181b
hsa-mir-213-precNo1	uc.77+	-0.5244	hsa-miR-181b
hsa-mir-213-precNo1	uc.139+	-0.5213	hsa-miR-181b
hsa-mir-213-precNo1	uc.465+A	-0.5145	hsa-miR-181b
hsa-mir-181b-1No1	uc.338+	-0.5071	hsa-miR-181b
hsa-mir-213-precNo1	uc.192+	-0.4984	hsa-miR-181b
hsa-mir-213-precNo1	uc.125+A	-0.4954	hsa-miR-181b
hsa-mir-213-precNo1	uc.262+A	-0.495	hsa-miR-181b
hsa-mir-213-precNo1	uc.172+A	-0.4932	hsa-miR-181b
hsa-mir-181b-1No1	uc.299+A	-0.4913	hsa-miR-181b
hsa-mir-213-precNo1	uc.177+	-0.4888	hsa-miR-181b
hsa-mir-181b-1No1	uc.117+	-0.4882	hsa-miR-181b
hsa-mir-181b-2No1	uc.165+	-0.4866	hsa-miR-181b
hsa-mir-181b-2No1	uc.419+A	-0.4865	hsa-miR-181b
hsa-mir-213-precNo1	uc.466+A	-0.4847	hsa-miR-181b
hsa-mir-181b-1No1	uc.419+A	-0.4828	hsa-miR-181b
hsa-mir-213-precNo1	uc.346+A	-0.4822	hsa-miR-181b
hsa-mir-213-precNo1	uc.462+	-0.4723	hsa-miR-181b
hsa-mir-213-precNo1	uc.34+A	-0.4583	hsa-miR-181b
hsa-mir-181b-1No1	uc.285+	-0.4539	hsa-miR-181b
hsa-mir-213-precNo1	uc.339+	-0.4538	hsa-miR-181b
hsa-mir-213-precNo1	uc.24+A	-0.4518	hsa-miR-181b
hsa-mir-213-precNo1	uc.128+A	-0.4508	hsa-miR-181b
hsa-mir-213-precNo1	uc.389+	-0.4494	hsa-miR-181b
hsa-mir-213-precNo1	uc.31+	-0.4489	hsa-miR-181b
hsa-mir-184-precNo2	uc.366+	-0.6711	hsa-mir-184
hsa-mir-184-precNo2	uc.389+	-0.6576	hsa-mir-184
hsa-mir-184-precNo2	uc.192+	-0.6345	hsa-mir-184
hsa-mir-184-precNo2	uc.478+	-0.5881	hsa-mir-184
hsa-mir-184-precNo2	uc.346+A	-0.5472	hsa-mir-184
hsa-mir-184-precNo2	uc.24+A	-0.5016	hsa-mir-184
hsa-mir-184-precNo2	uc.341+A	-0.479	hsa-mir-184
hsa-mir-184-precNo2	uc.34+A	-0.4743	hsa-mir-184
hsa-mir-184-precNo2	uc.73+	-0.4685	hsa-mir-184
hsa-mir-184-precNo2	uc.310+A	-0.4608	hsa-mir-184

Figure 18

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miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-185-precNo2	uc.462+	-0.553	hsa-mir-185
hsa-mir-185-precNo2	uc.345+	-0.5482	hsa-mir-185
hsa-mir-185-precNo2	uc.204+	-0.5346	hsa-mir-185
hsa-mir-185-precNo2	uc.229+	-0.5101	hsa-mir-185
hsa-mir-185-precNo2	uc.131+	-0.4978	hsa-mir-185
hsa-mir-185-precNo2	uc.177+	-0.4969	hsa-mir-185
hsa-mir-185-precNo2	uc.346+	-0.4961	hsa-mir-185
hsa-mir-185-precNo2	uc.41+	-0.4817	hsa-mir-185
hsa-mir-185-precNo2	uc.349+	-0.4518	hsa-mir-185
hsa-mir-191-prec	uc.41+	-0.5999	hsa-miR-191
hsa-mir-191-prec	uc.465+A	-0.5892	hsa-miR-191
hsa-mir-191-prec	uc.142+	-0.4801	hsa-miR-191
hsa-mir-191-prec	uc.73+	-0.4703	hsa-miR-191
hsa-mir-191-prec	uc.282+A	-0.4678	hsa-mir-191
hsa-mir-191-prec	uc.241+A	-0.4531	hsa-miR-191
hsa-mir-193-precNo2	uc.388+	-0.7732	hsa-mir-193a
hsa-mir-193-precNo2	uc.477+A	-0.7699	hsa-mir-193a
hsa-mir-193-precNo2	uc.287+A	-0.7676	hsa-mir-193a
hsa-mir-193-precNo2	uc.190+A	-0.7657	hsa-mir-193a
hsa-mir-193-precNo2	uc.20+A	-0.7459	hsa-mir-193a
hsa-mir-193-precNo2	uc.477+	-0.7449	hsa-mir-193a
hsa-mir-193-precNo2	uc.456+A	-0.7433	hsa-mir-193a
hsa-mir-193-precNo2	uc.20+	-0.7382	hsa-mir-193a
hsa-mir-193-precNo2	uc.378+	-0.7376	hsa-mir-193a
hsa-mir-193-precNo2	uc.468+A	-0.729	hsa-mir-193a
hsa-mir-193-precNo2	uc.378+A	-0.7006	hsa-mir-193a
hsa-mir-193-precNo2	uc.217+	-0.6952	hsa-mir-193a
hsa-mir-193-precNo2	uc.43+	-0.6917	hsa-mir-193a
hsa-mir-193-precNo2	uc.473+A	-0.6852	hsa-mir-193a
hsa-mir-193-precNo2	uc.362+	-0.6841	hsa-mir-193a
hsa-mir-193-precNo2	uc.354+A	-0.6795	hsa-mir-193a
hsa-mir-193-precNo2	uc.190+	-0.6704	hsa-mir-193a
hsa-mir-193-precNo2	uc.263+	-0.6594	hsa-mir-193a
hsa-mir-193-precNo2	uc.106+	-0.6571	hsa-mir-193a
hsa-mir-193-precNo2	uc.462+A	-0.6558	hsa-mir-193a
hsa-mir-193-precNo2	uc.448+A	-0.6482	hsa-mir-193a
hsa-mir-193-precNo2	uc.275+	-0.6458	hsa-mir-193a
hsa-mir-193-precNo2	uc.153+	-0.6408	hsa-mir-193a
hsa-mir-193-precNo2	uc.456+	-0.6334	hsa-mir-193a
hsa-mir-193-precNo2	uc.73+A	-0.6307	hsa-mir-193a
hsa-mir-193-precNo2	uc.362+A	-0.6287	hsa-mir-193a
hsa-mir-193-precNo2	uc.63+	-0.6281	hsa-mir-193a
hsa-mir-193-precNo2	uc.427+	-0.6069	hsa-mir-193a
hsa-mir-193-precNo2	uc.338+	-0.5983	hsa-mir-193a
hsa-mir-193-precNo2	uc.412+A	-0.5972	hsa-mir-193a
hsa-mir-193-precNo2	uc.448+	-0.5929	hsa-mir-193a
hsa-mir-193-precNo2	uc.153+A	-0.5863	hsa-mir-193a
hsa-mir-193-precNo2	uc.234+	-0.5721	hsa-mir-193a
hsa-mir-193-precNo2	uc.95+	-0.5709	hsa-mir-193a
hsa-mir-193-precNo2	uc.170+	-0.5703	hsa-mir-193a
hsa-mir-193-precNo2	uc.412+	-0.5652	hsa-mir-193a
hsa-mir-193-precNo2	uc.182+	-0.5558	hsa-mir-193a
hsa-mir-193-precNo2	uc.445+A	-0.5488	hsa-mir-193a
hsa-mir-193-precNo2	uc.200+	-0.5483	hsa-mir-193a
hsa-mir-193-precNo2	uc.468+	-0.5482	hsa-mir-193a
hsa-mir-193-precNo2	uc.248+	-0.545	hsa-mir-193a
hsa-mir-193-precNo2	uc.383+	-0.5417	hsa-mir-193a
hsa-mir-193-precNo2	uc.88+	-0.5295	hsa-mir-193a
hsa-mir-193-precNo2	uc.88+A	-0.5215	hsa-mir-193a
hsa-mir-193-precNo2	uc.475+A	-0.5077	hsa-mir-193a
hsa-mir-193-precNo2	uc.44+A	-0.5047	hsa-mir-193a
hsa-mir-193-precNo2	uc.189+	-0.5009	hsa-mir-193a
hsa-mir-193-precNo2	uc.48+A	-0.4902	hsa-mir-193a
hsa-mir-193-precNo2	uc.159+A	-0.4807	hsa-mir-193a
hsa-mir-193-precNo2	uc.217+A	-0.479	hsa-mir-193a
hsa-mir-193-precNo2	uc.177+A	-0.4761	hsa-mir-193a
hsa-mir-193-precNo2	uc.18+	-0.4545	hsa-mir-193a
hsa-mir-193-precNo2	uc.263+A	-0.454	hsa-mir-193a
hsa-mir-194-precNo1	uc.159+A	-0.6811	hsa-miR-194
hsa-mir-194-precNo1	uc.95+	-0.6761	hsa-miR-194
hsa-mir-194-precNo1	uc.287+A	-0.6403	hsa-miR-194
hsa-mir-194-precNo1	uc.88+A	-0.6004	hsa-miR-194
hsa-mir-194-precNo1	uc.200+	-0.5976	hsa-miR-194
hsa-mir-194-precNo1	uc.477+A	-0.5561	hsa-miR-194
hsa-mir-194-precNo1	uc.217+	-0.5458	hsa-miR-194
hsa-mir-194-precNo1	uc.73+A	-0.5439	hsa-miR-194
hsa-mir-194-precNo1	uc.475+A	-0.5427	hsa-miR-194
hsa-mir-194-precNo1	uc.448+	-0.5099	hsa-miR-194
hsa-mir-194-precNo1	uc.475+	-0.506	hsa-miR-194
hsa-mir-194-precNo1	uc.448+A	-0.4951	hsa-miR-194
hsa-mir-194-precNo1	uc.473+	-0.4945	hsa-miR-194
hsa-mir-194-precNo1	uc.362+A	-0.4914	hsa-miR-194
hsa-mir-194-precNo1	uc.412+	-0.4779	hsa-miR-194
hsa-mir-194-2No1	uc.1+	-0.4717	hsa-miR-194

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miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-194-2No1	uc.453+A	-0.462	hsa-miR-194
hsa-mir-194-precNo1	uc.388+	-0.4574	hsa-miR-194
hsa-mir-194-precNo1	uc.462+A	-0.4567	hsa-miR-194
hsa-mir-194-precNo1	uc.281+A	-0.456	hsa-miR-194
hsa-mir-194-precNo1	uc.63+	-0.4508	hsa-miR-194
hsa-mir-195-prec	uc.420+	-0.7876	hsa-miR-195
hsa-mir-195-prec	uc.189+	-0.7078	hsa-miR-195
hsa-mir-195-prec	uc.299+A	-0.6525	hsa-miR-195
hsa-mir-195-prec	uc.44+A	-0.6169	hsa-miR-195
hsa-mir-195-prec	uc.78+	-0.6154	hsa-miR-195
hsa-mir-195-prec	uc.412+A	-0.6149	hsa-miR-195
hsa-mir-195-prec	uc.462+A	-0.6119	hsa-miR-195
hsa-mir-195-prec	uc.33+A	-0.6097	hsa-miR-195
hsa-mir-195-prec	uc.412+	-0.6071	hsa-miR-195
hsa-mir-195-prec	uc.8+	-0.5817	hsa-miR-195
hsa-mir-195-prec	uc.338+	-0.5741	hsa-miR-195
hsa-mir-195-prec	uc.456+A	-0.5716	hsa-miR-195
hsa-mir-195-prec	uc.285+	-0.5586	hsa-miR-195
hsa-mir-195-prec	uc.151+	-0.5445	hsa-miR-195
hsa-mir-195-prec	uc.161+A	-0.5436	hsa-miR-195
hsa-mir-195-prec	uc.190+A	-0.5413	hsa-miR-195
hsa-mir-195-prec	uc.354+A	-0.5353	hsa-miR-195
hsa-mir-195-prec	uc.73+A	-0.5318	hsa-miR-195
hsa-mir-195-prec	uc.331+A	-0.5276	hsa-miR-195
hsa-mir-195-prec	uc.427+	-0.5234	hsa-miR-195
hsa-mir-195-prec	uc.456+	-0.5217	hsa-miR-195
hsa-mir-195-prec	uc.477+A	-0.5094	hsa-miR-195
hsa-mir-195-prec	uc.378+A	-0.5092	hsa-miR-195
hsa-mir-195-prec	uc.10+	-0.4824	hsa-miR-195
hsa-mir-195-prec	uc.134+	-0.4814	hsa-miR-195
hsa-mir-195-prec	uc.88+	-0.467	hsa-miR-195
hsa-mir-195-prec	uc.378+	-0.4667	hsa-miR-195
hsa-mir-195-prec	uc.275+	-0.4599	hsa-miR-195
hsa-mir-195-prec	uc.448+	-0.4581	hsa-miR-195
hsa-mir-195-prec	uc.234+	-0.4533	hsa-miR-195
hsa-mir-195-prec	uc.33+	-0.4519	hsa-miR-195
hsa-mir-195-prec	uc.153+A	-0.4503	hsa-miR-195
hsa-mir-196-2-precNo2	uc.366+	-0.674	hsa-miR-196a
hsa-mir-196-2-precNo2	uc.192+	-0.653	hsa-miR-196a
hsa-mir-196-2-precNo2	uc.230+	-0.5495	hsa-miR-196a
hsa-mir-196-2-precNo2	uc.478+	-0.5265	hsa-miR-196a
hsa-mir-196-2-precNo2	uc.181+A	-0.5243	hsa-miR-196a
hsa-mir-196-1-precNo1	uc.478+	-0.4941	hsa-miR-196a
hsa-mir-196-2-precNo2	uc.125+A	-0.4886	hsa-miR-196a
hsa-mir-196-2-precNo2	uc.345+A	-0.4551	hsa-miR-196a
hsa-mir-196-2-precNo2	uc.131+	-0.4493	hsa-miR-196a
hsa-mir-196bNo2	uc.192+	-0.5465	hsa-mir-196b
hsa-mir-196bNo2	uc.341+A	-0.5396	hsa-mir-196b
hsa-mir-196bNo2	uc.204+	-0.4733	hsa-mir-196b
hsa-mir-196bNo2	uc.41+	-0.4731	hsa-mir-196b
hsa-mir-196bNo2	uc.366+	-0.454	hsa-mir-196b
hsa-mir-197-prec	uc.229+	-0.745	hsa-miR-197
hsa-mir-197-prec	uc.466+A	-0.6606	hsa-miR-197
hsa-mir-197-prec	uc.73+	-0.6459	hsa-miR-197
hsa-mir-197-prec	uc.345+	-0.6329	hsa-miR-197
hsa-mir-197-prec	uc.349+	-0.6289	hsa-miR-197
hsa-mir-197-prec	uc.426+	-0.6162	hsa-miR-197
hsa-mir-197-prec	uc.483+	-0.6125	hsa-miR-197
hsa-mir-197-prec	uc.41+	-0.5966	hsa-miR-197
hsa-mir-197-prec	uc.204+	-0.5663	hsa-miR-197
hsa-mir-197-prec	uc.177+	-0.5607	hsa-miR-197
hsa-mir-197-prec	uc.278+	-0.543	hsa-miR-197
hsa-mir-197-prec	uc.134+A	-0.5007	hsa-miR-197
hsa-mir-197-prec	uc.346+	-0.4916	hsa-miR-197
hsa-mir-197-prec	uc.462+	-0.4872	hsa-miR-197
hsa-mir-197-prec	uc.128+A	-0.4698	hsa-miR-197
hsa-mir-197-prec	uc.131+	-0.4663	hsa-miR-197
hsa-mir-197-prec	uc.366+	-0.4641	hsa-miR-197
hsa-mir-197-prec	uc.77+	-0.4641	hsa-miR-197
hsa-mir-197-prec	uc.345+A	-0.4601	hsa-miR-197
hsa-mir-197-prec	uc.172+A	-0.4516	hsa-miR-197
hsa-mir-019b-1-prec	uc.117+	-0.5477	hsa-miR-19b
hsa-mir-019b-1-prec	uc.285+	-0.4772	hsa-miR-19b
hsa-mir-204-precNo2	uc.287+A	-0.7123	hsa-mir-204
hsa-mir-204-precNo2	uc.378+A	-0.6691	hsa-mir-204
hsa-mir-204-precNo2	uc.445+A	-0.6689	hsa-mir-204
hsa-mir-204-precNo2	uc.190+A	-0.6664	hsa-mir-204
hsa-mir-204-precNo2	uc.354+A	-0.659	hsa-mir-204
hsa-mir-204-precNo2	uc.275+	-0.6581	hsa-mir-204
hsa-mir-204-precNo2	uc.477+A	-0.6528	hsa-mir-204
hsa-mir-204-precNo2	uc.43+	-0.6526	hsa-mir-204
hsa-mir-204-precNo2	uc.473+A	-0.6519	hsa-mir-204
hsa-mir-204-precNo2	uc.462+A	-0.6483	hsa-mir-204
hsa-mir-204-precNo2	uc.383+	-0.6306	hsa-mir-204

Figure 18

Calin GA   14

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-204-precNo2	uc.420+	-0.614	hsa-mir-204
hsa-mir-204-precNo2	uc.189+	-0.6121	hsa-mir-204
hsa-mir-204-precNo2	uc.20+	-0.5883	hsa-mir-204
hsa-mir-204-precNo2	uc.468+	-0.5848	hsa-mir-204
hsa-mir-204-precNo2	uc.88+	-0.5815	hsa-mir-204
hsa-mir-204-precNo2	uc.217+A	-0.5741	hsa-mir-204
hsa-mir-204-precNo2	uc.362+A	-0.5707	hsa-mir-204
hsa-mir-204-precNo2	uc.378+	-0.5684	hsa-mir-204
hsa-mir-204-precNo2	uc.8+	-0.5606	hsa-mir-204
hsa-mir-204-precNo2	uc.20+A	-0.5593	hsa-mir-204
hsa-mir-204-precNo2	uc.412+A	-0.5556	hsa-mir-204
hsa-mir-204-precNo2	uc.468+A	-0.5538	hsa-mir-204
hsa-mir-204-precNo2	uc.388+	-0.5469	hsa-mir-204
hsa-mir-204-precNo2	uc.299+A	-0.5419	hsa-mir-204
hsa-mir-204-precNo2	uc.153+A	-0.5392	hsa-mir-204
hsa-mir-204-precNo2	uc.33+	-0.5329	hsa-mir-204
hsa-mir-204-precNo2	uc.73+A	-0.514	hsa-mir-204
hsa-mir-204-precNo2	uc.63+	-0.5134	hsa-mir-204
hsa-mir-204-precNo2	uc.106+	-0.5125	hsa-mir-204
hsa-mir-204-precNo2	uc.234+	-0.5107	hsa-mir-204
hsa-mir-204-precNo2	uc.153+	-0.5062	hsa-mir-204
hsa-mir-204-precNo2	uc.18+	-0.5051	hsa-mir-204
hsa-mir-204-precNo2	uc.338+	-0.4907	hsa-mir-204
hsa-mir-204-precNo2	uc.456+A	-0.4881	hsa-mir-204
hsa-mir-204-precNo2	uc.456+	-0.4788	hsa-mir-204
hsa-mir-204-precNo2	uc.217+	-0.4772	hsa-mir-204
hsa-mir-204-precNo2	uc.477+	-0.4756	hsa-mir-204
hsa-mir-204-precNo2	uc.182+	-0.4648	hsa-mir-204
hsa-mir-204-precNo2	uc.388+A	-0.4644	hsa-mir-204
hsa-mir-204-precNo2	uc.190+	-0.4643	hsa-mir-204
hsa-mir-204-precNo2	uc.475+A	-0.461	hsa-mir-204
hsa-mir-204-precNo2	uc.448+A	-0.4577	hsa-mir-204
hsa-mir-204-precNo2	uc.427+	-0.45	hsa-mir-204
hsa-mir-206-precNo1	uc.181+A	-0.6652	hsa-miR-206
hsa-mir-206-precNo2	uc.90+A	-0.6609	hsa-miR-206
hsa-mir-206-precNo2	uc.298+	-0.6521	hsa-miR-206
hsa-mir-206-precNo2	uc.159+A	-0.6404	hsa-miR-206
hsa-mir-206-precNo2	uc.278+A	-0.6383	hsa-miR-206
hsa-mir-206-precNo2	uc.95+	-0.6274	hsa-miR-206
hsa-mir-206-precNo2	uc.291+	-0.6115	hsa-miR-206
hsa-mir-206-precNo2	uc.217+	-0.5949	hsa-miR-206
hsa-mir-206-precNo2	uc.480+	-0.5927	hsa-miR-206
hsa-mir-206-precNo2	uc.392+	-0.5749	hsa-miR-206
hsa-mir-206-precNo2	uc.156+	-0.5645	hsa-miR-206
hsa-mir-206-precNo2	uc.88+A	-0.5614	hsa-miR-206
hsa-mir-206-precNo1	uc.125+A	-0.553	hsa-miR-206
hsa-mir-206-precNo1	uc.366+	-0.5487	hsa-miR-206
hsa-mir-206-precNo2	uc.223+A	-0.5471	hsa-miR-206
hsa-mir-206-precNo2	uc.475+A	-0.5422	hsa-miR-206
hsa-mir-206-precNo1	uc.192+	-0.5404	hsa-miR-206
hsa-mir-206-precNo1	uc.230+	-0.5395	hsa-miR-206
hsa-mir-206-precNo2	uc.456+	-0.5335	hsa-miR-206
hsa-mir-206-precNo2	uc.477+	-0.5185	hsa-miR-206
hsa-mir-206-precNo2	uc.477+A	-0.5149	hsa-miR-206
hsa-mir-206-precNo2	uc.378+	-0.5001	hsa-miR-206
hsa-mir-206-precNo1	uc.317+	-0.4959	hsa-miR-206
hsa-mir-206-precNo1	uc.389+	-0.4836	hsa-miR-206
hsa-mir-206-precNo2	uc.20+A	-0.4773	hsa-miR-206
hsa-mir-206-precNo2	uc.287+A	-0.4719	hsa-miR-206
hsa-mir-206-precNo1	uc.345+A	-0.4716	hsa-miR-206
hsa-mir-206-precNo2	uc.448+A	-0.459	hsa-miR-206
hsa-mir-206-precNo1	uc.31+	-0.4561	hsa-miR-206
hsa-mir-206-precNo2	uc.448+	-0.4504	hsa-miR-206
hsa-mir-020-prec	uc.160+	-0.6597	hsa-miR-20a
hsa-mir-020-prec	uc.325+	-0.6068	hsa-miR-20a
hsa-mir-020-prec	uc.478+A	-0.5995	hsa-miR-20a
hsa-mir-020-prec	uc.339+	-0.5973	hsa-miR-20a
hsa-mir-020-prec	uc.283+A	-0.5956	hsa-miR-20a
hsa-mir-020-prec	uc.282+A	-0.593	hsa-miR-20a
hsa-mir-020-prec	uc.465+A	-0.5781	hsa-miR-20a
hsa-mir-020-prec	uc.167+	-0.5697	hsa-miR-20a
hsa-mir-020-prec	uc.327+A	-0.5497	hsa-miR-20a
hsa-mir-020-prec	uc.117+	-0.5329	hsa-miR-20a
hsa-mir-020-prec	uc.48+A	-0.5303	hsa-miR-20a
hsa-mir-020-prec	uc.269+A	-0.5251	hsa-miR-20a
hsa-mir-020-prec	uc.300+A	-0.5206	hsa-miR-20a
hsa-mir-020-prec	uc.213+	-0.5038	hsa-miR-20a
hsa-mir-020-prec	uc.170+	-0.4686	hsa-miR-20a
hsa-mir-020-prec	uc.346+	-0.4629	hsa-miR-20a
hsa-mir-020-prec	uc.84+A	-0.4629	hsa-miR-20a
hsa-mir-020-prec	uc.285+	-0.4605	hsa-miR-20a
hsa-mir-020-prec	uc.153+A	-0.4507	hsa-miR-20a
hsa-mir-21No1	uc.33+A	-0.7553	hsa-miR-21
hsa-mir-21No1	uc.153+A	-0.7091	hsa-miR-21

Figure 18

Calin GA

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miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-021-prec-17No1	uc.88+	-0.7013	hsa-miR-21
hsa-mir-021-prec-17No1	uc.106+	-0.7002	hsa-miR-21
hsa-mir-021-prec-17No1	uc.33+A	-0.698	hsa-miR-21
hsa-mir-21No1	uc.106+	-0.6969	hsa-miR-21
hsa-mir-21No1	uc.213+	-0.695	hsa-miR-21
hsa-mir-021-prec-17No1	uc.473+A	-0.6828	hsa-miR-21
hsa-mir-21No1	uc.88+	-0.6739	hsa-miR-21
hsa-mir-021-prec-17No1	uc.217+A	-0.6686	hsa-miR-21
hsa-mir-021-prec-17No1	uc.153+	-0.6594	hsa-miR-21
hsa-mir-021-prec-17No1	uc.153+A	-0.6543	hsa-miR-21
hsa-mir-021-prec-17No1	uc.427+	-0.6481	hsa-miR-21
hsa-mir-21No1	uc.153+	-0.6477	hsa-miR-21
hsa-mir-21No1	uc.33+	-0.6461	hsa-miR-21
hsa-mir-021-prec-17No1	uc.263+	-0.6454	hsa-miR-21
hsa-mir-21No1	uc.420+	-0.6425	hsa-miR-21
hsa-mir-21No1	uc.383+	-0.6417	hsa-miR-21
hsa-mir-21No1	uc.285+	-0.6381	hsa-miR-21
hsa-mir-21No1	uc.263+	-0.6346	hsa-miR-21
hsa-mir-21No1	uc.18+	-0.6343	hsa-miR-21
hsa-mir-021-prec-17No1	uc.20+	-0.634	hsa-miR-21
hsa-mir-021-prec-17No1	uc.213+	-0.6292	hsa-miR-21
hsa-mir-021-prec-17No1	uc.448+	-0.6269	hsa-miR-21
hsa-mir-21No1	uc.217+A	-0.6255	hsa-miR-21
hsa-mir-021-prec-17No1	uc.462+A	-0.6247	hsa-miR-21
hsa-mir-021-prec-17No1	uc.383+	-0.6235	hsa-miR-21
hsa-mir-021-prec-17No1	uc.33+	-0.6214	hsa-miR-21
hsa-mir-021-prec-17No1	uc.275+	-0.6197	hsa-miR-21
hsa-mir-021-prec-17No1	uc.378+A	-0.6197	hsa-miR-21
hsa-mir-21No1	uc.473+A	-0.6179	hsa-miR-21
hsa-mir-021-prec-17No1	uc.170+	-0.6165	hsa-miR-21
hsa-mir-21No1	uc.275+	-0.6162	hsa-miR-21
hsa-mir-21No1	uc.427+	-0.6122	hsa-miR-21
hsa-mir-21No1	uc.388+A	-0.6096	hsa-miR-21
hsa-mir-021-prec-17No1	uc.420+	-0.6093	hsa-miR-21
hsa-mir-021-prec-17No1	uc.18+	-0.6089	hsa-miR-21
hsa-mir-21No1	uc.354+A	-0.6071	hsa-miR-21
hsa-mir-021-prec-17No1	uc.354+A	-0.6069	hsa-miR-21
hsa-mir-21No1	uc.327+A	-0.6025	hsa-miR-21
hsa-mir-21No1	uc.20+	-0.5999	hsa-miR-21
hsa-mir-021-prec-17No1	uc.448+A	-0.5961	hsa-miR-21
hsa-mir-21No1	uc.189+	-0.5936	hsa-miR-21
hsa-mir-021-prec-17No1	uc.48+A	-0.5889	hsa-miR-21
hsa-mir-21No1	uc.234+	-0.5864	hsa-miR-21
hsa-mir-021-prec-17No1	uc.378+	-0.5807	hsa-miR-21
hsa-mir-21No1	uc.448+	-0.5737	hsa-miR-21
hsa-mir-021-prec-17No1	uc.287+A	-0.5709	hsa-miR-21
hsa-mir-21No1	uc.48+A	-0.5696	hsa-miR-21
hsa-mir-021-prec-17No1	uc.477+A	-0.5659	hsa-miR-21
hsa-mir-021-prec-17No1	uc.73+A	-0.5624	hsa-miR-21
hsa-mir-21No1	uc.73+A	-0.5593	hsa-miR-21
hsa-mir-021-prec-17No1	uc.456+A	-0.5587	hsa-miR-21
hsa-mir-21No1	uc.456+A	-0.5581	hsa-miR-21
hsa-mir-021-prec-17No1	uc.44+A	-0.5571	hsa-miR-21
hsa-mir-21No1	uc.346+	-0.5571	hsa-miR-21
hsa-mir-21No1	uc.378+A	-0.5569	hsa-miR-21
hsa-mir-021-prec-17No1	uc.20+A	-0.5554	hsa-miR-21
hsa-mir-21No1	uc.190+A	-0.5522	hsa-miR-21
hsa-mir-021-prec-17No1	uc.234+	-0.5513	hsa-miR-21
hsa-mir-021-prec-17No1	uc.388+A	-0.5497	hsa-miR-21
hsa-mir-021-prec-17No1	uc.189+	-0.5494	hsa-miR-21
hsa-mir-021-prec-17No1	uc.327+A	-0.548	hsa-miR-21
hsa-mir-021-prec-17No1	uc.217+	-0.5479	hsa-miR-21
hsa-mir-021-prec-17No1	uc.445+A	-0.5446	hsa-miR-21
hsa-mir-021-prec-17No1	uc.285+	-0.5435	hsa-miR-21
hsa-mir-021-prec-17No1	uc.190+A	-0.5417	hsa-miR-21
hsa-mir-21No1	uc.44+A	-0.5414	hsa-miR-21
hsa-mir-21No1	uc.462+A	-0.5363	hsa-miR-21
hsa-mir-21No1	uc.172+A	-0.5303	hsa-miR-21
hsa-mir-21No1	uc.151+A	-0.5301	hsa-miR-21
hsa-mir-21No1	uc.170+	-0.5291	hsa-miR-21
hsa-mir-021-prec-17No1	uc.456+	-0.5264	hsa-miR-21
hsa-mir-21No1	uc.20+A	-0.5258	hsa-miR-21
hsa-mir-21No1	uc.468+	-0.5256	hsa-miR-21
hsa-mir-021-prec-17No1	uc.151+A	-0.5255	hsa-miR-21
hsa-mir-21No1	uc.378+	-0.523	hsa-miR-21
hsa-mir-21No1	uc.412+A	-0.522	hsa-miR-21
hsa-mir-021-prec-17No1	uc.362+A	-0.5192	hsa-miR-21
hsa-mir-21No1	uc.483+A	-0.5152	hsa-miR-21
hsa-mir-021-prec-17No1	uc.299+A	-0.5116	hsa-miR-21
hsa-mir-21No1	uc.477+A	-0.5086	hsa-miR-21
hsa-mir-021-prec-17No1	uc.468+A	-0.5035	hsa-miR-21
hsa-mir-21No1	uc.468+A	-0.4983	hsa-miR-21
hsa-mir-21No1	uc.388+	-0.4914	hsa-miR-21
hsa-mir-021-prec-17No1	uc.412+A	-0.4907	hsa-miR-21

Figure 18

Calin GA   16

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-21No1	uc.445+A	-0.4896	hsa-miR-21
hsa-mir-21No1	uc.299+A	-0.4883	hsa-miR-21
hsa-mir-021-prec-17No1	uc.388+	-0.4876	hsa-miR-21
hsa-mir-021-prec-17No1	uc.331+A	-0.4855	hsa-miR-21
hsa-mir-21No1	uc.287+A	-0.4752	hsa-miR-21
hsa-mir-021-prec-17No1	uc.483+A	-0.4745	hsa-miR-21
hsa-mir-21No1	uc.160+	-0.4736	hsa-miR-21
hsa-mir-021-prec-17No1	uc.263+A	-0.4725	hsa-miR-21
hsa-mir-21No1	uc.77+	-0.4692	hsa-miR-21
hsa-mir-021-prec-17No1	uc.167+	-0.4681	hsa-miR-21
hsa-mir-21No1	uc.43+	-0.4668	hsa-miR-21
hsa-mir-21No1	uc.217+	-0.4603	hsa-miR-21
hsa-mir-21No1	uc.456+	-0.4594	hsa-miR-21
hsa-mir-21No1	uc.465+A	-0.4578	hsa-miR-21
hsa-mir-021-prec-17No1	uc.95+	-0.4522	hsa-miR-21
hsa-mir-21No1	uc.263+A	-0.4515	hsa-miR-21
hsa-mir-21No1	uc.128+A	-0.4498	hsa-miR-21
hsa-mir-21No1	uc.183+	-0.4488	hsa-miR-21
hsa-mir-21No1	uc.331+A	-0.4487	hsa-miR-21
hsa-mir-210-prec	uc.159+A	-0.4855	hsa-miR-210
hsa-mir-210-prec	uc.298+	-0.461	hsa-miR-210
hsa-mir-210-prec	uc.278+A	-0.4527	hsa-miR-210
hsa-mir-212-precNo1	uc.483+	-0.6884	hsa-miR-212
hsa-mir-212-precNo1	uc.41+	-0.6482	hsa-miR-212
hsa-mir-212-precNo1	uc.77+	-0.5846	hsa-miR-212
hsa-mir-212-precNo2	uc.389+	-0.5803	hsa-mir-212
hsa-mir-212-precNo1	uc.229+	-0.5656	hsa-miR-212
hsa-mir-212-precNo2	uc.41+	-0.5624	hsa-mir-212
hsa-mir-212-precNo1	uc.128+A	-0.5609	hsa-miR-212
hsa-mir-212-precNo1	uc.177+	-0.5507	hsa-miR-212
hsa-mir-212-precNo2	uc.34+A	-0.5308	hsa-mir-212
hsa-mir-212-precNo2	uc.142+	-0.5306	hsa-mir-212
hsa-mir-212-precNo1	uc.172+A	-0.5202	hsa-miR-212
hsa-mir-212-precNo1	uc.204+	-0.5041	hsa-miR-212
hsa-mir-212-precNo1	uc.345+	-0.5016	hsa-miR-212
hsa-mir-212-precNo1	uc.346+	-0.4992	hsa-miR-212
hsa-mir-212-precNo1	uc.73+	-0.4991	hsa-miR-212
hsa-mir-212-precNo2	uc.310+A	-0.4986	hsa-mir-212
hsa-mir-212-precNo1	uc.466+A	-0.4863	hsa-miR-212
hsa-mir-212-precNo1	uc.426+	-0.4768	hsa-miR-212
hsa-mir-212-precNo2	uc.478+	-0.4719	hsa-mir-212
hsa-mir-212-precNo2	uc.204+A	-0.4713	hsa-mir-212
hsa-mir-212-precNo2	uc.483+	-0.4628	hsa-mir-212
hsa-mir-212-precNo1	uc.366+	-0.4568	hsa-miR-212
hsa-mir-212-precNo1	uc.349+	-0.4532	hsa-miR-212
hsa-mir-214-prec	uc.466+A	-0.6614	hsa-miR-214
hsa-mir-214-prec	uc.136+	-0.6576	hsa-miR-214
hsa-mir-214-prec	uc.426+	-0.6547	hsa-miR-214
hsa-mir-214-prec	uc.229+	-0.6505	hsa-miR-214
hsa-mir-214-prec	uc.345+A	-0.6157	hsa-miR-214
hsa-mir-214-prec	uc.73+	-0.6091	hsa-miR-214
hsa-mir-214-prec	uc.366+	-0.6015	hsa-miR-214
hsa-mir-214-prec	uc.349+	-0.5879	hsa-miR-214
hsa-mir-214-prec	uc.204+	-0.5678	hsa-miR-214
hsa-mir-214-prec	uc.278+	-0.5276	hsa-miR-214
hsa-mir-214-prec	uc.345+	-0.5223	hsa-miR-214
hsa-mir-214-prec	uc.177+	-0.5221	hsa-miR-214
hsa-mir-214-prec	uc.483+	-0.5202	hsa-miR-214
hsa-mir-214-prec	uc.462+	-0.5156	hsa-miR-214
hsa-mir-214-prec	uc.165+	-0.5051	hsa-miR-214
hsa-mir-214-prec	uc.346+	-0.5041	hsa-miR-214
hsa-mir-214-prec	uc.131+	-0.5017	hsa-miR-214
hsa-mir-214-prec	uc.41+	-0.4941	hsa-miR-214
hsa-mir-214-prec	uc.262+A	-0.4932	hsa-miR-214
hsa-mir-214-prec	uc.125+A	-0.4826	hsa-miR-214
hsa-mir-214-prec	uc.134+A	-0.4761	hsa-miR-214
hsa-mir-214-prec	uc.192+	-0.4684	hsa-miR-214
hsa-mir-215-precNo1	uc.151+A	-0.45	hsa-miR-215
hsa-mir-218-2-precNo2	uc.448+	-0.6982	hsa-miR-218
hsa-mir-218-2-precNo2	uc.456+	-0.686	hsa-miR-218
hsa-mir-218-2-precNo2	uc.477+A	-0.6519	hsa-miR-218
hsa-mir-218-2-precNo2	uc.20+	-0.6431	hsa-miR-218
hsa-mir-218-2-precNo2	uc.473+A	-0.6284	hsa-miR-218
hsa-mir-218-2-precNo2	uc.95+	-0.6152	hsa-miR-218
hsa-mir-218-2-precNo2	uc.287+A	-0.6065	hsa-miR-218
hsa-mir-218-2-precNo2	uc.475+A	-0.6013	hsa-miR-218
hsa-mir-218-2-precNo2	uc.263+	-0.5944	hsa-miR-218
hsa-mir-218-2-precNo2	uc.217+	-0.5942	hsa-miR-218
hsa-mir-218-2-precNo2	uc.20+A	-0.5892	hsa-miR-218
hsa-mir-218-2-precNo2	uc.448+A	-0.5858	hsa-miR-218
hsa-mir-218-2-precNo2	uc.427+	-0.5846	hsa-miR-218
hsa-mir-218-2-precNo2	uc.362+A	-0.5694	hsa-miR-218
hsa-mir-218-2-precNo2	uc.378+	-0.564	hsa-miR-218
hsa-mir-218-2-precNo2	uc.275+	-0.549	hsa-miR-218

Figure 18

Calin GA

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miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-218-2-precNo2	uc.378+A	-0.5473	hsa-miR-218
hsa-mir-218-2-precNo2	uc.170+	-0.5371	hsa-miR-218
hsa-mir-218-2-precNo2	uc.477+	-0.5153	hsa-miR-218
hsa-mir-218-2-precNo2	uc.468+A	-0.5117	hsa-miR-218
hsa-mir-218-2-precNo2	uc.88+	-0.5116	hsa-miR-218
hsa-mir-218-2-precNo2	uc.88+A	-0.5041	hsa-miR-218
hsa-mir-218-2-precNo2	uc.63+	-0.5025	hsa-miR-218
hsa-mir-218-2-precNo2	uc.383+	-0.4995	hsa-miR-218
hsa-mir-218-2-precNo2	uc.159+A	-0.4888	hsa-miR-218
hsa-mir-218-2-precNo2	uc.331+A	-0.4886	hsa-miR-218
hsa-mir-218-2-precNo2	uc.388+	-0.488	hsa-miR-218
hsa-mir-218-2-precNo2	uc.263+A	-0.4774	hsa-miR-218
hsa-mir-218-2-precNo2	uc.200+	-0.4738	hsa-miR-218
hsa-mir-218-2-precNo2	uc.462+A	-0.4668	hsa-miR-218
hsa-mir-218-2-precNo2	uc.190+A	-0.4628	hsa-miR-218
hsa-mir-218-2-precNo2	uc.412+	-0.4594	hsa-miR-218
hsa-mir-218-2-precNo2	uc.445+A	-0.4551	hsa-miR-218
hsa-mir-218-2-precNo2	uc.362+	-0.4504	hsa-miR-218
hsa-mir-218-2-precNo2	uc.456+A	-0.4495	hsa-miR-218
hsa-mir-218-2-precNo2	uc.44+A	-0.4477	hsa-miR-218
hsa-mir-219-1No1	uc.248+	-0.4836	hsa-miR-219
hsa-mir-219-1No1	uc.378+	-0.4756	hsa-miR-219
hsa-mir-219-1No1	uc.153+	-0.4548	hsa-miR-219
hsa-mir-219-1No1	uc.477+	-0.4536	hsa-miR-219
hsa-mir-219-1No1	uc.456+	-0.4534	hsa-miR-219
hsa-mir-219-1No2	uc.8+	-0.6477	hsa-mir-219-1
hsa-mir-219-1No2	uc.189+	-0.583	hsa-mir-219-1
hsa-mir-219-1No2	uc.190+A	-0.5699	hsa-mir-219-1
hsa-mir-219-1No2	uc.477+A	-0.5555	hsa-mir-219-1
hsa-mir-219-1No2	uc.420+	-0.5543	hsa-mir-219-1
hsa-mir-219-1No2	uc.378+	-0.5441	hsa-mir-219-1
hsa-mir-219-1No2	uc.412+A	-0.5309	hsa-mir-219-1
hsa-mir-219-1No2	uc.412+	-0.5279	hsa-mir-219-1
hsa-mir-219-1No2	uc.468+A	-0.5259	hsa-mir-219-1
hsa-mir-219-1No2	uc.462+A	-0.5229	hsa-mir-219-1
hsa-mir-219-1No2	uc.388+	-0.5183	hsa-mir-219-1
hsa-mir-219-1No2	uc.354+A	-0.5059	hsa-mir-219-1
hsa-mir-219-1No2	uc.287+A	-0.4809	hsa-mir-219-1
hsa-mir-219-1No2	uc.190+	-0.4782	hsa-mir-219-1
hsa-mir-219-1No2	uc.217+	-0.4717	hsa-mir-219-1
hsa-mir-219-1No2	uc.43+	-0.468	hsa-mir-219-1
hsa-mir-219-1No2	uc.445+A	-0.4672	hsa-mir-219-1
hsa-mir-219-1No2	uc.473+A	-0.4655	hsa-mir-219-1
hsa-mir-219-1No2	uc.456+	-0.4634	hsa-mir-219-1
hsa-mir-219-1No2	uc.378+A	-0.461	hsa-mir-219-1
hsa-mir-219-1No2	uc.275+	-0.4607	hsa-mir-219-1
hsa-mir-219-1No2	uc.338+	-0.4497	hsa-mir-219-1
hsa-mir-219-1No2	uc.477+	-0.4488	hsa-mir-219-1
hsa-mir-221-prec	uc.282+A	-0.6376	hsa-miR-221
hsa-mir-221-prec	uc.325+	-0.6289	hsa-miR-221
hsa-mir-221-prec	uc.346+A	-0.6232	hsa-miR-221
hsa-mir-221-prec	uc.339+	-0.596	hsa-miR-221
hsa-mir-221-prec	uc.465+A	-0.5944	hsa-miR-221
hsa-mir-221-prec	uc.283+A	-0.5151	hsa-miR-221
hsa-mir-221-prec	uc.204+	-0.4824	hsa-miR-221
hsa-mir-221-prec	uc.269+A	-0.4761	hsa-miR-221
hsa-mir-221-prec	uc.398+	-0.4728	hsa-miR-221
hsa-mir-221-prec	uc.300+A	-0.4688	hsa-miR-221
hsa-mir-222-precNo2	uc.331+A	-0.5434	hsa-mir-222
hsa-mir-222-precNo2	uc.213+	-0.5191	hsa-mir-222
hsa-mir-222-precNo2	uc.419+A	-0.5138	hsa-mir-222
hsa-mir-222-precNo2	uc.275+	-0.5104	hsa-mir-222
hsa-mir-222-precNo2	uc.465+A	-0.5054	hsa-mir-222
hsa-mir-222-precNo2	uc.285+	-0.5004	hsa-mir-222
hsa-mir-222-precNo2	uc.420+	-0.4996	hsa-mir-222
hsa-mir-222-precNo2	uc.33+A	-0.4881	hsa-mir-222
hsa-mir-222-precNo2	uc.172+A	-0.4818	hsa-mir-222
hsa-mir-222-precNo2	uc.456+A	-0.4695	hsa-mir-222
hsa-mir-222-precNo2	uc.282+A	-0.4683	hsa-mir-222
hsa-mir-222-precNo2	uc.398+A	-0.4659	hsa-mir-222
hsa-mir-222-precNo2	uc.173+	-0.4619	hsa-mir-222
hsa-mir-222-precNo2	uc.325+	-0.4502	hsa-mir-222
hsa-mir-223-prec	uc.18+	-0.5605	hsa-miR-223
hsa-mir-223-prec	uc.128+A	-0.5212	hsa-miR-223
hsa-mir-223-prec	uc.151+	-0.5035	hsa-miR-223
hsa-mir-223-prec	uc.33+	-0.496	hsa-miR-223
hsa-mir-223-prec	uc.177+	-0.4948	hsa-miR-223
hsa-mir-223-prec	uc.468+	-0.4941	hsa-miR-223
hsa-mir-223-prec	uc.483+A	-0.4941	hsa-miR-223
hsa-mir-223-prec	uc.388+A	-0.4912	hsa-miR-223
hsa-mir-223-prec	uc.172+A	-0.4797	hsa-miR-223
hsa-mir-223-prec	uc.299+A	-0.4656	hsa-miR-223
hsa-mir-223-prec	uc.483+	-0.4587	hsa-miR-223
hsa-mir-223-prec	uc.151+A	-0.4559	hsa-miR-223

Figure 18

Calin GA

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miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-223-prec	uc.153+	-0.4478	hsa-miR-223
hsa-mir-224-prec	uc.167+	-0.533	hsa-miR-224
hsa-mir-224-prec	uc.217+A	-0.4895	hsa-miR-224
hsa-mir-224-prec	uc.462+A	-0.458	hsa-miR-224
hsa-mir-224-prec	uc.48+A	-0.4522	hsa-miR-224
hsa-mir-023a-prec	uc.389+	-0.6337	hsa-miR-23a
hsa-mir-023a-prec	uc.346+A	-0.623	hsa-miR-23a
hsa-mir-023a-prec	uc.34+A	-0.5688	hsa-miR-23a
hsa-mir-023a-prec	uc.24+A	-0.5386	hsa-miR-23a
hsa-mir-023a-prec	uc.282+A	-0.5119	hsa-miR-23a
hsa-mir-023a-prec	uc.478+	-0.5053	hsa-miR-23a
hsa-mir-023a-prec	uc.366+	-0.4963	hsa-miR-23a
hsa-mir-023a-prec	uc.192+	-0.489	hsa-miR-23a
hsa-mir-023a-prec	uc.310+A	-0.4631	hsa-miR-23a
hsa-mir-023a-prec	uc.31+	-0.4617	hsa-miR-23a
hsa-mir-023a-prec	uc.125+A	-0.4556	hsa-miR-23a
hsa-mir-023a-prec	uc.73+	-0.4534	hsa-miR-23a
hsa-mir-023a-prec	uc.398+	-0.4503	hsa-miR-23a
hsa-mir-023b-prec	uc.389+	-0.6586	hsa-miR-23b
hsa-mir-023b-prec	uc.478+	-0.6064	hsa-miR-23b
hsa-mir-023b-prec	uc.346+A	-0.5747	hsa-miR-23b
hsa-mir-023b-prec	uc.192+	-0.5196	hsa-miR-23b
hsa-mir-023b-prec	uc.34+A	-0.481	hsa-miR-23b
hsa-mir-023b-prec	uc.24+A	-0.4542	hsa-miR-23b
hsa-mir-023b-prec	uc.341+A	-0.4531	hsa-miR-23b
hsa-mir-024-2-prec	uc.462+A	-0.7119	hsa-miR-24
hsa-mir-024-2-prec	uc.427+	-0.6964	hsa-miR-24
hsa-mir-024-2-prec	uc.44+A	-0.6715	hsa-miR-24
hsa-mir-024-1-precNo1	uc.465+A	-0.6419	hsa-miR-24
hsa-mir-024-2-prec	uc.167+	-0.6385	hsa-miR-24
hsa-mir-024-2-prec	uc.153+	-0.6366	hsa-miR-24
hsa-mir-024-2-prec	uc.73+A	-0.6354	hsa-miR-24
hsa-mir-024-2-prec	uc.48+A	-0.634	hsa-miR-24
hsa-mir-024-2-prec	uc.263+	-0.627	hsa-miR-24
hsa-mir-024-2-prec	uc.275+	-0.618	hsa-miR-24
hsa-mir-024-2-prec	uc.378+A	-0.6089	hsa-miR-24
hsa-mir-024-2-prec	uc.331+A	-0.608	hsa-miR-24
hsa-mir-024-2-prec	uc.456+A	-0.6023	hsa-miR-24
hsa-mir-024-1-precNo1	uc.153+A	-0.5931	hsa-miR-24
hsa-mir-024-2-prec	uc.153+A	-0.5877	hsa-miR-24
hsa-mir-024-1-precNo1	uc.160+	-0.5875	hsa-miR-24
hsa-mir-024-2-prec	uc.327+A	-0.586	hsa-miR-24
hsa-mir-024-2-prec	uc.420+	-0.584	hsa-miR-24
hsa-mir-024-2-prec	uc.448+	-0.582	hsa-miR-24
hsa-mir-024-2-prec	uc.287+A	-0.5777	hsa-miR-24
hsa-mir-024-2-prec	uc.477+A	-0.5732	hsa-miR-24
hsa-mir-024-2-prec	uc.388+	-0.5731	hsa-miR-24
hsa-mir-024-1-precNo1	uc.327+A	-0.5722	hsa-miR-24
hsa-mir-024-2-prec	uc.88+	-0.571	hsa-miR-24
hsa-mir-024-2-prec	uc.213+	-0.5686	hsa-miR-24
hsa-mir-024-1-precNo1	uc.48+A	-0.5656	hsa-miR-24
hsa-mir-024-2-prec	uc.338+	-0.5638	hsa-miR-24
hsa-mir-024-2-prec	uc.473+A	-0.5601	hsa-miR-24
hsa-mir-024-1-precNo1	uc.172+A	-0.5596	hsa-miR-24
hsa-mir-024-2-prec	uc.20+	-0.5571	hsa-miR-24
hsa-mir-024-1-precNo1	uc.282+A	-0.5557	hsa-miR-24
hsa-mir-024-2-prec	uc.362+	-0.5555	hsa-miR-24
hsa-mir-024-2-prec	uc.106+	-0.555	hsa-miR-24
hsa-mir-024-1-precNo1	uc.339+	-0.5524	hsa-miR-24
hsa-mir-024-2-prec	uc.456+	-0.5523	hsa-miR-24
hsa-mir-024-2-prec	uc.20+A	-0.5502	hsa-miR-24
hsa-mir-024-2-prec	uc.217+A	-0.5496	hsa-miR-24
hsa-mir-024-1-precNo1	uc.77+	-0.547	hsa-miR-24
hsa-mir-024-2-prec	uc.190+A	-0.5469	hsa-miR-24
hsa-mir-024-2-prec	uc.299+A	-0.545	hsa-miR-24
hsa-mir-024-1-precNo1	uc.285+	-0.544	hsa-miR-24
hsa-mir-024-2-prec	uc.478+A	-0.541	hsa-miR-24
hsa-mir-024-2-prec	uc.234+	-0.5386	hsa-miR-24
hsa-mir-024-2-prec	uc.378+	-0.5368	hsa-miR-24
hsa-mir-024-1-precNo1	uc.478+A	-0.5363	hsa-miR-24
hsa-mir-024-1-precNo1	uc.153+	-0.5355	hsa-miR-24
hsa-mir-024-2-prec	uc.33+A	-0.5343	hsa-miR-24
hsa-mir-024-2-prec	uc.448+A	-0.5342	hsa-miR-24
hsa-mir-024-2-prec	uc.170+	-0.5333	hsa-miR-24
hsa-mir-024-1-precNo1	uc.420+A	-0.5318	hsa-miR-24
hsa-mir-024-1-precNo1	uc.167+	-0.5288	hsa-miR-24
hsa-mir-024-1-precNo1	uc.234+	-0.5252	hsa-miR-24
hsa-mir-024-1-precNo1	uc.427+	-0.525	hsa-miR-24
hsa-mir-024-2-prec	uc.285+	-0.5236	hsa-miR-24
hsa-mir-024-1-precNo1	uc.151+	-0.5232	hsa-miR-24
hsa-mir-024-2-prec	uc.117+	-0.5203	hsa-miR-24
hsa-mir-024-2-prec	uc.465+A	-0.5181	hsa-miR-24
hsa-mir-024-1-precNo1	uc.420+	-0.5179	hsa-miR-24
hsa-mir-024-1-precNo1	uc.170+	-0.515	hsa-miR-24

Figure 18

Calin GA   19

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-024-2-prec	uc.354+A	-0.515	hsa-miR-24
hsa-mir-024-1-precNo1	uc.263+	-0.5141	hsa-miR-24
hsa-mir-024-1-precNo1	uc.106+	-0.5046	hsa-miR-24
hsa-mir-024-1-precNo1	uc.346+	-0.5038	hsa-miR-24
hsa-mir-024-2-prec	uc.383+	-0.5031	hsa-miR-24
hsa-mir-024-2-prec	uc.412+A	-0.5026	hsa-miR-24
hsa-mir-024-1-precNo1	uc.275+	-0.5003	hsa-miR-24
hsa-mir-024-1-precNo1	uc.217+A	-0.4991	hsa-miR-24
hsa-mir-024-2-prec	uc.63+	-0.4985	hsa-miR-24
hsa-mir-024-2-prec	uc.189+	-0.4978	hsa-miR-24
hsa-mir-024-1-precNo1	uc.173+	-0.4949	hsa-miR-24
hsa-mir-024-2-prec	uc.217+	-0.4926	hsa-miR-24
hsa-mir-024-1-precNo1	uc.213+	-0.4921	hsa-miR-24
hsa-mir-024-1-precNo1	uc.456+A	-0.4912	hsa-miR-24
hsa-mir-024-2-prec	uc.33+	-0.4912	hsa-miR-24
hsa-mir-024-2-prec	uc.362+A	-0.4899	hsa-miR-24
hsa-mir-024-2-prec	uc.88+A	-0.4895	hsa-miR-24
hsa-mir-024-1-precNo1	uc.331+A	-0.4842	hsa-miR-24
hsa-mir-024-1-precNo1	uc.419+A	-0.4814	hsa-miR-24
hsa-mir-024-1-precNo1	uc.151+A	-0.4792	hsa-miR-24
hsa-mir-024-2-prec	uc.151+A	-0.4789	hsa-miR-24
hsa-mir-024-1-precNo1	uc.378+A	-0.4758	hsa-miR-24
hsa-mir-024-1-precNo1	uc.128+A	-0.4752	hsa-miR-24
hsa-mir-024-2-prec	uc.145+A	-0.4718	hsa-miR-24
hsa-mir-024-2-prec	uc.233+A	-0.4695	hsa-miR-24
hsa-mir-024-1-precNo1	uc.462+A	-0.4678	hsa-miR-24
hsa-mir-024-1-precNo1	uc.473+A	-0.4674	hsa-miR-24
hsa-mir-024-1-precNo1	uc.354+A	-0.4668	hsa-miR-24
hsa-mir-024-1-precNo1	uc.88+	-0.4663	hsa-miR-24
hsa-mir-024-2-prec	uc.95+	-0.4652	hsa-miR-24
hsa-mir-024-2-prec	uc.445+A	-0.4628	hsa-miR-24
hsa-mir-024-1-precNo1	uc.33+A	-0.4612	hsa-miR-24
hsa-mir-024-2-prec	uc.200+	-0.4609	hsa-miR-24
hsa-mir-024-1-precNo1	uc.388+	-0.459	hsa-miR-24
hsa-mir-024-2-prec	uc.160+	-0.4582	hsa-miR-24
hsa-mir-024-1-precNo1	uc.362+	-0.4581	hsa-miR-24
hsa-mir-024-1-precNo1	uc.233+A	-0.4572	hsa-miR-24
hsa-mir-024-1-precNo1	uc.325+	-0.4497	hsa-miR-24
hsa-mir-024-1-precNo1	uc.20+	-0.4492	hsa-miR-24
hsa-mir-025-prec	uc.389+	-0.698	hsa-miR-25
hsa-mir-025-prec	uc.346+A	-0.6873	hsa-miR-25
hsa-mir-025-prec	uc.478+	-0.6722	hsa-miR-25
hsa-mir-025-prec	uc.398+	-0.6055	hsa-miR-25
hsa-mir-025-prec	uc.192+	-0.5962	hsa-miR-25
hsa-mir-025-prec	uc.366+	-0.5764	hsa-miR-25
hsa-mir-025-prec	uc.34+A	-0.5702	hsa-miR-25
hsa-mir-025-prec	uc.181+A	-0.5638	hsa-miR-25
hsa-mir-025-prec	uc.31+	-0.5488	hsa-miR-25
hsa-mir-025-prec	uc.125+A	-0.5441	hsa-miR-25
hsa-mir-025-prec	uc.24+A	-0.5203	hsa-miR-25
hsa-mir-025-prec	uc.283+A	-0.4882	hsa-miR-25
hsa-mir-26a-2No1	uc.128+A	-0.7743	hsa-miR-26a
hsa-mir-026a-precNo1	uc.73+A	-0.7387	hsa-miR-26a
hsa-mir-26a-2No1	uc.229+	-0.7132	hsa-miR-26a
hsa-mir-26a-2No1	uc.177+	-0.7103	hsa-miR-26a
hsa-mir-26a-1No1	uc.420+	-0.6998	hsa-miR-26a
hsa-mir-26a-2No1	uc.172+A	-0.6956	hsa-miR-26a
hsa-mir-26a-2No1	uc.346+	-0.6915	hsa-miR-26a
hsa-mir-26a-1No1	uc.106+	-0.6852	hsa-miR-26a
hsa-mir-026a-precNo1	uc.456+A	-0.6713	hsa-miR-26a
hsa-mir-26a-1No1	uc.383+	-0.6713	hsa-miR-26a
hsa-mir-26a-1No1	uc.73+A	-0.67	hsa-miR-26a
hsa-mir-26a-1No1	uc.18+	-0.6691	hsa-miR-26a
hsa-mir-26a-2No1	uc.77+	-0.6684	hsa-miR-26a
hsa-mir-026a-precNo1	uc.285+	-0.6632	hsa-miR-26a
hsa-mir-26a-1No1	uc.153+A	-0.6606	hsa-miR-26a
hsa-mir-26a-1No1	uc.33+	-0.6551	hsa-miR-26a
hsa-mir-26a-1No1	uc.213+	-0.649	hsa-miR-26a
hsa-mir-26a-1No1	uc.33+A	-0.6486	hsa-miR-26a
hsa-mir-26a-1No1	uc.462+A	-0.6426	hsa-miR-26a
hsa-mir-26a-2No1	uc.483+	-0.6256	hsa-miR-26a
hsa-mir-26a-1No1	uc.234+	-0.622	hsa-miR-26a
hsa-mir-026a-precNo1	uc.477+A	-0.6198	hsa-miR-26a
hsa-mir-26a-1No1	uc.153+	-0.6197	hsa-miR-26a
hsa-mir-26a-1No1	uc.412+A	-0.6184	hsa-miR-26a
hsa-mir-26a-1No1	uc.189+	-0.6139	hsa-miR-26a
hsa-mir-26a-1No1	uc.299+A	-0.6133	hsa-miR-26a
hsa-mir-26a-1No1	uc.354+A	-0.6118	hsa-miR-26a
hsa-mir-26a-1No1	uc.327+A	-0.6113	hsa-miR-26a
hsa-mir-26a-1No1	uc.285+	-0.6089	hsa-miR-26a
hsa-mir-026a-precNo1	uc.420+	-0.6062	hsa-miR-26a
hsa-mir-26a-2No1	uc.151+	-0.6037	hsa-miR-26a
hsa-mir-26a-2No1	uc.466+A	-0.6001	hsa-miR-26a
hsa-mir-26a-1No1	uc.378+	-0.5995	hsa-miR-26a

Figure 18

Calin GA   20

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-026a-precNo1	uc.378+	-0.5988	hsa-miR-26a
hsa-mir-26a-2No1	uc.173+	-0.5976	hsa-miR-26a
hsa-mir-026a-precNo1	uc.462+A	-0.5953	hsa-miR-26a
hsa-mir-026a-precNo1	uc.412+A	-0.5948	hsa-miR-26a
hsa-mir-26a-2No1	uc.465+A	-0.5927	hsa-miR-26a
hsa-mir-26a-1No1	uc.217+A	-0.5922	hsa-miR-26a
hsa-mir-26a-1No1	uc.456+A	-0.5915	hsa-miR-26a
hsa-mir-26a-1No1	uc.477+A	-0.5892	hsa-miR-26a
hsa-mir-026a-precNo1	uc.383+	-0.5886	hsa-miR-26a
hsa-mir-26a-1No1	uc.388+A	-0.5868	hsa-miR-26a
hsa-mir-26a-1No1	uc.44+A	-0.5867	hsa-miR-26a
hsa-mir-26a-1No1	uc.468+	-0.5845	hsa-miR-26a
hsa-mir-026a-precNo1	uc.106+	-0.584	hsa-miR-26a
hsa-mir-26a-1No1	uc.88+	-0.582	hsa-miR-26a
hsa-mir-26a-1No1	uc.173+	-0.581	hsa-miR-26a
hsa-mir-26a-2No1	uc.420+A	-0.5792	hsa-miR-26a
hsa-mir-26a-1No1	uc.388+	-0.5703	hsa-miR-26a
hsa-mir-026a-precNo1	uc.189+	-0.5662	hsa-miR-26a
hsa-mir-26a-1No1	uc.473+A	-0.565	hsa-miR-26a
hsa-mir-26a-1No1	uc.128+A	-0.5601	hsa-miR-26a
hsa-mir-26a-1No1	uc.263+	-0.5601	hsa-miR-26a
hsa-mir-26a-1No1	uc.427+	-0.5591	hsa-miR-26a
hsa-mir-26a-1No1	uc.190+A	-0.5586	hsa-miR-26a
hsa-mir-26a-2No1	uc.339+	-0.5576	hsa-miR-26a
hsa-mir-26a-1No1	uc.420+A	-0.5559	hsa-miR-26a
hsa-mir-26a-1No1	uc.151+	-0.5557	hsa-miR-26a
hsa-mir-026a-precNo1	uc.190+A	-0.5549	hsa-miR-26a
hsa-mir-26a-1No1	uc.8+	-0.5511	hsa-miR-26a
hsa-mir-26a-1No1	uc.20+	-0.5508	hsa-miR-26a
hsa-mir-026a-precNo1	uc.354+A	-0.5479	hsa-miR-26a
hsa-mir-26a-1No1	uc.445+A	-0.5467	hsa-miR-26a
hsa-mir-026a-precNo1	uc.213+	-0.5444	hsa-miR-26a
hsa-mir-26a-2No1	uc.278+	-0.544	hsa-miR-26a
hsa-mir-026a-precNo1	uc.299+A	-0.5424	hsa-miR-26a
hsa-mir-26a-1No1	uc.172+A	-0.5375	hsa-miR-26a
hsa-mir-026a-precNo1	uc.153+A	-0.5371	hsa-miR-26a
hsa-mir-026a-precNo1	uc.412+	-0.5329	hsa-miR-26a
hsa-mir-26a-1No1	uc.177+	-0.5315	hsa-miR-26a
hsa-mir-26a-1No1	uc.275+	-0.5312	hsa-miR-26a
hsa-mir-26a-2No1	uc.349+	-0.5307	hsa-miR-26a
hsa-mir-26a-2No1	uc.262+A	-0.5265	hsa-miR-26a
hsa-mir-26a-1No1	uc.151+A	-0.5261	hsa-miR-26a
hsa-mir-026a-precNo1	uc.217+	-0.5257	hsa-miR-26a
hsa-mir-026a-precNo1	uc.217+A	-0.5248	hsa-miR-26a
hsa-mir-026a-precNo1	uc.44+A	-0.5238	hsa-miR-26a
hsa-mir-026a-precNo1	uc.234+	-0.5182	hsa-miR-26a
hsa-mir-026a-precNo1	uc.327+A	-0.5149	hsa-miR-26a
hsa-mir-026a-precNo1	uc.20+	-0.5143	hsa-miR-26a
hsa-mir-026a-precNo1	uc.78+	-0.5101	hsa-miR-26a
hsa-mir-26a-1No1	uc.20+A	-0.5096	hsa-miR-26a
hsa-mir-26a-1No1	uc.217+	-0.5081	hsa-miR-26a
hsa-mir-26a-1No1	uc.43+	-0.508	hsa-miR-26a
hsa-mir-26a-1No1	uc.468+A	-0.5071	hsa-miR-26a
hsa-mir-26a-1No1	uc.378+A	-0.5064	hsa-miR-26a
hsa-mir-026a-precNo1	uc.427+	-0.5063	hsa-miR-26a
hsa-mir-026a-precNo1	uc.456+	-0.5047	hsa-miR-26a
hsa-mir-026a-precNo1	uc.190+	-0.5041	hsa-miR-26a
hsa-mir-26a-2No1	uc.18+	-0.503	hsa-miR-26a
hsa-mir-026a-precNo1	uc.20+A	-0.4995	hsa-miR-26a
hsa-mir-026a-precNo1	uc.153+	-0.4987	hsa-miR-26a
hsa-mir-026a-precNo1	uc.388+	-0.4984	hsa-miR-26a
hsa-mir-026a-precNo1	uc.287+A	-0.4972	hsa-miR-26a
hsa-mir-26a-2No1	uc.183+	-0.4957	hsa-miR-26a
hsa-mir-26a-2No1	uc.285+	-0.4952	hsa-miR-26a
hsa-mir-26a-2No1	uc.388+A	-0.494	hsa-miR-26a
hsa-mir-026a-precNo1	uc.18+	-0.4894	hsa-miR-26a
hsa-mir-026a-precNo1	uc.275+	-0.4886	hsa-miR-26a
hsa-mir-026a-precNo1	uc.33+A	-0.4872	hsa-miR-26a
hsa-mir-26a-1No1	uc.287+A	-0.4856	hsa-miR-26a
hsa-mir-26a-2No1	uc.8+	-0.4815	hsa-miR-26a
hsa-mir-26a-1No1	uc.263+A	-0.48	hsa-miR-26a
hsa-mir-026a-precNo1	uc.473+A	-0.4796	hsa-miR-26a
hsa-mir-026a-precNo1	uc.468+	-0.4789	hsa-miR-26a
hsa-mir-026a-precNo1	uc.33+	-0.475	hsa-miR-26a
hsa-mir-26a-2No1	uc.33+A	-0.4745	hsa-miR-26a
hsa-mir-26a-2No1	uc.420+	-0.4732	hsa-miR-26a
hsa-mir-026a-precNo1	uc.8+	-0.4726	hsa-miR-26a
hsa-mir-26a-2No1	uc.483+A	-0.4722	hsa-miR-26a
hsa-mir-26a-2No1	uc.213+	-0.4704	hsa-miR-26a
hsa-mir-26a-1No1	uc.190+	-0.4692	hsa-miR-26a
hsa-mir-026a-precNo1	uc.263+	-0.4632	hsa-miR-26a
hsa-mir-026a-precNo1	uc.420+A	-0.4616	hsa-miR-26a
hsa-mir-026a-precNo1	uc.43+	-0.4589	hsa-miR-26a
hsa-mir-026a-precNo1	uc.378+A	-0.4581	hsa-miR-26a

Figure 18

Calin GA   21

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-26a-1No1	uc.77+	-0.453	hsa-miR-26a
hsa-mir-026a-precNo1	uc.173+	-0.4478	hsa-miR-26a
hsa-mir-26a-1No2	uc.229+	-0.7848	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.466+A	-0.7637	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.177+	-0.7241	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.349+	-0.6869	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.346+	-0.6334	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.128+A	-0.6276	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.172+A	-0.6271	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.483+	-0.6171	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.77+	-0.6104	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.426+	-0.5757	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.151+	-0.5346	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.134+A	-0.527	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.278+	-0.524	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.8+	-0.5154	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.262+A	-0.5069	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.204+	-0.5047	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.173+	-0.4692	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.134+	-0.4678	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.165+	-0.4653	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.73+	-0.4614	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.420+A	-0.4584	hsa-mir-26a-1
hsa-mir-26a-1No2	uc.136+	-0.4485	hsa-mir-26a-1
hsa-mir-027a-prec	uc.159+A	-0.6883	hsa-miR-27a
hsa-mir-027a-prec	uc.44+A	-0.6488	hsa-miR-27a
hsa-mir-027a-prec	uc.73+A	-0.6343	hsa-miR-27a
hsa-mir-027a-prec	uc.217+	-0.6231	hsa-miR-27a
hsa-mir-027a-prec	uc.448+	-0.6211	hsa-miR-27a
hsa-mir-027a-prec	uc.477+A	-0.6075	hsa-miR-27a
hsa-mir-027a-prec	uc.475+A	-0.5957	hsa-miR-27a
hsa-mir-027a-prec	uc.142+A	-0.5905	hsa-miR-27a
hsa-mir-027a-prec	uc.287+A	-0.5796	hsa-miR-27a
hsa-mir-027a-prec	uc.338+	-0.5745	hsa-miR-27a
hsa-mir-027a-prec	uc.20+A	-0.5728	hsa-miR-27a
hsa-mir-027a-prec	uc.331+A	-0.5709	hsa-miR-27a
hsa-mir-027a-prec	uc.95+	-0.5648	hsa-miR-27a
hsa-mir-027a-prec	uc.462+A	-0.5534	hsa-miR-27a
hsa-mir-027a-prec	uc.278+A	-0.5491	hsa-miR-27a
hsa-mir-027a-prec	uc.427+	-0.5478	hsa-miR-27a
hsa-mir-027a-prec	uc.291+	-0.5375	hsa-miR-27a
hsa-mir-027a-prec	uc.223+A	-0.5367	hsa-miR-27a
hsa-mir-027a-prec	uc.90+A	-0.5292	hsa-miR-27a
hsa-mir-027a-prec	uc.263+	-0.5258	hsa-miR-27a
hsa-mir-027a-prec	uc.456+	-0.5236	hsa-miR-27a
hsa-mir-027a-prec	uc.298+	-0.5211	hsa-miR-27a
hsa-mir-027a-prec	uc.299+	-0.5208	hsa-miR-27a
hsa-mir-027a-prec	uc.48+A	-0.5141	hsa-miR-27a
hsa-mir-027a-prec	uc.475+	-0.506	hsa-miR-27a
hsa-mir-027a-prec	uc.378+	-0.504	hsa-miR-27a
hsa-mir-027a-prec	uc.412+	-0.4942	hsa-miR-27a
hsa-mir-027a-prec	uc.448+A	-0.4864	hsa-miR-27a
hsa-mir-027a-prec	uc.275+	-0.486	hsa-miR-27a
hsa-mir-027a-prec	uc.456+A	-0.4804	hsa-miR-27a
hsa-mir-027a-prec	uc.477+	-0.4748	hsa-miR-27a
hsa-mir-027a-prec	uc.388+	-0.4692	hsa-miR-27a
hsa-mir-027a-prec	uc.117+	-0.462	hsa-miR-27a
hsa-mir-027a-prec	uc.299+A	-0.4552	hsa-miR-27a
hsa-mir-027a-prec	uc.362+A	-0.4492	hsa-miR-27a
hsa-mir-027a-prec	uc.362+	-0.448	hsa-miR-27a
hsa-mir-029a-2No1	uc.33+A	-0.7241	hsa-miR-29a
hsa-mir-029a-2No1	uc.18+	-0.7165	hsa-miR-29a
hsa-mir-029a-2No1	uc.153+A	-0.7101	hsa-miR-29a
hsa-mir-029a-2No1	uc.106+	-0.6964	hsa-miR-29a
hsa-mir-029a-2No1	uc.172+A	-0.6841	hsa-miR-29a
hsa-mir-029a-2No1	uc.420+	-0.6822	hsa-miR-29a
hsa-mir-029a-2No1	uc.388+A	-0.6634	hsa-miR-29a
hsa-mir-029a-2No1	uc.33+	-0.6613	hsa-miR-29a
hsa-mir-029a-2No1	uc.213+	-0.6581	hsa-miR-29a
hsa-mir-029a-2No1	uc.354+A	-0.6547	hsa-miR-29a
hsa-mir-029a-2No1	uc.383+	-0.6536	hsa-miR-29a
hsa-mir-029a-2No1	uc.346+	-0.6487	hsa-miR-29a
hsa-mir-029a-2No1	uc.77+	-0.6462	hsa-miR-29a
hsa-mir-029a-2No1	uc.234+	-0.6449	hsa-miR-29a
hsa-mir-029a-2No1	uc.128+A	-0.6403	hsa-miR-29a
hsa-mir-029a-2No1	uc.327+A	-0.6293	hsa-miR-29a
hsa-mir-029a-2No1	uc.153+	-0.6226	hsa-miR-29a
hsa-mir-029a-2No1	uc.285+	-0.6206	hsa-miR-29a
hsa-mir-029a-2No1	uc.468+	-0.6194	hsa-miR-29a
hsa-mir-029a-2No1	uc.177+	-0.6126	hsa-miR-29a
hsa-mir-029a-2No1	uc.217+A	-0.598	hsa-miR-29a
hsa-mir-029a-2No1	uc.462+A	-0.5977	hsa-miR-29a
hsa-mir-029a-2No1	uc.88+	-0.5851	hsa-miR-29a
hsa-mir-029a-2No1	uc.465+A	-0.5818	hsa-miR-29a

Figure 18

Calin GA

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miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-029a-2No1	uc.427+	-0.5684	hsa-miR-29a
hsa-mir-029a-2No1	uc.263+	-0.5658	hsa-miR-29a
hsa-mir-029a-2No1	uc.190+A	-0.5606	hsa-miR-29a
hsa-mir-029a-2No1	uc.473+A	-0.5553	hsa-miR-29a
hsa-mir-029a-2No1	uc.189+	-0.5484	hsa-miR-29a
hsa-mir-029a-2No1	uc.173+	-0.5473	hsa-miR-29a
hsa-mir-029a-2No1	uc.20+	-0.5473	hsa-miR-29a
hsa-mir-029a-2No1	uc.456+A	-0.5383	hsa-miR-29a
hsa-mir-029a-2No1	uc.412+A	-0.5377	hsa-miR-29a
hsa-mir-029a-2No1	uc.483+A	-0.5375	hsa-miR-29a
hsa-mir-029a-2No1	uc.151+	-0.5365	hsa-miR-29a
hsa-mir-029a-2No1	uc.151+A	-0.5348	hsa-miR-29a
hsa-mir-029a-2No1	uc.445+A	-0.5315	hsa-miR-29a
hsa-mir-029a-2No1	uc.468+A	-0.5282	hsa-miR-29a
hsa-mir-029a-2No1	uc.183+	-0.5259	hsa-miR-29a
hsa-mir-029a-2No1	uc.420+A	-0.5204	hsa-miR-29a
hsa-mir-029a-2No1	uc.275+	-0.5156	hsa-miR-29a
hsa-mir-029a-2No1	uc.388+	-0.5115	hsa-miR-29a
hsa-mir-029a-2No1	uc.378+A	-0.4976	hsa-miR-29a
hsa-mir-029a-2No1	uc.8+	-0.4922	hsa-miR-29a
hsa-mir-029a-2No1	uc.43+	-0.4883	hsa-miR-29a
hsa-mir-029a-2No1	uc.48+A	-0.4857	hsa-miR-29a
hsa-mir-029a-2No1	uc.160+	-0.4856	hsa-miR-29a
hsa-mir-029a-2No1	uc.44+A	-0.4708	hsa-miR-29a
hsa-mir-029a-2No1	uc.229+	-0.4696	hsa-miR-29a
hsa-mir-029a-2No1	uc.96+	-0.4694	hsa-miR-29a
hsa-mir-029a-2No1	uc.378+	-0.4688	hsa-miR-29a
hsa-mir-029a-2No1	uc.299+A	-0.4679	hsa-miR-29a
hsa-mir-029a-2No1	uc.483+	-0.4599	hsa-miR-29a
hsa-mir-029a-2No1	uc.73+A	-0.4546	hsa-miR-29a
hsa-mir-029a-2No1	uc.339+	-0.4531	hsa-miR-29a
hsa-mir-29b-1No1	uc.33+A	-0.807	hsa-miR-29b
hsa-mir-29b-1No1	uc.106+	-0.8012	hsa-miR-29b
hsa-mir-102-prec-1	uc.106+	-0.7814	hsa-miR-29b
hsa-mir-29b-1No1	uc.153+A	-0.7787	hsa-miR-29b
hsa-mir-102-prec-1	uc.33+A	-0.7718	hsa-miR-29b
hsa-mir-29b-1No1	uc.18+	-0.7641	hsa-miR-29b
hsa-mir-102-prec-1	uc.383+	-0.7596	hsa-miR-29b
hsa-mir-29b-1No1	uc.213+	-0.7533	hsa-miR-29b
hsa-mir-29b-1No1	uc.420+	-0.7426	hsa-miR-29b
hsa-mir-102-prec-1	uc.153+A	-0.7389	hsa-miR-29b
hsa-mir-29b-1No1	uc.153+	-0.7381	hsa-miR-29b
hsa-mir-29b-1No1	uc.354+A	-0.7284	hsa-miR-29b
hsa-mir-102-prec-1	uc.18+	-0.7283	hsa-miR-29b
hsa-mir-29b-1No1	uc.234+	-0.7262	hsa-miR-29b
hsa-mir-29b-1No1	uc.88+	-0.7207	hsa-miR-29b
hsa-mir-29b-1No1	uc.383+	-0.7198	hsa-miR-29b
hsa-mir-102-prec-1	uc.153+	-0.7124	hsa-miR-29b
hsa-mir-102-prec-1	uc.462+A	-0.7117	hsa-miR-29b
hsa-mir-102-prec-1	uc.354+A	-0.7044	hsa-miR-29b
hsa-mir-29b-1No1	uc.462+A	-0.6981	hsa-miR-29b
hsa-mir-102-prec-1	uc.420+	-0.694	hsa-miR-29b
hsa-mir-102-prec-1	uc.263+	-0.6934	hsa-miR-29b
hsa-mir-102-prec-1	uc.468+	-0.6931	hsa-miR-29b
hsa-mir-29b-1No1	uc.33+	-0.6924	hsa-miR-29b
hsa-mir-102-prec-1	uc.213+	-0.6881	hsa-miR-29b
hsa-mir-29b-1No1	uc.217+A	-0.6856	hsa-miR-29b
hsa-mir-29b-1No1	uc.263+	-0.6855	hsa-miR-29b
hsa-mir-102-prec-1	uc.88+	-0.6851	hsa-miR-29b
hsa-mir-29b-1No1	uc.473+A	-0.683	hsa-miR-29b
hsa-mir-29b-1No1	uc.468+	-0.6816	hsa-miR-29b
hsa-mir-29b-1No1	uc.327+A	-0.6814	hsa-miR-29b
hsa-mir-29b-1No1	uc.189+	-0.6811	hsa-miR-29b
hsa-mir-102-prec-1	uc.190+A	-0.6782	hsa-miR-29b
hsa-mir-102-prec-1	uc.473+A	-0.671	hsa-miR-29b
hsa-mir-102-prec-1	uc.33+	-0.6708	hsa-miR-29b
hsa-mir-102-prec-1	uc.20+	-0.6697	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.465+A	-0.6666	hsa-miR-29b
hsa-mir-102-prec-1	uc.427+	-0.6642	hsa-miR-29b
hsa-mir-29b-1No1	uc.388+A	-0.6638	hsa-miR-29b
hsa-mir-102-prec-1	uc.275+	-0.6635	hsa-miR-29b
hsa-mir-102-prec-1	uc.234+	-0.662	hsa-miR-29b
hsa-mir-102-prec-1	uc.456+A	-0.6592	hsa-miR-29b
hsa-mir-29b-1No1	uc.20+	-0.6588	hsa-miR-29b
hsa-mir-102-prec-1	uc.217+A	-0.6576	hsa-miR-29b
hsa-mir-29b-1No1	uc.427+	-0.6568	hsa-miR-29b
hsa-mir-29b-1No1	uc.275+	-0.6548	hsa-miR-29b
hsa-mir-29b-1No1	uc.190+A	-0.6547	hsa-miR-29b
hsa-mir-29b-1No1	uc.388+	-0.6521	hsa-miR-29b
hsa-mir-29b-1No1	uc.456+A	-0.6521	hsa-miR-29b
hsa-mir-102-prec-1	uc.378+	-0.6481	hsa-miR-29b
hsa-mir-29b-1No1	uc.468+A	-0.6473	hsa-miR-29b
hsa-mir-29b-1No1	uc.412+A	-0.6444	hsa-miR-29b
hsa-mir-102-prec-1	uc.388+	-0.6424	hsa-miR-29b

Figure 18

Calin GA   23

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-29b-1No1	uc.378+	-0.6417	hsa-miR-29b
hsa-mir-29b-1No1	uc.445+A	-0.6408	hsa-miR-29b
hsa-mir-102-prec-1	uc.189+	-0.6373	hsa-miR-29b
hsa-mir-102-prec-1	uc.73+A	-0.6347	hsa-miR-29b
hsa-mir-102-prec-1	uc.20+A	-0.6344	hsa-miR-29b
hsa-mir-102-prec-1	uc.287+A	-0.6329	hsa-miR-29b
hsa-mir-102-prec-1	uc.477+A	-0.6322	hsa-miR-29b
hsa-mir-102-prec-1	uc.388+A	-0.6321	hsa-miR-29b
hsa-mir-29b-1No1	uc.73+A	-0.6311	hsa-miR-29b
hsa-mir-102-prec-1	uc.468+A	-0.6279	hsa-miR-29b
hsa-mir-29b-1No1	uc.285+	-0.6216	hsa-miR-29b
hsa-mir-29b-1No1	uc.378+A	-0.6176	hsa-miR-29b
hsa-mir-102-prec-1	uc.378+A	-0.6157	hsa-miR-29b
hsa-mir-102-prec-1	uc.412+A	-0.6069	hsa-miR-29b
hsa-mir-102-prec-1	uc.217+	-0.6014	hsa-miR-29b
hsa-mir-102-prec-1	uc.445+A	-0.598	hsa-miR-29b
hsa-mir-29b-1No1	uc.43+	-0.5968	hsa-miR-29b
hsa-mir-29b-1No1	uc.477+A	-0.5946	hsa-miR-29b
hsa-mir-29b-1No1	uc.20+A	-0.5915	hsa-miR-29b
hsa-mir-102-prec-1	uc.327+A	-0.5913	hsa-miR-29b
hsa-mir-29b-1No1	uc.173+	-0.5912	hsa-miR-29b
hsa-mir-29b-1No1	uc.287+A	-0.5847	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.173+	-0.5795	hsa-miR-29b
hsa-mir-29b-1No1	uc.128+A	-0.5777	hsa-miR-29b
hsa-mir-102-prec-1	uc.43+	-0.574	hsa-miR-29b
hsa-mir-29b-1No1	uc.172+A	-0.5726	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.151+	-0.5721	hsa-miR-29b
hsa-mir-29b-1No1	uc.299+A	-0.5715	hsa-miR-29b
hsa-mir-29b-1No1	uc.448+	-0.5623	hsa-miR-29b
hsa-mir-29b-1No1	uc.44+A	-0.5602	hsa-miR-29b
hsa-mir-29b-1No1	uc.8+	-0.5596	hsa-miR-29b
hsa-mir-102-prec-1	uc.299+A	-0.5586	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.151+A	-0.558	hsa-miR-29b
hsa-mir-102-prec-1	uc.44+A	-0.5579	hsa-miR-29b
hsa-mir-102-prec-1	uc.190+	-0.5573	hsa-miR-29b
hsa-mir-29b-1No1	uc.151+A	-0.5569	hsa-miR-29b
hsa-mir-102-prec-1	uc.285+	-0.5563	hsa-miR-29b
hsa-mir-29b-1No1	uc.170+	-0.5562	hsa-miR-29b
hsa-mir-102-prec-1	uc.483+A	-0.5488	hsa-miR-29b
hsa-mir-102-prec-1	uc.448+	-0.5482	hsa-miR-29b
hsa-mir-102-prec-1	uc.263+A	-0.5465	hsa-miR-29b
hsa-mir-102-prec-1	uc.456+	-0.5464	hsa-miR-29b
hsa-mir-29b-1No1	uc.217+	-0.5452	hsa-miR-29b
hsa-mir-29b-1No1	uc.483+A	-0.5409	hsa-miR-29b
hsa-mir-29b-1No1	uc.420+A	-0.5406	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.420+	-0.5394	hsa-miR-29b
hsa-mir-29b-1No1	uc.190+	-0.5322	hsa-miR-29b
hsa-mir-102-prec-1	uc.170+	-0.5312	hsa-miR-29b
hsa-mir-29b-1No1	uc.263+A	-0.5248	hsa-miR-29b
hsa-mir-29b-1No1	uc.77+	-0.5215	hsa-miR-29b
hsa-mir-29b-1No1	uc.151+	-0.5207	hsa-miR-29b
hsa-mir-29b-1No1	uc.362+	-0.5194	hsa-miR-29b
hsa-mir-29b-1No1	uc.177+	-0.5176	hsa-miR-29b
hsa-mir-102-prec-1	uc.151+A	-0.517	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.420+A	-0.5147	hsa-miR-29b
hsa-mir-29b-1No1	uc.456+	-0.5118	hsa-miR-29b
hsa-mir-29b-1No1	uc.182+	-0.5111	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.77+	-0.5099	hsa-miR-29b
hsa-mir-102-prec-1	uc.448+A	-0.5098	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.128+A	-0.5098	hsa-miR-29b
hsa-mir-102-prec-1	uc.48+A	-0.5069	hsa-miR-29b
hsa-mir-102-prec-1	uc.362+	-0.5056	hsa-miR-29b
hsa-mir-29b-1No1	uc.346+	-0.5014	hsa-miR-29b
hsa-mir-102-prec-1	uc.362+A	-0.5013	hsa-miR-29b
hsa-mir-29b-1No1	uc.362+A	-0.4977	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.172+A	-0.4976	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.300+A	-0.4972	hsa-miR-29b
hsa-mir-102-prec-1	uc.8+	-0.497	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.134+	-0.4959	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.269+A	-0.4947	hsa-miR-29b
hsa-mir-29b-1No1	uc.183+	-0.492	hsa-miR-29b
hsa-mir-102-prec-1	uc.182+	-0.4911	hsa-miR-29b
hsa-mir-29b-1No1	uc.48+A	-0.491	hsa-miR-29b
hsa-mir-29b-1No1	uc.10+	-0.4825	hsa-miR-29b
hsa-mir-102-prec-1	uc.477+	-0.4808	hsa-miR-29b
hsa-mir-102-prec-1	uc.173+	-0.4807	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.33+A	-0.4764	hsa-miR-29b
hsa-mir-102-prec-1	uc.63+	-0.4762	hsa-miR-29b
hsa-mir-29b-1No1	uc.63+	-0.4738	hsa-miR-29b
hsa-mir-102-prec-1	uc.172+A	-0.4735	hsa-miR-29b
hsa-mir-29b-1No1	uc.448+A	-0.4733	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.325+	-0.466	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.183+	-0.4653	hsa-miR-29b
hsa-mir-29b-2=102prec7.1=7.2	uc.419+A	-0.4647	hsa-miR-29b

Figure 18

Calin GA   24

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-29b-2=102prec7.1=7.2	uc.204+	-0.4619	hsa-miR-29b
hsa-mir-29b-1No1	uc.248+	-0.4617	hsa-miR-29b
hsa-mir-29b-1No1	uc.233+A	-0.4594	hsa-miR-29b
hsa-mir-102-prec-1	uc.200+	-0.4591	hsa-miR-29b
hsa-mir-102-prec-1	uc.248+	-0.4555	hsa-miR-29b
hsa-mir-29b-1No1	uc.477+	-0.455	hsa-miR-29b
hsa-mir-29b-1No1	uc.465+A	-0.454	hsa-miR-29b
hsa-mir-29b-1No1	uc.167+	-0.4507	hsa-miR-29b
hsa-mir-29b-1No1	uc.200+	-0.4495	hsa-miR-29b
hsa-mir-029c-prec	uc.106+	-0.7586	hsa-miR-29c
hsa-mir-029c-prec	uc.153+A	-0.7466	hsa-miR-29c
hsa-mir-029c-prec	uc.354+A	-0.7247	hsa-miR-29c
hsa-mir-029c-prec	uc.383+	-0.7195	hsa-miR-29c
hsa-mir-029c-prec	uc.33+A	-0.7185	hsa-miR-29c
hsa-mir-029c-prec	uc.462+A	-0.7154	hsa-miR-29c
hsa-mir-029c-prec	uc.456+A	-0.7066	hsa-miR-29c
hsa-mir-029c-prec	uc.190+A	-0.7064	hsa-miR-29c
hsa-mir-029c-prec	uc.234+	-0.7034	hsa-miR-29c
hsa-mir-029c-prec	uc.18+	-0.7017	hsa-miR-29c
hsa-mir-029c-prec	uc.468+	-0.6997	hsa-miR-29c
hsa-mir-029c-prec	uc.427+	-0.6947	hsa-miR-29c
hsa-mir-029c-prec	uc.388+	-0.6915	hsa-miR-29c
hsa-mir-029c-prec	uc.213+	-0.688	hsa-miR-29c
hsa-mir-029c-prec	uc.153+	-0.6869	hsa-miR-29c
hsa-mir-029c-prec	uc.73+A	-0.6835	hsa-miR-29c
hsa-mir-029c-prec	uc.420+	-0.6784	hsa-miR-29c
hsa-mir-029c-prec	uc.263+	-0.67	hsa-miR-29c
hsa-mir-029c-prec	uc.473+A	-0.6687	hsa-miR-29c
hsa-mir-029c-prec	uc.275+	-0.6662	hsa-miR-29c
hsa-mir-029c-prec	uc.20+	-0.6608	hsa-miR-29c
hsa-mir-029c-prec	uc.287+A	-0.6604	hsa-miR-29c
hsa-mir-029c-prec	uc.477+A	-0.6599	hsa-miR-29c
hsa-mir-029c-prec	uc.217+A	-0.6569	hsa-miR-29c
hsa-mir-029c-prec	uc.378+	-0.6539	hsa-miR-29c
hsa-mir-029c-prec	uc.20+A	-0.6522	hsa-miR-29c
hsa-mir-029c-prec	uc.88+	-0.647	hsa-miR-29c
hsa-mir-029c-prec	uc.378+A	-0.6368	hsa-miR-29c
hsa-mir-029c-prec	uc.33+	-0.6322	hsa-miR-29c
hsa-mir-029c-prec	uc.388+A	-0.6228	hsa-miR-29c
hsa-mir-029c-prec	uc.412+A	-0.6209	hsa-miR-29c
hsa-mir-029c-prec	uc.189+	-0.6208	hsa-miR-29c
hsa-mir-029c-prec	uc.468+A	-0.6189	hsa-miR-29c
hsa-mir-029c-prec	uc.445+A	-0.6083	hsa-miR-29c
hsa-mir-029c-prec	uc.217+	-0.6001	hsa-miR-29c
hsa-mir-029c-prec	uc.43+	-0.5863	hsa-miR-29c
hsa-mir-029c-prec	uc.327+A	-0.5852	hsa-miR-29c
hsa-mir-029c-prec	uc.44+A	-0.5792	hsa-miR-29c
hsa-mir-029c-prec	uc.170+	-0.5568	hsa-miR-29c
hsa-mir-029c-prec	uc.285+	-0.5559	hsa-miR-29c
hsa-mir-029c-prec	uc.299+A	-0.555	hsa-miR-29c
hsa-mir-029c-prec	uc.263+A	-0.5516	hsa-miR-29c
hsa-mir-029c-prec	uc.448+	-0.5516	hsa-miR-29c
hsa-mir-029c-prec	uc.362+	-0.5513	hsa-miR-29c
hsa-mir-029c-prec	uc.448+A	-0.5469	hsa-miR-29c
hsa-mir-029c-prec	uc.190+	-0.5464	hsa-miR-29c
hsa-mir-029c-prec	uc.48+A	-0.545	hsa-miR-29c
hsa-mir-029c-prec	uc.362+A	-0.5366	hsa-miR-29c
hsa-mir-029c-prec	uc.456+	-0.5164	hsa-miR-29c
hsa-mir-029c-prec	uc.151+A	-0.5074	hsa-miR-29c
hsa-mir-029c-prec	uc.173+	-0.5017	hsa-miR-29c
hsa-mir-029c-prec	uc.200+	-0.4979	hsa-miR-29c
hsa-mir-029c-prec	uc.477+	-0.4973	hsa-miR-29c
hsa-mir-029c-prec	uc.8+	-0.4934	hsa-miR-29c
hsa-mir-029c-prec	uc.63+	-0.4924	hsa-miR-29c
hsa-mir-029c-prec	uc.483+A	-0.4923	hsa-miR-29c
hsa-mir-029c-prec	uc.172+A	-0.4851	hsa-miR-29c
hsa-mir-029c-prec	uc.420+A	-0.4814	hsa-miR-29c
hsa-mir-029c-prec	uc.182+	-0.4763	hsa-miR-29c
hsa-mir-029c-prec	uc.248+	-0.4746	hsa-miR-29c
hsa-mir-029c-prec	uc.233+A	-0.4698	hsa-miR-29c
hsa-mir-029c-prec	uc.10+	-0.4508	hsa-miR-29c
hsa-mir-029c-prec	uc.128+A	-0.4479	hsa-miR-29c
hsa-mir-030a-precNo1	uc.282+A	-0.7	hsa-miR-30a-5p
hsa-mir-030a-precNo1	uc.465+A	-0.633	hsa-miR-30a-5p
hsa-mir-030a-precNo1	uc.325+	-0.6138	hsa-miR-30a-5p
hsa-mir-030a-precNo1	uc.346+A	-0.5258	hsa-miR-30a-5p
hsa-mir-030a-precNo1	uc.339+	-0.5164	hsa-miR-30a-5p
hsa-mir-030a-precNo1	uc.151+A	-0.5097	hsa-miR-30a-5p
hsa-mir-030a-precNo1	uc.142+	-0.4975	hsa-miR-30a-5p
hsa-mir-030a-precNo1	uc.285+	-0.4758	hsa-miR-30a-5p
hsa-mir-030a-precNo1	uc.142+A	-0.4757	hsa-miR-30a-5p
hsa-mir-030a-precNo1	uc.77+	-0.4573	hsa-miR-30a-5p
hsa-mir-030a-precNo1	uc.172+A	-0.4541	hsa-miR-30a-5p
hsa-mir-030a-precNo1	uc.346+	-0.4496	hsa-miR-30a-5p

Figure 18

Calin GA   25

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-030c-prec	uc.420+	-0.6341	hsa-miR-30c
hsa-mir-30c-1No1	uc.339+	-0.6082	hsa-miR-30c
hsa-mir-30c-1No1	uc.346+	-0.5928	hsa-miR-30c
hsa-mir-030c-prec	uc.189+	-0.5918	hsa-miR-30c
hsa-mir-30c-1No1	uc.172+A	-0.5838	hsa-miR-30c
hsa-mir-030c-prec	uc.339+	-0.5644	hsa-miR-30c
hsa-mir-030c-prec	uc.285+	-0.5631	hsa-miR-30c
hsa-mir-30c-1No1	uc.285+	-0.5622	hsa-miR-30c
hsa-mir-30c-1No1	uc.177+	-0.545	hsa-miR-30c
hsa-mir-030c-prec	uc.299+A	-0.5439	hsa-miR-30c
hsa-mir-30c-1No1	uc.213+	-0.5393	hsa-miR-30c
hsa-mir-030c-prec	uc.172+A	-0.5363	hsa-miR-30c
hsa-mir-30c-1No1	uc.278+	-0.532	hsa-miR-30c
hsa-mir-30c-1No1	uc.151+	-0.531	hsa-miR-30c
hsa-mir-030c-prec	uc.468+	-0.5264	hsa-miR-30c
hsa-mir-030c-prec	uc.73+A	-0.5231	hsa-miR-30c
hsa-mir-030c-prec	uc.213+	-0.5135	hsa-miR-30c
hsa-mir-30c-1No1	uc.229+	-0.5097	hsa-miR-30c
hsa-mir-030c-prec	uc.128+A	-0.5092	hsa-miR-30c
hsa-mir-30c-1No1	uc.189+	-0.508	hsa-miR-30c
hsa-mir-30c-1No1	uc.465+A	-0.5036	hsa-miR-30c
hsa-mir-30c-1No1	uc.128+A	-0.5012	hsa-miR-30c
hsa-mir-030c-prec	uc.278+	-0.498	hsa-miR-30c
hsa-mir-30c-1No1	uc.420+	-0.4974	hsa-miR-30c
hsa-mir-30c-1No1	uc.466+A	-0.4963	hsa-miR-30c
hsa-mir-30c-1No1	uc.77+	-0.4963	hsa-miR-30c
hsa-mir-30c-1No1	uc.349+	-0.496	hsa-miR-30c
hsa-mir-30c-1No1	uc.234+	-0.4921	hsa-miR-30c
hsa-mir-30c-1No1	uc.173+	-0.488	hsa-miR-30c
hsa-mir-030c-prec	uc.465+A	-0.4874	hsa-miR-30c
hsa-mir-030c-prec	uc.173+	-0.4871	hsa-miR-30c
hsa-mir-30c-1No1	uc.18+	-0.4869	hsa-miR-30c
hsa-mir-030c-prec	uc.234+	-0.4851	hsa-miR-30c
hsa-mir-030c-prec	uc.8+	-0.4842	hsa-miR-30c
hsa-mir-030c-prec	uc.160+	-0.484	hsa-miR-30c
hsa-mir-030c-prec	uc.151+	-0.4826	hsa-miR-30c
hsa-mir-30c-1No1	uc.419+A	-0.4825	hsa-miR-30c
hsa-mir-30c-1No1	uc.153+A	-0.4823	hsa-miR-30c
hsa-mir-030c-prec	uc.33+A	-0.481	hsa-miR-30c
hsa-mir-030c-prec	uc.217+A	-0.4775	hsa-miR-30c
hsa-mir-030c-prec	uc.419+A	-0.4775	hsa-miR-30c
hsa-mir-030c-prec	uc.177+	-0.4754	hsa-miR-30c
hsa-mir-030c-prec	uc.233+A	-0.4738	hsa-miR-30c
hsa-mir-030c-prec	uc.18+	-0.4729	hsa-miR-30c
hsa-mir-030c-prec	uc.153+A	-0.472	hsa-miR-30c
hsa-mir-30c-1No1	uc.468+	-0.4717	hsa-miR-30c
hsa-mir-030c-prec	uc.183+	-0.4713	hsa-miR-30c
hsa-mir-030c-prec	uc.262+A	-0.4678	hsa-miR-30c
hsa-mir-30c-1No1	uc.388+A	-0.464	hsa-miR-30c
hsa-mir-030c-prec	uc.134+A	-0.462	hsa-miR-30c
hsa-mir-030c-prec	uc.354+A	-0.4614	hsa-miR-30c
hsa-mir-030c-prec	uc.282+A	-0.4607	hsa-miR-30c
hsa-mir-30c-1No1	uc.33+	-0.4602	hsa-miR-30c
hsa-mir-030c-prec	uc.412+A	-0.4571	hsa-miR-30c
hsa-mir-30c-1No1	uc.183+	-0.4554	hsa-miR-30c
hsa-mir-30c-1No1	uc.299+A	-0.4544	hsa-miR-30c
hsa-mir-30c-1No1	uc.33+A	-0.4504	hsa-miR-30c
hsa-mir-030c-prec	uc.420+A	-0.4491	hsa-miR-30c
hsa-mir-030c-prec	uc.44+A	-0.4483	hsa-miR-30c
hsa-mir-030c-prec	uc.466+A	-0.4481	hsa-miR-30c
hsa-mir-030d-precNo2	uc.325+	-0.6363	hsa-miR-30d
hsa-mir-030d-precNo2	uc.465+A	-0.6068	hsa-miR-30d
hsa-mir-030d-precNo2	uc.282+A	-0.533	hsa-miR-30d
hsa-mir-030d-precNo2	uc.339+	-0.4846	hsa-miR-30d
hsa-mir-30eNo1	uc.285+	-0.6838	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.420+	-0.6583	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.33+A	-0.6517	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.153+A	-0.6433	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.73+A	-0.6378	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.213+	-0.631	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.234+	-0.6107	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.327+A	-0.6071	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.18+	-0.5974	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.462+A	-0.5968	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.106+	-0.595	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.275+	-0.5876	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.388+A	-0.5848	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.44+A	-0.5762	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.189+	-0.5713	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.153+	-0.5619	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.33+	-0.5613	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.465+A	-0.561	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.88+	-0.5554	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.173+	-0.5536	hsa-miR-30e-5p

Figure 18

Calin GA   26

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-30eNo1	uc.354+A	-0.5512	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.383+	-0.5499	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.388+	-0.5358	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.299+A	-0.5345	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.217+A	-0.5278	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.151+A	-0.5268	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.172+A	-0.5259	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.346+	-0.5255	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.151+	-0.5234	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.183+	-0.5203	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.456+A	-0.519	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.8+	-0.5157	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.427+	-0.5153	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.117+	-0.5067	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.177+	-0.5023	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.167+	-0.4966	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.77+	-0.4959	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.412+A	-0.4889	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.263+	-0.4869	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.473+A	-0.4836	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.128+A	-0.4823	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.190+A	-0.4798	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.468+	-0.4784	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.48+A	-0.47	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.420+A	-0.4697	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.478+A	-0.4692	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.20+A	-0.466	hsa-miR-30e-5p
hsa-mir-30eNo1	uc.190+	-0.4498	hsa-miR-30e-5p
hsa-mir-032-precNo2	uc.478+	-0.6778	hsa-miR-32
hsa-mir-032-precNo2	uc.1+	-0.6241	hsa-miR-32
hsa-mir-032-precNo2	uc.475+	-0.483	hsa-miR-32
hsa-mir-032-precNo2	uc.192+	-0.471	hsa-miR-32
hsa-mir-032-precNo2	uc.389+	-0.4667	hsa-miR-32
hsa-mir-320No1	uc.262+A	-0.6262	hsa-miR-320
hsa-mir-320No1	uc.278+	-0.618	hsa-miR-320
hsa-mir-320No1	uc.160+	-0.6056	hsa-miR-320
hsa-mir-320No1	uc.339+	-0.6013	hsa-miR-320
hsa-mir-320No1	uc.269+A	-0.5776	hsa-miR-320
hsa-mir-320No1	uc.349+	-0.563	hsa-miR-320
hsa-mir-320No2	uc.229+	-0.5378	hsa-mir-320
hsa-mir-320No2	uc.466+A	-0.5314	hsa-mir-320
hsa-mir-320No1	uc.136+	-0.5267	hsa-miR-320
hsa-mir-320No1	uc.73+	-0.5223	hsa-miR-320
hsa-mir-320No1	uc.400+A	-0.5113	hsa-miR-320
hsa-mir-320No1	uc.229+	-0.508	hsa-miR-320
hsa-mir-320No1	uc.204+	-0.475	hsa-miR-320
hsa-mir-320No1	uc.317+	-0.4726	hsa-miR-320
hsa-mir-320No1	uc.398+	-0.4724	hsa-miR-320
hsa-mir-320No1	uc.285+	-0.4659	hsa-miR-320
hsa-mir-320No1	uc.186+A	-0.4629	hsa-miR-320
hsa-mir-320No1	uc.377+A	-0.4596	hsa-miR-320
hsa-mir-320No2	uc.345+	-0.4594	hsa-mir-320
hsa-mir-320No1	uc.466+A	-0.4551	hsa-miR-320
hsa-miR-324-5pNo1	uc.378+	-0.6435	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.88+	-0.6372	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.287+A	-0.6257	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.477+A	-0.6203	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.473+A	-0.6191	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.468+A	-0.6112	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.217+A	-0.6071	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.462+A	-0.5899	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.63+	-0.5893	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.445+A	-0.5876	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.477+	-0.5781	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.388+	-0.5754	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.153+	-0.5736	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.354+A	-0.5702	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.378+A	-0.5702	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.170+	-0.5645	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.20+A	-0.562	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.182+	-0.5558	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.217+	-0.5518	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.190+A	-0.5457	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.362+A	-0.5423	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.106+	-0.5351	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.43+	-0.5339	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.263+	-0.5321	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.190+	-0.5253	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.33+	-0.5147	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.189+	-0.51	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.338+	-0.5086	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.20+	-0.4955	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.383+	-0.4933	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.95+	-0.4919	hsa-miR-324-5p

Figure 18

Calin GA   27

miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-miR-324-5pNo1	uc.234+	-0.4877	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.275+	-0.4865	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.420+	-0.4815	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.88+A	-0.4798	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.153+A	-0.4773	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.362+	-0.4721	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.468+	-0.4719	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.412+	-0.4669	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.299+A	-0.457	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.412+A	-0.4554	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.475+A	-0.4516	hsa-miR-324-5p
hsa-miR-324-5pNo1	uc.448+A	-0.4483	hsa-miR-324-5p
hsa-mir-328No1	uc.229+	-0.6749	hsa-miR-328
hsa-mir-328No1	uc.483+	-0.6617	hsa-miR-328
hsa-mir-328No1	uc.466+A	-0.5846	hsa-miR-328
hsa-mir-328No1	uc.128+A	-0.5712	hsa-miR-328
hsa-mir-328No1	uc.177+	-0.5702	hsa-miR-328
hsa-mir-328No1	uc.346+	-0.5528	hsa-miR-328
hsa-mir-328No1	uc.77+	-0.5454	hsa-miR-328
hsa-mir-328No1	uc.172+A	-0.5328	hsa-miR-328
hsa-mir-328No1	uc.142+	-0.4902	hsa-miR-328
hsa-mir-328No1	uc.345+	-0.4807	hsa-miR-328
hsa-mir-328No1	uc.41+	-0.4667	hsa-miR-328
hsa-mir-331No2	uc.366+	-0.5883	hsa-mir-331
hsa-mir-331No2	uc.125+A	-0.5798	hsa-mir-331
hsa-mir-331No2	uc.345+A	-0.5671	hsa-mir-331
hsa-mir-331No2	uc.136+	-0.548	hsa-mir-331
hsa-mir-331No2	uc.73+	-0.5026	hsa-mir-331
hsa-mir-331No2	uc.192+	-0.4928	hsa-mir-331
hsa-mir-331No2	uc.230+	-0.4886	hsa-mir-331
hsa-mir-331No2	uc.31+	-0.4558	hsa-mir-331
hsa-mir-033b-prec	uc.159+A	-0.5238	hsa-miR-33b
hsa-mir-340No2	uc.383+	-0.5595	hsa-mir-340
hsa-mir-340No2	uc.462+A	-0.5231	hsa-mir-340
hsa-mir-340No2	uc.20+A	-0.4993	hsa-mir-340
hsa-mir-340No2	uc.48+A	-0.4757	hsa-mir-340
hsa-mir-340No2	uc.63+	-0.4736	hsa-mir-340
hsa-mir-340No2	uc.477+	-0.4717	hsa-mir-340
hsa-mir-340No2	uc.153+	-0.4698	hsa-mir-340
hsa-mir-340No2	uc.20+	-0.4698	hsa-mir-340
hsa-mir-340No2	uc.263+	-0.4673	hsa-mir-340
hsa-mir-340No2	uc.287+A	-0.4579	hsa-mir-340
hsa-mir-340No2	uc.468+A	-0.4483	hsa-mir-340
hsa-mir-340No2	uc.388+	-0.4477	hsa-mir-340
hsa-mir-342No1	uc.192+	-0.7322	hsa-miR-342
hsa-mir-342No1	uc.389+	-0.7241	hsa-miR-342
hsa-mir-342No1	uc.478+	-0.6819	hsa-miR-342
hsa-mir-342No1	uc.366+	-0.6742	hsa-miR-342
hsa-mir-342No2	uc.136+	-0.5518	hsa-mir-342
hsa-mir-342No1	uc.125+A	-0.5505	hsa-miR-342
hsa-mir-342No1	uc.346+A	-0.5347	hsa-miR-342
hsa-mir-342No1	uc.24+A	-0.5191	hsa-miR-342
hsa-mir-342No1	uc.73+	-0.5188	hsa-miR-342
hsa-mir-342No1	uc.181+A	-0.5034	hsa-miR-342
hsa-mir-342No1	uc.230+	-0.5023	hsa-miR-342
hsa-mir-342No2	uc.110+A	-0.4937	hsa-mir-342
hsa-mir-342No1	uc.31+	-0.4617	hsa-miR-342
hsa-mir-342No1	uc.345+A	-0.4516	hsa-miR-342
hsa-mir-346No1	uc.462+	-0.6113	hsa-miR-346
hsa-mir-346No1	uc.204+	-0.6083	hsa-miR-346
hsa-mir-346No1	uc.229+	-0.544	hsa-miR-346
hsa-mir-346No1	uc.345+	-0.5386	hsa-miR-346
hsa-mir-346No1	uc.131+	-0.4891	hsa-miR-346
hsa-mir-346No1	uc.41+	-0.4822	hsa-miR-346
hsa-mir-346No1	uc.73+	-0.4746	hsa-miR-346
hsa-mir-346No1	uc.177+	-0.4563	hsa-miR-346
hsa-mir-346No1	uc.483+	-0.4557	hsa-miR-346
hsa-mir-346No1	uc.346+	-0.4534	hsa-miR-346
hsa-mir-346No1	uc.192+	-0.4531	hsa-miR-346
hsa-mir-346No1	uc.349+	-0.4507	hsa-miR-346
hsa-mir-346No1	uc.366+	-0.4497	hsa-miR-346
hsa-miR-373No1	uc.181+A	-0.7065	hsa-miR-373
hsa-miR-373No1	uc.125+A	-0.681	hsa-miR-373
hsa-miR-373No1	uc.366+	-0.6479	hsa-miR-373
hsa-miR-373No1	uc.345+A	-0.6197	hsa-miR-373
hsa-miR-373No1	uc.192+	-0.5652	hsa-miR-373
hsa-miR-373No1	uc.230+	-0.5647	hsa-miR-373
hsa-miR-373No1	uc.317+	-0.4556	hsa-miR-373
hsa-mir-009-3No1	uc.477+A	-0.6051	hsa-miR-9
hsa-mir-009-1No1	uc.345+A	-0.6035	hsa-miR-9
hsa-mir-009-1No1	uc.125+A	-0.5789	hsa-miR-9
hsa-mir-009-3No1	uc.287+A	-0.555	hsa-miR-9
hsa-mir-009-1No1	uc.31+	-0.5493	hsa-miR-9
hsa-mir-009-1No1	uc.192+	-0.5477	hsa-miR-9

Figure 18

Calin GA

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miRNA probe on array	UCR probe on array	Correlations (Spearman Method)	miRNA
hsa-mir-009-1No1	uc.366+	-0.5436	hsa-miR-9
hsa-mir-009-3No1	uc.477+	-0.5428	hsa-miR-9
hsa-mir-009-3No1	uc.217+	-0.5426	hsa-miR-9
hsa-mir-009-3No1	uc.378+	-0.5219	hsa-miR-9
hsa-mir-009-3No1	uc.159+A	-0.5153	hsa-miR-9
hsa-mir-009-1No1	uc.230+	-0.5152	hsa-miR-9
hsa-mir-009-3No1	uc.362+A	-0.4909	hsa-miR-9
hsa-mir-009-3No1	uc.95+	-0.4895	hsa-miR-9
hsa-mir-009-3No1	uc.448+A	-0.4804	hsa-miR-9
hsa-mir-009-1No1	uc.136+	-0.4591	hsa-miR-9
hsa-mir-009-3No1	uc.475+A	-0.453	hsa-miR-9
hsa-mir-009-3No1	uc.338+	-0.4526	hsa-miR-9
hsa-mir-009-3No1	uc.412+	-0.451	hsa-miR-9
hsa-mir-009-3No1	uc.20+A	-0.4482	hsa-miR-9
hsa-mir-092-prec-X=092-2	uc.478+	-0.7591	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.478+	-0.7553	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.389+	-0.7431	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.192+	-0.7375	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.389+	-0.7308	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.192+	-0.7224	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.346+A	-0.7064	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.366+	-0.6828	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.346+A	-0.6735	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.366+	-0.6722	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.24+A	-0.5623	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.181+A	-0.5452	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.24+A	-0.5418	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.34+A	-0.5234	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.125+A	-0.523	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.34+A	-0.5132	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.341+A	-0.5126	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.73+	-0.503	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.31+	-0.4945	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.31+	-0.4884	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.125+A	-0.4787	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.230+	-0.4745	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.181+A	-0.4655	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.204+A	-0.4646	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.73+	-0.4646	hsa-miR-92
hsa-mir-092-prec-13=092-1No2	uc.398+	-0.4624	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.341+A	-0.4594	hsa-miR-92
hsa-mir-092-prec-X=092-2	uc.230+	-0.4581	hsa-miR-92
hsa-mir-093-prec-7.1=093-1	uc.465+A	-0.6446	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.346+A	-0.6245	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.167+	-0.6053	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.283+A	-0.5887	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.478+A	-0.5851	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.300+A	-0.5787	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.282+A	-0.5446	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.84+A	-0.5424	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.325+	-0.531	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.269+A	-0.5227	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.352+	-0.4992	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.398+	-0.495	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.160+	-0.4929	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.117+	-0.482	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.48+A	-0.4761	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.299+	-0.4755	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.339+	-0.4717	hsa-miR-93
hsa-mir-093-prec-7.1=093-1	uc.110+A	-0.4521	hsa-miR-93
hsa-mir-095-prec-4	uc.204+	-0.6042	hsa-miR-95
hsa-mir-095-prec-4	uc.345+	-0.5157	hsa-miR-95
hsa-mir-095-prec-4	uc.73+	-0.5079	hsa-miR-95
hsa-mir-095-prec-4	uc.192+	-0.4705	hsa-miR-95
hsa-mir-095-prec-4	uc.41+	-0.4661	hsa-miR-95
hsa-mir-095-prec-4	uc.346+A	-0.4615	hsa-miR-95
hsa-mir-095-prec-4	uc.366+	-0.4572	hsa-miR-95
hsa-mir-095-prec-4	uc.465+A	-0.451	hsa-miR-95
hsa-mir-095-prec-4	uc.341+A	-0.4507	hsa-miR-95
hsa-mir-095-prec-4	uc.462+	-0.4506	hsa-miR-95

Figure 18

SEQUENCE LISTING

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<151> 2007-08-03

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<210> 4
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> 4
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<212> DNA
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<220>
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<210> 6
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<400> 8
tggagataca acaagataac attaatgagt   30