

## **miR-16 and miR-125b are involved in barrier function dysregulation through the modulation of claudin-2 and cingulin expression in the jejunum of irritable bowel syndrome with diarrhoea**

**Martinez et al.**

### **Supplementary Methods**

#### **RNA isolation**

Total RNA was isolated from jejunal biopsies. Briefly, samples were disrupted in 1 mL of Trizol and the aqueous phase cleaned-up through the miRVANA columns following the manufacturer's instructions. The organic phase was then stored at -80°C until isolation of proteins according to the recommendation of the manufacturer.

Prior to expression analysis, RNA quantity and quality were confirmed by capillary electrophoresis (Agilent 2100 Bioanalyzer; Agilent Technologies). Average RNA integrity number (RIN) was 7.5 (range 5.5 to 9.6). Samples showing RIN values <8 were excluded for RNAseq analysis and 16 samples from the remaining (8 IBS-D and 8 healthy controls) were then blindly selected for RNAseq and showed an average RIN value of 8.4 (range 8.1 to 8.8).

#### **miRNA and mRNA expression profiling**

a) miRNA profiling was performed using two different profiling technologies: Agilent microarrays (Agilent's Unrestricted\_Human\_miRNA\_V16.0) and the nCounter system (NanoString Technologies, USA, [www.nanostring.com](http://www.nanostring.com)). For microarray profiling, RNA processing and hybridisation steps were carried out at the Gene Core facility of the European Molecular Biology Laboratory (EMBL, Heidelberg, Germany, <http://genecore3.genecore.embl.de/genecore3/index.cfm>). nCounter profiling, was carried out at the nCounter Core Facility of the University of Heidelberg (Heidelberg, Germany, [www.ncounter.uni-hd.de](http://www.ncounter.uni-hd.de)) using the Human v2 miRNA Expression Assay Kit assessing expression of 800 human miRNAs derived from miRBase v.14.

b) mRNA profiles were generated by RNAseq on an Illumina Hi-Seq 2000 at the Genomics Core Facility of the EMBL (Heidelberg, Germany). Briefly, one microgram of total RNA was used to create a polyA<sup>+</sup> stranded barcoded cDNA library using standard protocols. Six samples were pooled for each lane for Illumina Hi-seq 2000 sequencing.

#### **cDNA synthesis and quantitative Real Time PCR (qPCR)**

cDNA synthesis was performed using 20 ng of total RNA with the Universal cDNA Synthesis Kit II (Exiqon, Denmark). qPCR was performed on an ABI PRISM® 7500 FAST Sequence Detection System (Life Technologies, Germany) using LNA-primers (Exiqon, Denmark). Each sample, including distilled water as negative control, was run in triplicate and data was analysed by the  $2^{-\Delta\Delta C_t}$  method, as previously described.[1] The expression of each miRNA was normalised to the average of 3 selected reference small RNAs (U6, RNU5G and SNORD44) and the fold-change was calculated individually respect to the average of the HC group.

#### nCounter mRNA analysis

One hundred ng of total RNA were used as input material in the quantitative expression analysis using the nCounter system (NanoString Technologies, USA) hybridising a customized Gene Expression CodeSet, as recommended by the manufacturer. Background correction and normalisation of data was performed using the NanoString software nSolver 2.0 (NanoString Technologies, USA). Expression of the target genes was normalised by taking the geometric mean of the expression of four reference genes (*GAPDH*, *RPS17*, *TBP* and *UBC*) into account.[2]

#### Protein isolation and Western blot analysis

Protein was isolated from the organic phase stored after total RNA isolation applying the Trizol protocol and quantified by the Bradford method. Equal amounts of protein were separated by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) and transferred to a poly(vinylidene difluoride) membrane. Subsequently, membranes were blocked with Odyssey® Blocking Buffer (LI-COR® Biotechnology, Germany) and incubated with primary antibodies (supplementary table 3). After three cycles of washing in 1x TBS-Tween, membranes were incubated with secondary antibodies (supplementary table 3) protected from light. Membranes were washed three times with 1x TBS-Tween, scanned with a LICOR® Odyssey Infrared Imaging System (LI-COR® Biotechnology, Germany) and analysed by the Image Studio v4.0 software, provided by the manufacturer.

#### Cell culture

T84 human colon carcinoma cells (ATCC CCL-248) were maintained in 50:50 mixture of Dulbecco's modified Eagle's medium (DMEM) and F12 (GibCo) supplemented with 10% heat-inactivated fetal bovine serum (FBS) and 1% penicillin/streptomycin (Gibco). Colo320 cells were maintained in DMEM-GlutaMax medium supplemented with 10% heat-inactivated FBS (Life Technologies, Germany) and

100 U/ml penicillin and 100 µg/ml streptomycin (Life Technologies, Germany). Cells were maintained in a humidified atmosphere containing 5% CO<sub>2</sub> at 37°C.

#### Plasmid generation and mutagenesis

miRNA precursors were amplified from genomic DNA and cloned in the pEP-miR vector (Cell Biolabs, Germany) via *Bam*HI and *Nhe*I restriction sites. Site-specific mutagenesis was performed using the QuikChange® Lightning Site-Directed Mutagenesis Kit (Stratagene, Germany) following manufacturer's instructions. Plasmids were purified using the PureLink® HiPure Plasmid Filter Midiprep Kit (Life Technologies, Germany) and inserted sequences verified by Sanger sequencing (GATC Biotech, Germany). All primers used for cloning purposes are listed in Supplementary Table 4.

#### Transfection of cell lines

Transfections for In-Cell Western (ICW) experiments were carried out seeding cells at 80% density onto Poly-L-Lysine (Sigma, Germany) coated 96-well plates one day prior to transfection. pEP-miR wild-type or mutated vectors with or without mirVANA inhibitors (Life Technologies, Germany) were co-transfected using polyethylenimine (PEI), as follows. A PEI (µl) to plasmid DNA ratio (µg) of 3:1 was used to transfect cells in 96-well plates, according to general protocols. Briefly, PEI was diluted in OptiMem (Life Technologies, Germany) and incubated for 5 min at room temperature. A total of 150 ng of pEP-miR vectors, 50 ng of a GFP-expressing vector and 50-150 pmol of mirVANA inhibitors were diluted in OptiMem and then combined with the diluted PEI. Mixture was incubated for 30 min at room temperature and then added to each well containing cells and medium. Plates were then incubated for 8h followed by a medium change. Cells were further incubated at 37°C and 5% CO<sub>2</sub> for 48h until analysis.

#### Production of stable cell lines.

T84 cells were seeded onto 6-well plates. One day post-seeding cells were transduced with lentivirus expressing the miRNA constructs. Three days post-transduction, new lentiviruses were added to cells. Three days post-second transduction media was removed and replaced with media containing 10µg/mL puromycin. Cells were selected until all control cells had died. Media was then replaced with normal culture media and cells were grown to confluency.

#### Polarization of T84 cells on transwell inserts.

1.2x10<sup>5</sup> T84 cells were seeded on polycarbonate transwell inserts (Corning, polycarbonate, 3.0µM) in DMEM/F12 medium. Medium was replaced 24h post-seeding and every two days subsequently. The trans-epithelial electrical resistance (TEER) was tested as indicated with EVOM<sup>2</sup> apparatus (World

Precision Instrument). When the TEER reached 1000 Ohm/cm<sup>2</sup>, the T84 cells were considered polarized. Polarization was controlled by immunostaining of the tight junction protein ZO-1 (see indirect immunofluorescence assay).

#### Indirect Immunofluorescence Assay.

Cells were fixed in 2% paraformaldehyde (PFA) for 20mins at room temperature (RT). Cells were washed and permeabilized in 0.5% Triton-X for 15 mins at RT. Primary antibodies were diluted in phosphate-buffered saline (PBS) and incubated for 1h at RT. Membranes were washed in 1X PBS three times and incubated with secondary antibodies for 45mins at RT. Membranes were washed in 1X PBS three times and mounted on slides with ProLong Gold DAPI (Molecular Probes). Cells were imaged by epifluorescence on a Nikon Eclipse Ti-S (Nikon) or by confocal tile scans on a Zeiss LSM 780 (Zeiss).

#### In-cell Western analysis

Forty-eight hours after transfection, cells were washed once with PBS and immediately fixed with 4% PFA for 15 min. Afterwards, cells were washed three times and permeabilised with 0.1% Triton X-100 (5 min/wash) and subsequently blocked with Odyssey® Blocking Buffer (LI-COR® Biotechnology, Germany). Incubation with 1:300 diluted primary antibodies (supplementary table 3) was carried out in Odyssey® Blocking Buffer followed by another three wash cycles with PBS. Then, cells were incubated with secondary antibody (supplementary table 3) protected from light, washed three times with PBS, scanned with a LICOR® Odyssey Infrared Imaging System and analysed by the Image Studio v4.0 software, provided by the manufacturer.

#### **Statistical Analysis of miRNA profiling data**

Analysis of raw data was done using R version 2.15.2 (R Development Core Team).

The R package AgiMicroRNA [3] was applied to raw data from Agilent miRNA microarrays using RMA normalization. AgiMicroRNA was specifically developed for data pre-processing of Agilent microRNA microarrays in order to take advantage of the probe replication in the Agilent microRNA arrays and demonstrated to be equal quantile normalization and even superior in terms of variability reduction at low signal intensities.[4]

On the other hand, raw nCounter data were normalized with R package NanoStringNorm [5] using variance stabilizing normalization (VSN) that allows for better precision for genes with low expression where variance is generally greater [6] which was therefore preferable in our data set. In a comparison of normalization methods [7], VSN was among the methods that produced smallest mean square error

(due to smallest variance and smallest bias), showed high correlation to qPCR results, and performed comparable to quantile and lowess normalization when differential expression was analyzed.

To select miRNAs exhibiting variation among the analysed samples, the Median Average Deviation (MAD) of each miRNA was calculated. The miRNAs associated with the highest 5% of all MAD values were used for further analysis. After separating the data samples into the respective groups for comparison, the Wilcoxon two-sided rank test was applied to select those miRNAs which corresponding data had *P*-values below a threshold of 0.05. Adjusted *P*-values were calculated to correct for multiple hypothesis testing using the method of Benjamini and Hochberg.[8]

### **Statistical Analysis of RNAseq Data**

An average of  $29 \pm 7.9$  millions reads were produced for each sample, in accordance with standard requirements for minimal sequencing coverage.[9,10] The sequencing reads were mapped to a total of 15,000 genes using the ENSEMBL/GRCh37 *Homo sapiens* reference genome obtained from the iGenomes project page in July 2013 (<https://ccb.jhu.edu/software/tophat/igenomes.shtml>) using tophat2 [11] with default options. Gene level count tables were obtained using the count script of the HTSeq python library.[12] The alignment quality statistics were obtained from the tophat2 output. Only uniquely aligned reads unambiguously mapped to exons of annotated genes having an alignment score of greater than 10 were considered for differential expression analysis. Gene level count tables were obtained using the count script of the HTSeq python library [12] with default options.

The differential expression analysis was then performed using the Bioconductor package DESeq2,[13,14] which is based on the negative binomial distribution. Size-factor based normalisation and dispersion estimation was performed using the package defaults. For the differential expression analysis, independent filtering [13] was performed by only including genes showing a mean expression across samples of greater than 5 normalised counts. Raw *P*-values as returned by DESeq2 were used as input to fdrtool [15] in order to compute q-values. Genes with a q-value (=FDR)<0.05 were considered as significantly differentially expressed.

### **Ingenuity Pathway Analysis**

#### mRNA and miRNA core analysis

The list of miRNAs or genes obtained in profiling experiments was overlaid onto a global molecular network developed from information contained in the IPA knowledge base (IPKB). For network analysis, IPA computed a score ( $P\text{-score} = -\log_{10}(P\text{-value})$ ) according to the fit of the set of supplied genes and a list of biological functions stored in the IPKB. The score takes into account the number of

genes in the network and the size of the network to approximate how relevant this network is to the original list of genes and allows the networks to be prioritised for further studies. A score  $>3$  ( $P < 0.001$ ) indicates a  $>99.9\%$  confidence that a gene network was not generated by chance alone. The network identified is presented as a graph indicating the molecular relationships between genes/gene products. Moreover, networks are preferentially enriched for genes with the most extensive interactions, and for which interactions are specific with the other genes in the network (rather than genes that are promiscuous, those that interact with a broad selection of genes throughout IPKB).

The functional analysis identified the biological functions and the canonical signaling pathways that were most significant to the input data set. The significance of the association between the input data set and the functions or pathways was determined based on the following parameters: (1) a ratio of the number of genes from the data set that map to the function/pathway divided by the total number of genes that map to the function/pathway; (2) a  $P$ -value calculated using Fischer's exact test determining the probability that the association between the genes in the dataset and the function/pathway is explained by chance alone; (3) predicted activation state which is computed using the direction of change of gene expression in the input dataset; and (4) a statistical quantity is computed, called the activation z-score, for each category. More information on this can be found in the IPA upstream regulator analysis whitepaper:

[http://pages.ingenuity.com/rs/ingenuity/images/0812%20downstream\\_effects\\_analysis\\_whitepaper.pdf](http://pages.ingenuity.com/rs/ingenuity/images/0812%20downstream_effects_analysis_whitepaper.pdf)

#### Upstream regulator analysis

The output of the core analysis includes the identification of upstream regulators that can explain the observed gene expression changes in the input dataset. This analysis examines how many known targets of each known upstream regulator are present in our dataset, and compares their direction in expression to what is expected from the literature in order to predict likely relevant transcriptional regulators. For each potential upstream regulator two statistical measures, an overlap  $P$ -value and an activation z-score, are computed. The overlap  $P$ -value is calculated using Fisher's Exact Test and calls likely upstream regulators based on significant overlap between dataset genes and known targets regulated by a given transcriptional (upstream) regulator. The activation z-score is used to infer the activation states of predicted transcriptional regulators based on comparison with a model that assigns random regulation directions. More information on this can be found in the IPA upstream regulator analysis whitepaper:

[http://pages.ingenuity.com/rs/ingenuity/images/0812%20upstream\\_regulator\\_analysis\\_whitepaper.pdf](http://pages.ingenuity.com/rs/ingenuity/images/0812%20upstream_regulator_analysis_whitepaper.pdf)

### miRNA target filter plus miRNA/mRNA pairing analysis

This combined analysis of miRNA and mRNA profiles was carried out by investigating the co-expression profile of miRNA-mRNA pairs. Data was then filtered by the following criteria:

- mRNAs predicted with a high confidence and/or experimentally validated targets for the differentially expressed miRNAs.
- mRNAs showing inversed expression respect to their putative targeting miRNA (up-regulation of miRNA and down-regulation of the target mRNA, and vice versa).

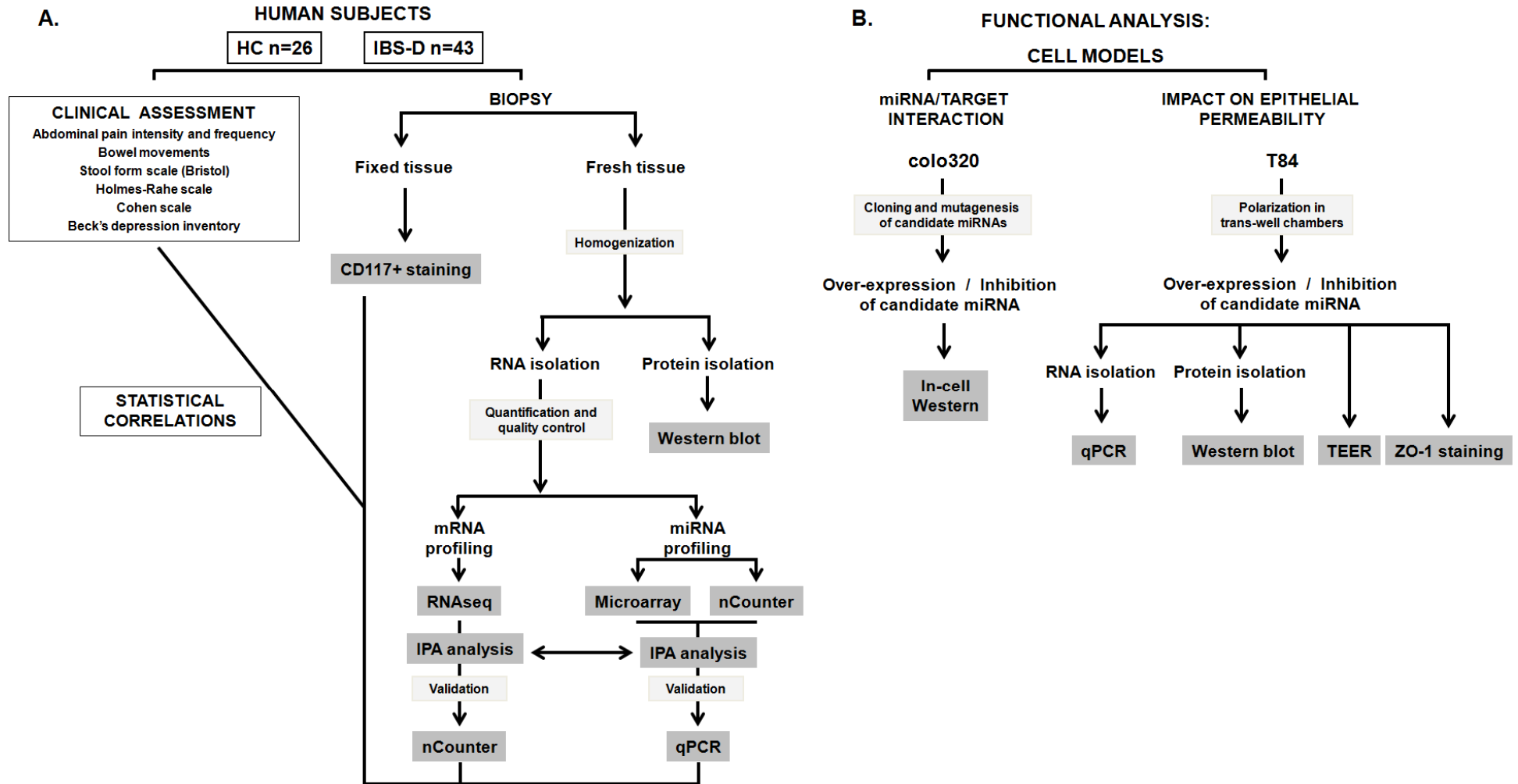
Putative mRNA targets selected based on above criteria were further evaluated by IPA mRNA core analysis as described in the supplementary methods section.

### **Supplementary References**

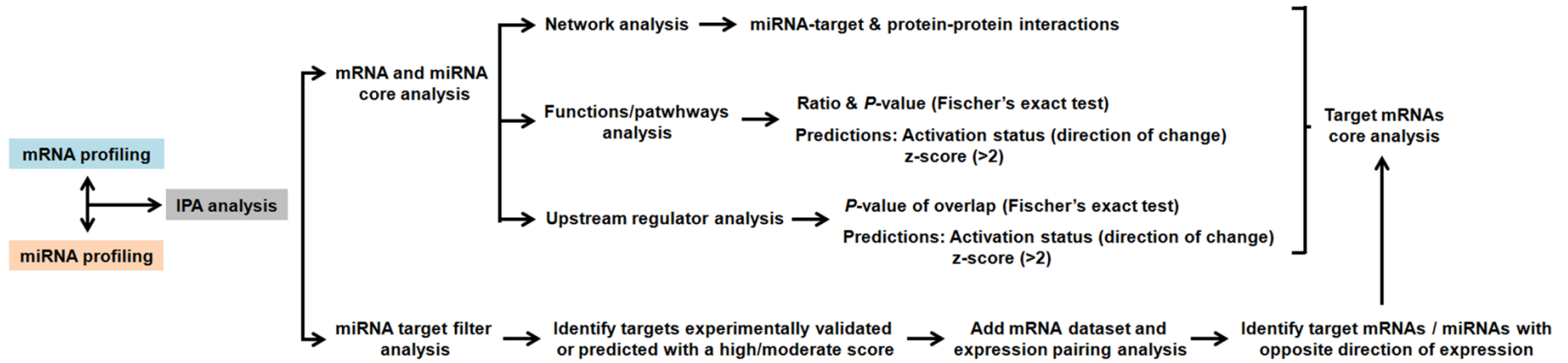
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**Supplementary figure 1. Experimental design. A.** Workflow of the analysis done in human subjects. **B.** Workflow of experiments done with cell models.



Supplementary figure 2. Ingenuity Pathway Analysis (IPA) pipeline.

Supplementary table 1. Experimental procedures.

| Group | Sample ID | miRNA profiling | RNAseq | miRNA qPCR | nCounter Gene expression assay | Western blot |
|-------|-----------|-----------------|--------|------------|--------------------------------|--------------|
| IBS-D | BCN1      | x               | x      | x          |                                | x            |
| IBS-D | BCN2      | x               | x      | x          |                                | x            |
| IBS-D | BCN3      | x               | x      | x          |                                | x            |
| IBS-D | BCN4      | x               | x      | x          |                                | x            |
| IBS-D | BCN5      | x               | x      | x          |                                | x            |
| IBS-D | BCN6      | x               | x      | x          |                                | x            |
| IBS-D | BCN7      | x               | x      | x          |                                | x            |
| HC    | BCN8      | x               | x      | x          | x                              | x            |
| HC    | BCN9      | x               | x      | x          |                                | x            |
| HC    | BCN10     | x               | x      | x          | x                              | x            |
| HC    | BCN11     | x               | x      | x          | x                              | x            |
| HC    | BCN12     | x               | x      | x          |                                | x            |
| IBS-D | BCN13     | x               | x      | x          |                                | x            |
| IBS-D | BCN14     |                 |        | x          | x                              | x            |
| IBS-D | BCN15     |                 |        | x          | x                              | x            |
| IBS-D | BCN16     |                 |        | x          |                                | x            |
| IBS-D | BCN17     |                 |        | x          |                                | x            |
| IBS-D | BCN18     |                 |        | x          |                                | x            |
| IBS-D | BCN19     |                 |        | x          |                                | x            |
| HC    | BCN21     | x               | x      | x          |                                |              |
| HC    | BCN22     | x               | x      | x          |                                | x            |
| HC    | BCN24     | x               | x      | x          |                                |              |
| HC    | BCN25     |                 |        | x          | x                              |              |
| HC    | BCN26     |                 |        | x          | x                              |              |
| HC    | BCN27     |                 |        | x          | x                              | x            |
| HC    | BCN28     |                 |        | x          | x                              | x            |
| HC    | BCN29     |                 |        | x          |                                |              |
| HC    | BCN30     |                 |        | x          |                                |              |
| HC    | BCN31     |                 |        | x          |                                | x            |
| HC    | BCN32     |                 |        | x          | x                              |              |
| HC    | BCN33     |                 |        | x          |                                |              |
| HC    | BCN34     |                 |        | x          | x                              | x            |
| HC    | BCN35     |                 |        |            | x                              | x            |
| HC    | BCN36     |                 |        |            | x                              |              |
| HC    | BCN37     |                 |        |            | x                              |              |
| HC    | BCN38     |                 |        |            | x                              |              |
| HC    | BCN39     |                 |        |            | x                              |              |
| HC    | BCN41     |                 |        |            | x                              |              |
| IBS-D | BCN42     |                 |        |            | x                              | x            |

|       |              |  |  |  |   |   |
|-------|--------------|--|--|--|---|---|
| IBS-D | <b>BCN44</b> |  |  |  | x | x |
| IBS-D | <b>BCN45</b> |  |  |  | x | x |
| IBS-D | <b>BCN47</b> |  |  |  | x |   |
| IBS-D | <b>BCN48</b> |  |  |  | x |   |
| IBS-D | <b>BCN49</b> |  |  |  | x |   |
| IBS-D | <b>BCN50</b> |  |  |  | x |   |
| IBS-D | <b>BCN51</b> |  |  |  | x |   |
| IBS-D | <b>BCN52</b> |  |  |  | x |   |
| IBS-D | <b>BCN54</b> |  |  |  | x |   |
| IBS-D | <b>BCN55</b> |  |  |  | x |   |
| IBS-D | <b>BCN56</b> |  |  |  | x |   |
| IBS-D | <b>BCN57</b> |  |  |  | x | x |
| IBS-D | <b>BCN58</b> |  |  |  | x | x |
| IBS-D | <b>BCN59</b> |  |  |  | x |   |
| IBS-D | <b>BCN60</b> |  |  |  | x |   |
| IBS-D | <b>BCN61</b> |  |  |  | x |   |
| IBS-D | <b>BCN62</b> |  |  |  | x |   |
| IBS-D | <b>BCN63</b> |  |  |  | x |   |
| IBS-D | <b>BCN64</b> |  |  |  | x |   |
| HC    | <b>BCN65</b> |  |  |  | x | x |
| HC    | <b>BCN66</b> |  |  |  | x | x |
| IBS-D | <b>BCN70</b> |  |  |  | x |   |
| IBS-D | <b>BCN71</b> |  |  |  | x |   |
| IBS-D | <b>BCN72</b> |  |  |  | x |   |
| IBS-D | <b>BCN73</b> |  |  |  | x |   |
| IBS-D | <b>BCN74</b> |  |  |  | x |   |
| IBS-D | <b>BCN78</b> |  |  |  |   | x |
| IBS-D | <b>BCN83</b> |  |  |  |   | x |
| IBS-D | <b>BCN84</b> |  |  |  |   | x |
| IBS-D | <b>BCN85</b> |  |  |  |   | x |

Note: IBS-D, diarrhoea-irritable bowel syndrome; HC, healthy control; miRNA, microRNA; qPCR, quantitative real-time PCR

**Supplementary table 2. nCounter probes**

| Gene name  | Gene Symbol        | Accession number | Probe sequence 5'>3'  |
|--|--------------------|------------------|---|
| cadherin 1, type 1, E-cadherin (epithelial)              | <i>CDH1</i>        | NM_004360.2      | GAATTGCTCACATTTCCCAACTCCTCTCCTGGCCTCAGAAGACAGAAGAG<br>AGACTGGGTTATTCCCTCCCATCAGCTGCCAGAAAATGAAAAAGGCCAT   |
| CUGBP, Elav-like family member 1                         | <i>CELF1</i>       | NM_006560.2      | GGTTCCAAGGACCTGGTCTGAAAAGGACTTGCGGAACTCTTCGAACAGT<br>ATGGTGTCTGTATGAAATCAACGTCCTAAGGGATAGGAGCCAAAACCCG    |
| cingulin   | <i>CGN</i>         | NM_020770.2      | TCAGCAATAAGCTGATAGATGGACTTTCCACTGTAGGAGTGGACATTTCA<br>AGCCAACCTGAGCCTTTTCCTCAAGTGCCGACACCTCCCTCATCTCTCTTA |
| catenin (cadherin-associated protein), alpha 1           | <i>CTNNA1</i>      | NM_001903.2      | TCAGAGATGGACAACCTATGAGCCAGGAGTCTACACAGAGAAGGTTCTGGA<br>AGCCACTAAGCTGCTCTCCAACACAGTCATGCCACGTTTTACTGAGCAAG |
| catenin (cadherin-associated protein), beta 1            | <i>CTNNB1</i>      | NM_001904.3      | GCCACAAGATTACAAGAAACGGCTTTCAGTTGAGCTGACCAGCTCTCTCT<br>TCAGAACAGAGCCAATGGCTTGAATGAGACTGCTGATCTTGGACTTGAT   |
| F11 receptor (junction adhesion molecule 1)              | <i>F11R (JAM1)</i> | NM_144503.1      | GGAAGCAGAGGTGATTTCATGGCTCTGTGAATTTGAGGTGAATGGTTCCTT<br>ATTGTCTAGGCCACTTGTGAAGAATATGAGTCAGTTATTGCCAGCCTTGG |
| junction adhesion molecule 2                             | <i>JAM2</i>        | NM_021219.2      | TTCTGTGAAGCCCGCAATTCTGTTGGATATCGCAGGTGTCTCTGGGAAAC<br>GAATGCAAGTAGATGATCTCAACATAAGTGGCATCATAGCAGCCGTAGTA  |
| junction adhesion molecule 3                             | <i>JAM3</i>        | NM_032801.3      | AATTATTGGGGGGTTCGGTTGTCCTTGCTGTACTGGCCCTGATCACGT<br>TGGGCATCTGCTGTGCATACAGACGTGGCTACTTCATCAACAATAAACAG    |
| pleckstrin homology domain containing, family A member 7 | <i>PLEKHA7</i>     | NM_175058.4      | CTCTAACTGGCCTGTGCTACTTATTACCGGGCTTGTAATAGCGGTTCTTG<br>TCTCCATAGCCTGTTGAGTGTTCAGATGTGACTCACCTTTCTGCTGCC    |
| glyceraldehyde-3-phosphate dehydrogenase                 | <i>GAPDH</i>       | NM_002046.3      | CCTCCTCCACCTTTGACGCTGGGGCTGGCATTGCCCTCAACGACCACTT<br>TGTCAAGCTCATTTCCCTGGTATGACAACGAATTTGGCTACAGCAACAGGG  |
| ribosomal protein S17                                    | <i>RPS17</i>       | NM_001021.3      | AAGGAGAGACAATTATGTTCCCTGAGGTCTCAGCCTTGGATCAGGAGATTA<br>TTGAAGTAGATCCTGACACTAAGGAAATGCTGAAGCTTTTGGACTTCGGC |

|                          |            |                |  |
|--------------------------|------------|----------------|--|
| TATA box binding protein | <i>TBP</i> | NM_001172085.1 | ACAGTGAATCTTGGTTGTAACTTGACCTAAAGACCATTGCACTTCGTGC<br>CCGAAACGCCGAATATAATCCCAAGCGTTTGCTGCGGTAATCATGAGGA   |
| ubiquitin C              | <i>UBC</i> | NM_021009.3    | TGCAGATCTTCGTGAAGACCCTGACTGGTAAGACCATCACTCTCGAAGTG<br>GAGCCGAGTGACACCATTGAGAATGTCAAGGCAAAGATCCAAGACAAGGA |

**Supplementary table 3. Antibodies used**

|                             | <b>Target</b>          | <b>Company</b>    | <b>Catalog number</b> | <b>raised in</b> | <b>type</b>               | <b>WB dilution</b> | <b>ICW dilution</b> |
|-----------------------------|------------------------|-------------------|-----------------------|------------------|---------------------------|--------------------|---------------------|
| <b>Primary antibodies</b>   | Cingulin               | Abcam             | ab117778              | rabbit           | polyclonal                | 1:2000             | 1:300               |
|                             | Claudin 2              | Life Technologies | 32-5600               | mouse            | monoclonal (clone 12H12)  | 1:1000             | 1:300               |
|                             | Zonula occludens 1     | Santa Cruz        |                       |                  |                           | 1:1000             | NA                  |
|                             | GAPDH                  | Abcam             | ab9484                | mouse            | monoclonal                | 1:2000             | NA                  |
|                             | GAPDH                  | Abcam             | ab9485                | rabbit           | polyclonal                | 1:2000             | NA                  |
|                             | GFP                    | Sigma             | G6539                 | mouse            | monoclonal (clone GFP-20) | NA                 | 1:500               |
|                             | GFP                    | Life Technologies | G10362                | rabbit           | monoclonal                | NA                 | 1:500               |
| <b>Secondary antibodies</b> | mouse IgG IRDye 680    | LI-COR            | 925-68022             | donkey           | polyclonal                | 1:10000            | 1:800               |
|                             | mouse IgG IRDye 800CW  | LI-COR            | 926-32212             | donkey           | polyclonal                | 1:10000            | 1:800               |
|                             | rabbit IgG IRDye 680   | LI-COR            | 925-68023             | donkey           | polyclonal                | 1:10000            | 1:800               |
|                             | rabbit IgG IRDye 800CW | LI-COR            | 926-32213             | donkey           | polyclonal                | 1:10000            | 1:800               |

**Supplementary table 4. Primer used for cloning**

| <b>Amplicon</b> | <b>Purpose</b>                               | <b>Primer name</b>   | <b>Sequence 5'&gt;3'</b>                      |
|-----------------|--|----------------------|---|
| hsa-miR-125b-1  | To clone into pEP-miR                        | miR-125b-1_BamHI-F1  | TCGAGGGATCCACCATACCACCTGTTG                   |
|                 |  | miR-125b-1_NheI-R1   | TCGAGCTAGCATGAAAACCTCAGAGGTATACTC             |
| hsa-miR-125b-1  | Mutagenesis primers to destroy seed sequence | hsa-miR-125b-1_mut_F | GTTGCGCTCCTCTCAGTAAAGACGACCCTAACTTGTGATG      |
|                 |  | hsa-miR-125b-1_mut_R | CATCACAAGTTAGGGTCGTCTTTACTGAGAGGAGCGCAAC      |
| hsa-miR-16-1    | To clone into pEP-miR                        | miR-16-1_BamHI-F1    | TCATAGGGATCCTGAAAAGGTGCAGGCCATATTG            |
|                 |  | miR-16-1_NheI-R1     | CCTTAGCTAGCTAAAAATAACAAGATTATCAATAATACTG      |
| hsa-miR-16-1    | Mutagenesis primers to destroy seed sequence | hsa-miR-16_mut_F     | GCAATGTCAGCAGTGCCTTATAGTAGCGTAAATATTGGCGTTAAG |
|                 |  | hsa-miR-16_mut_R     | CTTAACGCCAATATTTACGCTACTATAAGGCACTGCTGACATTGC |
| hsa-miR-510     | To clone into pEP-miR                        | miR-510_BamHI-F      | ATAGGGATCCACGGCCACTTACAGACTG                  |
|                 |  | miR-510_NheI-R       | CCTTAGCTAGCTTGAGGAGGGTACCAGATG                |



**Supplementary table 5. Clinical and demographic characteristics of sub-groups of participants used for the different analysis.**

|  | RNAseq + miRNA profiling |              |                     | qPCR         |              |                       | nCounter     |               |                       | Western Blot |               |                       | P-value |      |
|--|--------------------------|--------------|---------------------|--------------|--------------|-----------------------|--------------|---------------|-----------------------|--------------|---------------|-----------------------|---------|------|
|  | IBS-D (n=8)              | HC (n=8)     | P-value             | IBS-D (n=14) | HC (n=18)    | P-value               | IBS-D (n=31) | HC (n=17)     | P-value               | IBS-D (n=25) | HC (n=15)     | P-value               | IBS-D   | HC   |
| Age, years                               | 35 (22-50)               | 28 (22-49)   | 0.10                | 36 (22-51)   | 31 (22-54)   | 0.10                  | 37 (20-60)   | 32 (19-50)    | 0.11                  | 38 (22-54)   | 32 (23-53)    | 0.14                  | 0.72    | 0.52 |
| Gender, M:F                              | 3:5                      | 4:4          | 0.09                | 5:9          | 9:9          | 0.41                  | 10:21        | 7:10          | 0.54                  | 6:19         | 7:8           | 0.19                  | 0.83    | 0.96 |
| Body mass index                          | 21.1 ± 2.8               | 23.1 ± 3.9   | 0.65                | 22.7 ± 4.0   | 23.7 ± 3.4   | 0.58                  | 23.7 ± 3.7   | 22.0 ± 2.5    | 0.12                  | 23.0 ± 3.9   | 22.3 ± 3.0    | 0.47                  | 0.28    | 0.73 |
| Functional dyspepsia                     | 4/8                      | 0/8          | -                   | 7/14         | 0/18         | -                     | 15/31        | 0/17          | -                     | 15/25        | 0/15          | -                     | 0.84    |      |
| Severity of the disease, Francis score   | 254.5 ± 55.6             | -            | -                   | 246.0 ± 73.6 | -            | -                     | 260.3 ± 88.2 | -             | -                     | 255.8 ± 93.2 | -             | -                     | 0.95    |      |
| Abdominal Pain Intensity, score          | 40.1 ± 25.6              | -            | -                   | 36.1 ± 21.0  | -            | -                     | 43.3 ± 23.1  | -             | -                     | 42.6 ± 24.9  | -             | -                     | 0.96    |      |
| Abdominal Pain Frequency, number of days | 5.1 (2-10)               | -            | -                   | 5.2 (2-10)   | -            | -                     | 6.11 (2-10)  | -             | -                     | 5.7 (2-10)   | -             | -                     | 0.92    |      |
| Bowel movements, number                  | 4.5 ± 1.8                | 1.3 ± 0.7    | <b>&lt;0.01</b> **  | 4.4 ± 1.5    | 1.6 ± 0.6    | <b>&lt;0.0001</b> *** | 3.5 ± 1.7    | 1.3 ± 0.5     | <b>&lt;0.0001</b> *** | 3.8 ± 1.6    | 1.5 ± 0.5     | <b>&lt;0.001</b> **   | 0.25    | 0.51 |
| Stool form, Bristol score                | 6.1 ± 0.6                | 3.6 ± 0.7    | <b>&lt;0.001</b> ** | 5.9 ± 0.6    | 3.5 ± 0.6    | <b>&lt;0.0001</b> *** | 5.6 ± 1.0    | 3.8 ± 0.7     | <b>&lt;0.0001</b> *** | 5.7 ± 1.1    | 3.4 ± 0.6     | <b>&lt;0.0001</b> *** | 0.40    | 0.50 |
| Holmes-Rahe scale                        | 157.5 ± 71.3             | 152.8 ± 94.1 | 0.96                | 165.5 ± 83.3 | 133.2 ± 74.1 | 0.31                  | 140.9 ± 87.1 | 136.8 ± 100.4 | 0.82                  | 143.5 ± 84.4 | 152.0 ± 100.2 | 0.94                  | 0.87    | 0.96 |
| Cohen scale                              | 27.5 ± 6.8               | 16.9 ± 7.6   | <b>0.02</b> *       | 26.4 ± 5.6   | 17.2 ± 7.7   | <b>0.002</b> *        | 22.4 ± 6.3   | 16.2 ± 6.4    | <b>0.001</b> **       | 24.5 ± 6.8   | 17.1 ± 6.8    | <b>0.004</b> **       | 0.23    | 0.97 |
| Beck's index                             | 12.8 ± 9.3               | 1.1 ± 2.1    | <b>&lt;0.01</b> **  | 10.6 ± 8.3   | 1.6 ± 3.0    | <b>&lt;0.001</b> **   | 8.1 ± 7.4    | 1.3 ± 2.8     | <b>&lt;0.001</b> **   | 10.0 ± 8.8   | 2.0 ± 3.3     | <b>&lt;0.0001</b> **  | 0.47    | 0.85 |

Note: Values represent median (range) or mean ± standard deviation.

IBS-D patients and healthy controls were compared using the non-parametric Mann Whitney U-test. Differences among sub-analysis (last column) were assessed using the non-parametric ANOVA. Gender and functional dyspepsia proportions were compared by the  $\chi^2$  test. P-values are indicated and those considered significant are shown in bold: \* < 0.05; \*\* <0.001; \*\*\* <0.0001

F, female; M, male; HC, healthy controls; IBS-D, diarrhoea-predominant IBS

**Supplementary table 6. Comparison analysis of patients with and without functional dyspepsia**

|                     | <b>Gene ID</b>      | <b>Fold-change vs. Non-FD</b> | <b>FDR</b> |
|---------------------|---------------------|-------------------------------|------------|
| <b>nCounter</b>     | <i>CDH1</i>         | 1.0                           | 1.07       |
|                     | <i>CELF1</i>        | 1.1                           | 0.27       |
|                     | <i>CGN</i>          | -1.0                          | 1.14       |
|                     | <i>CTNNA1</i>       | 1.0                           | 1.13       |
|                     | <i>CTNNB1</i>       | -1.0                          | 1.19       |
|                     | <i>F11R (JAM1)</i>  | -1.1                          | 1.09       |
|                     | <i>JAM2</i>         | 1.2                           | 1.09       |
|                     | <i>JAM3</i>         | 1.3                           | 0.86       |
|                     | <i>PLEKHA7</i>      | 1.1                           | 0.84       |
| <b>qPCR</b>         | <b>hsa-miR-125b</b> | 1.1                           | 0.30       |
|                     | <b>hsa-miR-16</b>   | -1.1                          | 0.37       |
| <b>Western Blot</b> | <b>Cingulin</b>     | 1.1                           | 0.18       |
|                     | <b>Claudin 2</b>    | -1.1                          | 0.42       |

Note: FD: functional dyspepsia; FDR: false discovery rate, *P*-values are adjusted for multiple testing correction by the Benjamini and Hochberg method.

**Supplementary table 7. Predicted miRNA sites on Cingulin 3' UTR region produced by miRWalk and other programs**

| Gene       | miRNA               | StemLoopID            | miRanda  | miRDB    | miRWalk  | RNA22    | Targetscan | SUM      |
|------------|---------------------|-----------------------|----------|----------|----------|----------|------------|----------|
| CGN        | hsa-miR-124         | hsa-mir-124-3         | 1        | 1        | 1        | 0        | 1          | 4        |
| CGN        | hsa-miR-125a-5p     | hsa-mir-125a          | 1        | 1        | 1        | 0        | 1          | 4        |
| CGN        | hsa-miR-1236        | hsa-mir-1236          | 1        | 1        | 1        | 0        | 1          | 4        |
| <b>CGN</b> | <b>hsa-miR-125b</b> | <b>hsa-mir-125b-2</b> | <b>1</b> | <b>1</b> | <b>1</b> | <b>0</b> | <b>1</b>   | <b>4</b> |
| CGN        | hsa-miR-298         | hsa-mir-298           | 1        | 1        | 1        | 0        | 1          | 4        |
| CGN        | hsa-miR-506         | hsa-mir-506           | 1        | 1        | 1        | 0        | 1          | 4        |
| CGN        | hsa-miR-590-3p      | hsa-mir-590           | 1        | 1        | 1        | 0        | 1          | 4        |
| CGN        | hsa-miR-539         | hsa-mir-539           | 1        | 1        | 1        | 0        | 1          | 4        |
| CGN        | hsa-miR-659         | hsa-mir-659           | 1        | 1        | 1        | 0        | 1          | 4        |
| CGN        | hsa-miR-570         | hsa-mir-570           | 1        | 1        | 1        | 0        | 1          | 4        |
| CGN        | hsa-miR-9           | hsa-mir-9-1           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-660         | hsa-mir-660           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-19b         | hsa-mir-19b-1         | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-202         | hsa-mir-202           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-1321        | hsa-mir-1321          | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-107         | hsa-mir-107           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-571         | hsa-mir-571           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-150         | hsa-mir-150           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-541         | hsa-mir-541           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-15b         | hsa-mir-15b           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-616         | hsa-mir-616           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-296-5p      | hsa-mir-296           | 1        | 1        | 0        | 0        | 1          | 3        |
| CGN        | hsa-miR-381         | hsa-mir-381           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-1291        | hsa-mir-1291          | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-758         | hsa-mir-758           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-19b         | hsa-mir-19b-2         | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-497         | hsa-mir-497           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-320d        | hsa-mir-320d-1        | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-575         | hsa-mir-575           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-185         | hsa-mir-185           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-889         | hsa-mir-889           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-9           | hsa-mir-9-2           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-1224-5p     | hsa-mir-1224          | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-21          | hsa-mir-21            | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-181d        | hsa-mir-181d          | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-320c        | hsa-mir-320c-2        | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-139-5p      | hsa-mir-139           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-579         | hsa-mir-579           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-186         | hsa-mir-186           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-124         | hsa-mir-124-1         | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-623         | hsa-mir-623           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-323-3p      | hsa-mir-323           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-320b        | hsa-mir-320b-1        | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-24          | hsa-mir-24-1          | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-518a-5p     | hsa-mir-518a-1        | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-320d        | hsa-mir-320d-2        | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-181a        | hsa-mir-181a-2        | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-582-5p      | hsa-mir-582           | 1        | 0        | 1        | 0        | 1          | 3        |
| CGN        | hsa-miR-195         | hsa-mir-195           | 1        | 0        | 1        | 0        | 1          | 3        |

|     |                 |                |   |   |   |   |   |   |
|-----|-----------------|----------------|---|---|---|---|---|---|
| CGN | hsa-miR-543     | hsa-mir-543    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-124     | hsa-mir-124-2  | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-628-5p  | hsa-mir-628    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-483-3p  | hsa-mir-483    | 1 | 1 | 0 | 0 | 1 | 3 |
| CGN | hsa-miR-339-5p  | hsa-mir-339    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-1253    | hsa-mir-1253   | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-9       | hsa-mir-9-3    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-320c    | hsa-mir-320c-1 | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-24      | hsa-mir-24-2   | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-518a-5p | hsa-mir-518a-2 | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-181b    | hsa-mir-181b-1 | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-583     | hsa-mir-583    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-320a    | hsa-mir-320a   | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-922     | hsa-mir-922    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-527     | hsa-mir-527    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-181c    | hsa-mir-181c   | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-155     | hsa-mir-155    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-125b    | hsa-mir-125b-1 | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-637     | hsa-mir-637    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-424     | hsa-mir-424    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-320b    | hsa-mir-320b-2 | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-502-5p  | hsa-mir-502    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-137     | hsa-mir-137    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-642     | hsa-mir-642    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-433     | hsa-mir-433    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-1274a   | hsa-mir-1274a  | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-203     | hsa-mir-203    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-590-5p  | hsa-mir-590    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-181b    | hsa-mir-181b-2 | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-1237    | hsa-mir-1237   | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-654-5p  | hsa-mir-654    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-1274b   | hsa-mir-1274b  | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-129-3p  | hsa-mir-129-2  | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-300     | hsa-mir-300    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-181a    | hsa-mir-181a-1 | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-188-5p  | hsa-mir-188    | 1 | 1 | 0 | 0 | 1 | 3 |
| CGN | hsa-miR-34b     | hsa-mir-34b    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-140-3p  | hsa-mir-140    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-654-3p  | hsa-mir-654    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-15a     | hsa-mir-15a    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-486-3p  | hsa-mir-486    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-1284    | hsa-mir-1284   | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-220c    | hsa-mir-220c   | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-103     | hsa-mir-103-2  | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-214     | hsa-mir-214    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-1286    | hsa-mir-1286   | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-143     | hsa-mir-143    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-19a     | hsa-mir-19a    | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-1252    | hsa-mir-1252   | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-103     | hsa-mir-103-1  | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-224     | hsa-mir-224    | 1 | 0 | 1 | 1 | 0 | 3 |
| CGN | hsa-miR-1287    | hsa-mir-1287   | 1 | 0 | 1 | 0 | 1 | 3 |
| CGN | hsa-miR-379     | hsa-mir-379    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-513a-5p | hsa-mir-513a-1 | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-134     | hsa-mir-134    | 0 | 0 | 0 | 1 | 1 | 2 |
| CGN | hsa-miR-199a-5p | hsa-mir-199a-2 | 1 | 0 | 0 | 0 | 1 | 2 |

|     |                  |                |   |   |   |   |   |   |
|-----|------------------|----------------|---|---|---|---|---|---|
| CGN | hsa-miR-615-5p   | hsa-mir-615    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-9*       | hsa-mir-9-1    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-513a-5p  | hsa-mir-513a-2 | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-204      | hsa-mir-204    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-129*     | hsa-mir-129-1  | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-16       | hsa-mir-16-2   | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-576-3p   | hsa-mir-576    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-620      | hsa-mir-620    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-15b*     | hsa-mir-15b    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-548c-3p  | hsa-mir-548c   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-330-3p   | hsa-mir-330    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-382      | hsa-mir-382    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-340      | hsa-mir-340    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-211      | hsa-mir-211    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-885-3p   | hsa-mir-885    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-873      | hsa-mir-873    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-1248     | hsa-mir-1248   | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-let-7a*      | hsa-let-7a-1   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-1243     | hsa-mir-1243   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-767-3p   | hsa-mir-767    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-9*       | hsa-mir-9-2    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-337-3p   | hsa-mir-337    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-296-3p   | hsa-mir-296    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-let-7a*      | hsa-let-7a-3   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-345      | hsa-mir-345    | 0 | 0 | 0 | 1 | 1 | 2 |
| CGN | hsa-miR-199a-5p  | hsa-mir-199a-1 | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-532-3p   | hsa-mir-532    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-1914*    | hsa-mir-1914   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-219-1-3p | hsa-mir-219-1  | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-96       | hsa-mir-96     | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-629*     | hsa-mir-629    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-let-7b*      | hsa-let-7b     | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-1254     | hsa-mir-1254   | 0 | 0 | 1 | 0 | 1 | 2 |
| CGN | hsa-miR-1271     | hsa-mir-1271   | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-9*       | hsa-mir-9-3    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-769-3p   | hsa-mir-769    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-27a*     | hsa-mir-27a    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-1915*    | hsa-mir-1915   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-550*     | hsa-mir-550-1  | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-1226*    | hsa-mir-1226   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-362-5p   | hsa-mir-362    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-1270     | hsa-mir-1270   | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-let-7d       | hsa-let-7d     | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-1255a    | hsa-mir-1255a  | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-455-3p   | hsa-mir-455    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-92a-2*   | hsa-mir-92a-2  | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-1915     | hsa-mir-1915   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-591      | hsa-mir-591    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-182*     | hsa-mir-182    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-550*     | hsa-mir-550-2  | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-942      | hsa-mir-942    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-155*     | hsa-mir-155    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-646      | hsa-mir-646    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-520a-5p  | hsa-mir-520a   | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-let-7f-1*    | hsa-let-7f-1   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-29b-1*   | hsa-mir-29b-1  | 1 | 0 | 1 | 0 | 0 | 2 |

|     |                 |                 |   |   |   |   |   |   |
|-----|-----------------|-----------------|---|---|---|---|---|---|
| CGN | hsa-miR-206     | hsa-mir-206     | 1 | 0 | 0 | 1 | 0 | 2 |
| CGN | hsa-miR-138     | hsa-mir-138-2   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-525-5p  | hsa-mir-525     | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-501-5p  | hsa-mir-501     | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-let-7f-2*   | hsa-let-7f-2    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-410     | hsa-mir-410     | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-let-7e      | hsa-let-7e      | 1 | 0 | 0 | 1 | 0 | 2 |
| CGN | hsa-miR-29b-2*  | hsa-mir-29b-2   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-532-5p  | hsa-mir-532     | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-1225-5p | hsa-mir-1225    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-1238    | hsa-mir-1238    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-649     | hsa-mir-649     | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-16      | hsa-mir-16-1    | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-128     | hsa-mir-128-1   | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-138     | hsa-mir-138-1   | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-34c-3p  | hsa-mir-34c     | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-504     | hsa-mir-504     | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-202*    | hsa-mir-202     | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-149*    | hsa-mir-149     | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-888*    | hsa-mir-888     | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-573     | hsa-mir-573     | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-613     | hsa-mir-613     | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-128     | hsa-mir-128-2   | 1 | 0 | 0 | 0 | 1 | 2 |
| CGN | hsa-miR-376c    | hsa-mir-376c    | 1 | 0 | 1 | 0 | 0 | 2 |
| CGN | hsa-miR-548d-3p | hsa-mir-548d-1  | 1 | 0 | 0 | 0 | 0 | 1 |
|     |                 | hsa-mir-1255b-2 |   |   |   |   |   |   |
| CGN | hsa-miR-1255b   | 2               | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-135a*   | hsa-mir-135a-1  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-450b-3p | hsa-mir-450b    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-20a*    | hsa-mir-20a     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-511     | hsa-mir-511-1   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-576-5p  | hsa-mir-576     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-194*    | hsa-mir-194-2   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1295    | hsa-mir-1295    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-196a    | hsa-mir-196a-1  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-661     | hsa-mir-661     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-589     | hsa-mir-589     | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-380     | hsa-mir-380     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1308    | hsa-mir-1308    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-135a    | hsa-mir-135a-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-890     | hsa-mir-890     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1207-5p | hsa-mir-1207    | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-29a     | hsa-mir-29a     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-511     | hsa-mir-511-2   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-29c     | hsa-mir-29c     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1304    | hsa-mir-1304    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1305    | hsa-mir-1305    | 0 | 0 | 1 | 0 | 0 | 1 |
| CGN | hsa-miR-197     | hsa-mir-197     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-548d-3p | hsa-mir-548d-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-541*    | hsa-mir-541     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-507     | hsa-mir-507     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-664*    | hsa-mir-664     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-515-5p  | hsa-mir-515-2   | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-181c*   | hsa-mir-181c    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-142-5p  | hsa-mir-142     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-100     | hsa-mir-100     | 0 | 0 | 0 | 0 | 1 | 1 |

|     |                 |                |   |   |   |   |   |   |
|-----|-----------------|----------------|---|---|---|---|---|---|
| CGN | hsa-miR-32*     | hsa-mir-32     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-511     | hsa-mir-511-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-581     | hsa-mir-581    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-625*    | hsa-mir-625    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-760     | hsa-mir-760    | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-299-3p  | hsa-mir-299    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-198     | hsa-mir-198    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-let-7a      | hsa-let-7a-1   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-509-3p  | hsa-mir-509-1  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-513b    | hsa-mir-513b   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-218-1*  | hsa-mir-218-1  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-582-3p  | hsa-mir-582    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-125a-3p | hsa-mir-125a   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-877*    | hsa-mir-877    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-519a    | hsa-mir-519a-2 | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-33a*    | hsa-mir-33a    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-146b-3p | hsa-mir-146b   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-627     | hsa-mir-627    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1257    | hsa-mir-1257   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1468    | hsa-mir-1468   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-27b     | hsa-mir-27b    | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-let-7a      | hsa-let-7a-2   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-331-5p  | hsa-mir-331    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-513c    | hsa-mir-513c   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-548b-3p | hsa-mir-548b   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-625     | hsa-mir-625    | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-143*    | hsa-mir-143    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-136*    | hsa-mir-136    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-920     | hsa-mir-920    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-633     | hsa-mir-633    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-490-3p  | hsa-mir-490    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-361-5p  | hsa-mir-361    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-520g    | hsa-mir-520g   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1265    | hsa-mir-1265   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-132     | hsa-mir-132    | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-335*    | hsa-mir-335    | 0 | 0 | 1 | 0 | 0 | 1 |
| CGN | hsa-miR-10a     | hsa-mir-10a    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-let-7a      | hsa-let-7a-3   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-324-5p  | hsa-mir-324    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-455-5p  | hsa-mir-455    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1470    | hsa-mir-1470   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-221*    | hsa-mir-221    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-589*    | hsa-mir-589    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1275    | hsa-mir-1275   | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-885-5p  | hsa-mir-885    | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-146a*   | hsa-mir-146a   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-509-3p  | hsa-mir-509-3  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-516a-3p | hsa-mir-516a-2 | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-96*     | hsa-mir-96     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-641     | hsa-mir-641    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-497*    | hsa-mir-497    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-520h    | hsa-mir-520h   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1200    | hsa-mir-1200   | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-187     | hsa-mir-187    | 0 | 0 | 0 | 1 | 0 | 1 |
| CGN | hsa-miR-10b     | hsa-mir-10b    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-let-7g      | hsa-let-7g     | 1 | 0 | 0 | 0 | 0 | 1 |

|     |                 |               |   |   |   |   |   |   |
|-----|-----------------|---------------|---|---|---|---|---|---|
| CGN | hsa-miR-1301    | hsa-mir-1301  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-let-7b      | hsa-let-7b    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-338-5p  | hsa-mir-338   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1909    | hsa-mir-1909  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-99b     | hsa-mir-99b   | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-149     | hsa-mir-149   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-98      | hsa-mir-98    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-212     | hsa-mir-212   | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-302b*   | hsa-mir-302b  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-522     | hsa-mir-522   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1276    | hsa-mir-1276  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-34a*    | hsa-mir-34a   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-let-7i      | hsa-let-7i    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-454*    | hsa-mir-454   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-421     | hsa-mir-421   | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-let-7c      | hsa-let-7c    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-384     | hsa-mir-384   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-555     | hsa-mir-555   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1910    | hsa-mir-1910  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-595     | hsa-mir-595   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-186*    | hsa-mir-186   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1182    | hsa-mir-1182  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-491-5p  | hsa-mir-491   | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-100*    | hsa-mir-100   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-647     | hsa-mir-647   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-302d*   | hsa-mir-302d  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1282    | hsa-mir-1282  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-519b-3p | hsa-mir-519b  | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-182     | hsa-mir-182   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-15a*    | hsa-mir-15a   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1       | hsa-mir-1-2   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-766     | hsa-mir-766   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-196b    | hsa-mir-196b  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-557     | hsa-mir-557   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1911*   | hsa-mir-1911  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-596     | hsa-mir-596   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-572     | hsa-mir-572   | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-31      | hsa-mir-31    | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-200c*   | hsa-mir-200c  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-668     | hsa-mir-668   | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-29b     | hsa-mir-29b-1 | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-409-3p  | hsa-mir-409   | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-370     | hsa-mir-370   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-503     | hsa-mir-503   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1288    | hsa-mir-1288  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-519c-3p | hsa-mir-519c  | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-183     | hsa-mir-183   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-509-3p  | hsa-mir-509-2 | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-let-7f      | hsa-let-7f-1  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-423-5p  | hsa-mir-423   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-551b*   | hsa-mir-551b  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1912    | hsa-mir-1912  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-605     | hsa-mir-605   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-27a     | hsa-mir-27a   | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-610     | hsa-mir-610   | 0 | 0 | 1 | 0 | 0 | 1 |
| CGN | hsa-miR-195*    | hsa-mir-195   | 1 | 0 | 0 | 0 | 0 | 1 |



|     |                 |                 |   |   |   |   |   |   |
|-----|-----------------|-----------------|---|---|---|---|---|---|
| CGN | hsa-miR-1       | hsa-mir-1-1     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1231    | hsa-mir-1231    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-29b     | hsa-mir-29b-2   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-651     | hsa-mir-651     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-412     | hsa-mir-412     | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-612     | hsa-mir-612     | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-374a*   | hsa-mir-374a    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1255b   | hsa-mir-1255b-1 | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-135b    | hsa-mir-135b    | 0 | 0 | 0 | 1 | 0 | 1 |
| CGN | hsa-miR-196a    | hsa-mir-196a-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-135a    | hsa-mir-135a-1  | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-450b-5p | hsa-mir-450b    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1285    | hsa-mir-1285-2  | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-99a     | hsa-mir-99a     | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-let-7f      | hsa-let-7f-2    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-511     | hsa-mir-511-1   | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-188-3p  | hsa-mir-188     | 0 | 0 | 0 | 0 | 1 | 1 |
| CGN | hsa-miR-614     | hsa-mir-614     | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-1293    | hsa-mir-1293    | 1 | 0 | 0 | 0 | 0 | 1 |
| CGN | hsa-miR-16-2*   | hsa-mir-16-2    | 1 | 0 | 0 | 0 | 0 | 1 |

**Supplementary table 8. Predicted miRNA sites on Claudin-2 3' UTR region produced by miRWalk and other programs**

| Gene         | miRNA             | StemLoopID          | miRanda  | miRDB    | miRWalk  | RNA22    | Targetscan | SUM      |
|--------------|-------------------|---------------------|----------|----------|----------|----------|------------|----------|
| CLDN2        | hsa-miR-497       | hsa-mir-497         | 1        | 1        | 1        | 1        | 1          | 5        |
| CLDN2        | hsa-miR-15a       | hsa-mir-15a         | 1        | 1        | 1        | 1        | 1          | 5        |
| <b>CLDN2</b> | <b>hsa-miR-16</b> | <b>hsa-mir-16-2</b> | <b>1</b> | <b>1</b> | <b>1</b> | <b>1</b> | <b>1</b>   | <b>5</b> |
| CLDN2        | hsa-miR-15b       | hsa-mir-15b         | 1        | 1        | 1        | 1        | 1          | 5        |
| CLDN2        | hsa-miR-424       | hsa-mir-424         | 1        | 1        | 1        | 1        | 1          | 5        |
| CLDN2        | hsa-miR-195       | hsa-mir-195         | 1        | 1        | 1        | 1        | 1          | 5        |
| CLDN2        | hsa-miR-637       | hsa-mir-637         | 1        | 1        | 1        | 0        | 1          | 4        |
| CLDN2        | hsa-miR-1275      | hsa-mir-1275        | 1        | 1        | 1        | 0        | 1          | 4        |
| CLDN2        | hsa-miR-532-3p    | hsa-mir-532         | 1        | 1        | 1        | 0        | 1          | 4        |
| CLDN2        | hsa-miR-1289      | hsa-mir-1289-2      | 1        | 1        | 1        | 0        | 1          | 4        |
| CLDN2        | hsa-miR-31        | hsa-mir-31          | 1        | 0        | 1        | 1        | 1          | 4        |
| CLDN2        | hsa-miR-299-5p    | hsa-mir-299         | 1        | 1        | 1        | 0        | 1          | 4        |
| CLDN2        | hsa-miR-512-5p    | hsa-mir-512-2       | 1        | 0        | 1        | 1        | 1          | 4        |
| CLDN2        | hsa-miR-296-3p    | hsa-mir-296         | 1        | 1        | 1        | 0        | 1          | 4        |
| CLDN2        | hsa-miR-628-5p    | hsa-mir-628         | 1        | 1        | 1        | 0        | 1          | 4        |
| CLDN2        | hsa-miR-1257      | hsa-mir-1257        | 1        | 1        | 1        | 0        | 1          | 4        |
| CLDN2        | hsa-miR-1224-3p   | hsa-mir-1224        | 1        | 1        | 1        | 0        | 1          | 4        |
| CLDN2        | hsa-miR-1208      | hsa-mir-1208        | 1        | 1        | 1        | 0        | 1          | 4        |
| CLDN2        | hsa-miR-515-5p    | hsa-mir-515-2       | 1        | 0        | 1        | 1        | 1          | 4        |
| CLDN2        | hsa-miR-146b-3p   | hsa-mir-146b        | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-27a       | hsa-mir-27a         | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-362-5p    | hsa-mir-362         | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-508-5p    | hsa-mir-508         | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-1233      | hsa-mir-1233        | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-151-3p    | hsa-mir-151         | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-579       | hsa-mir-579         | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-1287      | hsa-mir-1287        | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-129-3p    | hsa-mir-129-2       | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-1301      | hsa-mir-1301        | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-182       | hsa-mir-182         | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-483-3p    | hsa-mir-483         | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-548f      | hsa-mir-548f-4      | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-516b      | hsa-mir-516b-2      | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-920       | hsa-mir-920         | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-1292      | hsa-mir-1292        | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-532-5p    | hsa-mir-532         | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-1237      | hsa-mir-1237        | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-106a      | hsa-mir-106a        | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-580       | hsa-mir-580         | 1        | 0        | 1        | 0        | 1          | 3        |
| CLDN2        | hsa-miR-1289      | hsa-mir-1289-1      | 1        | 0        | 1        | 0        | 1          | 3        |

|       |                 |                |   |   |   |   |   |   |
|-------|-----------------|----------------|---|---|---|---|---|---|
| CLDN2 | hsa-miR-548f    | hsa-mir-548f-5 | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-516b    | hsa-mir-516b-1 | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-922     | hsa-mir-922    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1280    | hsa-mir-1280   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-365     | hsa-mir-365-1  | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1238    | hsa-mir-1238   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-148b    | hsa-mir-148b   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-582-3p  | hsa-mir-582    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-892a    | hsa-mir-892a   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-218     | hsa-mir-218-1  | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-488     | hsa-mir-488    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-610     | hsa-mir-610    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1245    | hsa-mir-1245   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-938     | hsa-mir-938    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-512-5p  | hsa-mir-512-1  | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-646     | hsa-mir-646    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1321    | hsa-mir-1321   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-365     | hsa-mir-365-2  | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-539     | hsa-mir-539    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1201    | hsa-mir-1201   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-331-3p  | hsa-mir-331    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-548a-3p | hsa-mir-548a-1 | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1291    | hsa-mir-1291   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-154     | hsa-mir-154    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-218     | hsa-mir-218-2  | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-490-5p  | hsa-mir-490    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-16      | hsa-mir-16-1   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-939     | hsa-mir-939    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-142-3p  | hsa-mir-142    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-661     | hsa-mir-661    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1825    | hsa-mir-1825   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-663b    | hsa-mir-663b   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-338-5p  | hsa-mir-338    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-587     | hsa-mir-587    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1293    | hsa-mir-1293   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-874     | hsa-mir-874    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1251    | hsa-mir-1251   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-17      | hsa-mir-17     | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-940     | hsa-mir-940    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-152     | hsa-mir-152    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-498     | hsa-mir-498    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1826    | hsa-mir-1826   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-556-5p  | hsa-mir-556    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1205    | hsa-mir-1205   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-548a-3p | hsa-mir-548a-  | 1 | 0 | 1 | 0 | 1 | 3 |

|       |                 |                |   |   |   |   |   |   |
|-------|-----------------|----------------|---|---|---|---|---|---|
| CLDN2 | hsa-miR-1297    | hsa-mir-1297   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-491-5p  | hsa-mir-491    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-625     | hsa-mir-625    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1253    | hsa-mir-1253   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-20a     | hsa-mir-20a    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-502-5p  | hsa-mir-502    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1178    | hsa-mir-1178   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1206    | hsa-mir-1206   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-9       | hsa-mir-9-1    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-421     | hsa-mir-421    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1827    | hsa-mir-1827   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-382     | hsa-mir-382    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-558     | hsa-mir-558    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-370     | hsa-mir-370    | 1 | 0 | 0 | 1 | 1 | 3 |
| CLDN2 | hsa-miR-148a    | hsa-mir-148a   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-550     | hsa-mir-550-1  | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1299    | hsa-mir-1299   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-188-3p  | hsa-mir-188    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-875-3p  | hsa-mir-875    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-504     | hsa-mir-504    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1182    | hsa-mir-1182   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1207-5p | hsa-mir-1207   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-9       | hsa-mir-9-2    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-515-5p  | hsa-mir-515-1  | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-93      | hsa-mir-93     | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-383     | hsa-mir-383    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-550     | hsa-mir-550-2  | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-193a-5p | hsa-mir-193a   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-885-5p  | hsa-mir-885    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-27b     | hsa-mir-27b    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-629     | hsa-mir-629    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1260    | hsa-mir-1260   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-570     | hsa-mir-570    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-1207-3p | hsa-mir-1207   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-9       | hsa-mir-9-3    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-328     | hsa-mir-328    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-20b     | hsa-mir-20b    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-548f    | hsa-mir-548f-1 | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-519d    | hsa-mir-519d   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-885-3p  | hsa-mir-885    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-122     | hsa-mir-122    | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-548g    | hsa-mir-548g   | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-26a     | hsa-mir-26a-1  | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-26a     | hsa-mir-26a-2  | 1 | 0 | 1 | 0 | 1 | 3 |
| CLDN2 | hsa-miR-513a-5p | hsa-mir-513a-1 | 1 | 0 | 1 | 0 | 1 | 3 |

|              |                        |                     |          |          |          |          |          |          |
|--------------|------------------------|---------------------|----------|----------|----------|----------|----------|----------|
| CLDN2        | hsa-miR-342-5p         | hsa-mir-342         | 1        | 0        | 1        | 0        | 1        | 3        |
| <b>CLDN2</b> | <b>hsa-miR-125a-5p</b> | <b>hsa-mir-125a</b> | <b>1</b> | <b>0</b> | <b>1</b> | <b>0</b> | <b>1</b> | <b>3</b> |
| CLDN2        | hsa-miR-1296           | hsa-mir-1296        | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-548a-3p        | hsa-mir-548a-3      | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-548f           | hsa-mir-548f-2      | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-760            | hsa-mir-760         | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-125b           | hsa-mir-125b-1      | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-511            | hsa-mir-511-2       | 1        | 0        | 1        | 1        | 0        | 3        |
| CLDN2        | hsa-miR-636            | hsa-mir-636         | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-26b            | hsa-mir-26b         | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-361-3p         | hsa-mir-361         | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-513a-5p        | hsa-mir-513a-2      | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-1233           | hsa-mir-1233        | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-151-5p         | hsa-mir-151         | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-575            | hsa-mir-575         | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-548e           | hsa-mir-548e        | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-125b           | hsa-mir-125b-2      | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-452            | hsa-mir-452         | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-601            | hsa-mir-601         | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-548f           | hsa-mir-548f-3      | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-510            | hsa-mir-510         | 1        | 0        | 0        | 1        | 1        | 3        |
| CLDN2        | hsa-miR-106b           | hsa-mir-106b        | 1        | 0        | 1        | 0        | 1        | 3        |
| CLDN2        | hsa-miR-329            | hsa-mir-329-1       | 1        | 0        | 0        | 0        | 1        | 2        |
| CLDN2        | hsa-miR-877            | hsa-mir-877         | 1        | 0        | 0        | 0        | 1        | 2        |
| CLDN2        | hsa-miR-130a           | hsa-mir-130a        | 1        | 0        | 1        | 0        | 0        | 2        |
| CLDN2        | hsa-miR-150            | hsa-mir-150         | 1        | 0        | 0        | 0        | 1        | 2        |
| CLDN2        | hsa-miR-29b-2*         | hsa-mir-29b-2       | 1        | 0        | 1        | 0        | 0        | 2        |
| CLDN2        | hsa-miR-199a-5p        | hsa-mir-199a-2      | 1        | 0        | 0        | 0        | 1        | 2        |
| CLDN2        | hsa-miR-520f           | hsa-mir-520f        | 1        | 0        | 0        | 0        | 1        | 2        |
| CLDN2        | hsa-miR-1303           | hsa-mir-1303        | 1        | 0        | 0        | 0        | 1        | 2        |
| CLDN2        | hsa-miR-519c-3p        | hsa-mir-519c        | 1        | 0        | 1        | 0        | 0        | 2        |
| CLDN2        | hsa-miR-379            | hsa-mir-379         | 0        | 0        | 0        | 1        | 1        | 2        |
| CLDN2        | hsa-miR-326            | hsa-mir-326         | 1        | 0        | 0        | 0        | 1        | 2        |
| CLDN2        | hsa-miR-758            | hsa-mir-758         | 1        | 0        | 0        | 0        | 1        | 2        |
| CLDN2        | hsa-miR-603            | hsa-mir-603         | 1        | 0        | 1        | 0        | 0        | 2        |
| CLDN2        | hsa-miR-30c-1*         | hsa-mir-30c-1       | 1        | 0        | 1        | 0        | 0        | 2        |
| CLDN2        | hsa-miR-329            | hsa-mir-329-2       | 1        | 0        | 0        | 0        | 1        | 2        |
| CLDN2        | hsa-miR-543            | hsa-mir-543         | 1        | 0        | 0        | 0        | 1        | 2        |
| CLDN2        | hsa-miR-132*           | hsa-mir-132         | 1        | 0        | 1        | 0        | 0        | 2        |
| CLDN2        | hsa-miR-193b*          | hsa-mir-193b        | 1        | 0        | 1        | 0        | 0        | 2        |
| CLDN2        | hsa-miR-638            | hsa-mir-638         | 1        | 0        | 1        | 0        | 0        | 2        |
| CLDN2        | hsa-miR-588            | hsa-mir-588         | 1        | 0        | 0        | 0        | 1        | 2        |

|       |                 |               |   |   |   |   |   |   |
|-------|-----------------|---------------|---|---|---|---|---|---|
| CLDN2 | hsa-miR-29a*    | hsa-mir-29a   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-363*    | hsa-mir-363   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-626     | hsa-mir-626   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-148b*   | hsa-mir-148b  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-199b-5p | hsa-mir-199b  | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-146a*   | hsa-mir-146a  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-520a-3p | hsa-mir-520a  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-766     | hsa-mir-766   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-362-3p  | hsa-mir-362   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-182*    | hsa-mir-182   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-485-5p  | hsa-mir-485   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-604     | hsa-mir-604   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-34b*    | hsa-mir-34b   | 1 | 0 | 1 | 0 | 0 | 2 |
|       |                 | hsa-mir-199a- |   |   |   |   |   |   |
| CLDN2 | hsa-miR-199a-5p | 1             | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-483-5p  | hsa-mir-483   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-942     | hsa-mir-942   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-140-5p  | hsa-mir-140   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-642     | hsa-mir-642   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-30a*    | hsa-mir-30a   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-627     | hsa-mir-627   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-106a*   | hsa-mir-106a  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-214     | hsa-mir-214   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-149*    | hsa-mir-149   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-526b*   | hsa-mir-526b  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-324-5p  | hsa-mir-324   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-1324    | hsa-mir-1324  | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-34c-5p  | hsa-mir-34c   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-517*    | hsa-mir-517c  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-141*    | hsa-mir-141   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-595     | hsa-mir-595   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-519b-3p | hsa-mir-519b  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-220b    | hsa-mir-220b  | 0 | 0 | 1 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-324-3p  | hsa-mir-324   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-613     | hsa-mir-613   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-1248    | hsa-mir-1248  | 1 | 0 | 1 | 0 | 0 | 2 |
|       |                 | hsa-mir-519a- |   |   |   |   |   |   |
| CLDN2 | hsa-miR-519a    | 1             | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-1184    | hsa-mir-1184  | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-206     | hsa-mir-206   | 1 | 0 | 0 | 1 | 0 | 2 |
| CLDN2 | hsa-miR-31*     | hsa-mir-31    | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-371-3p  | hsa-mir-371   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-555     | hsa-mir-555   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-640     | hsa-mir-640   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-129*    | hsa-mir-129-1 | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-185*    | hsa-mir-185   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-520b    | hsa-mir-520b  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-29a     | hsa-mir-29a   | 1 | 0 | 0 | 1 | 0 | 2 |

|       |                 |                |   |   |   |   |   |   |
|-------|-----------------|----------------|---|---|---|---|---|---|
| CLDN2 | hsa-miR-221*    | hsa-mir-221    | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-490-3p  | hsa-mir-490    | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-548c-3p | hsa-mir-548c   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-138     | hsa-mir-138-2  | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-301a    | hsa-mir-301a   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-519a    | hsa-mir-519a-2 | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-147     | hsa-mir-147    | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-493     | hsa-mir-493    | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-1184    | hsa-mir-1184   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-449b    | hsa-mir-449b   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-1       | hsa-mir-1-1    | 1 | 0 | 0 | 1 | 0 | 2 |
| CLDN2 | hsa-miR-32*     | hsa-mir-32     | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-372     | hsa-mir-372    | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-148a*   | hsa-mir-148a   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-335*    | hsa-mir-335    | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-1254    | hsa-mir-1254   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-188-5p  | hsa-mir-188    | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-520c-3p | hsa-mir-520c   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-892b    | hsa-mir-892b   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-335     | hsa-mir-335    | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-140-3p  | hsa-mir-140    | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-544     | hsa-mir-544    | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-494     | hsa-mir-494    | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-1184    | hsa-mir-1184   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-520e    | hsa-mir-520e   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-29c     | hsa-mir-29c    | 1 | 0 | 0 | 1 | 0 | 2 |
| CLDN2 | hsa-miR-611     | hsa-mir-611    | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-92a-1*  | hsa-mir-92a-1  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-518c*   | hsa-mir-518c   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-422a    | hsa-mir-422a   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-23b*    | hsa-mir-23b    | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-511     | hsa-mir-511-1  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-103     | hsa-mir-103-1  | 1 | 0 | 0 | 1 | 0 | 2 |
| CLDN2 | hsa-miR-130b    | hsa-mir-130b   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-561     | hsa-mir-561    | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-1224-5p | hsa-mir-1224   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-1909    | hsa-mir-1909   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-612     | hsa-mir-612    | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-30c-2*  | hsa-mir-30c-2  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-18b*    | hsa-mir-18b    | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-1300    | hsa-mir-1300   | 0 | 0 | 1 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-1265    | hsa-mir-1265   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-517*    | hsa-mir-517a   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-423-5p  | hsa-mir-423    | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-511     | hsa-mir-511-1  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-107     | hsa-mir-107    | 1 | 0 | 0 | 1 | 0 | 2 |

|       |                 |               |   |   |   |   |   |   |
|-------|-----------------|---------------|---|---|---|---|---|---|
| CLDN2 | hsa-miR-22      | hsa-mir-22    | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-30e*    | hsa-mir-30e   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-505*    | hsa-mir-505   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-1226*   | hsa-mir-1226  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-512-3p  | hsa-mir-512-1 | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-519e*   | hsa-mir-519e  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-1914*   | hsa-mir-1914  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-93*     | hsa-mir-93    | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-30d*    | hsa-mir-30d   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-596     | hsa-mir-596   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-503     | hsa-mir-503   | 1 | 0 | 0 | 1 | 0 | 2 |
| CLDN2 | hsa-miR-1274a   | hsa-mir-1274a | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-18b     | hsa-mir-18b   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-511     | hsa-mir-511-2 | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-629*    | hsa-mir-629   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-138     | hsa-mir-138-1 | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-1229    | hsa-mir-1229  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-572     | hsa-mir-572   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-512-3p  | hsa-mir-512-2 | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-519e    | hsa-mir-519e  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-34c-3p  | hsa-mir-34c   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-622     | hsa-mir-622   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-100*    | hsa-mir-100   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-18a     | hsa-mir-18a   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-378     | hsa-mir-378   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-139-3p  | hsa-mir-139   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-20b*    | hsa-mir-20b   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-194*    | hsa-mir-194-2 | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-520d-3p | hsa-mir-520d  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-29b     | hsa-mir-29b-2 | 1 | 0 | 0 | 1 | 0 | 2 |
| CLDN2 | hsa-miR-1261    | hsa-mir-1261  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-581     | hsa-mir-581   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-29b-1*  | hsa-mir-29b-1 | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-183     | hsa-mir-183   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-1294    | hsa-mir-1294  | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-1271    | hsa-mir-1271  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-296-5p  | hsa-mir-296   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-330-5p  | hsa-mir-330   | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-34a*    | hsa-mir-34a   | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-1252    | hsa-mir-1252  | 1 | 0 | 0 | 0 | 1 | 2 |
| CLDN2 | hsa-miR-517*    | hsa-mir-517b  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-301b    | hsa-mir-301b  | 1 | 0 | 1 | 0 | 0 | 2 |
| CLDN2 | hsa-miR-16-2*   | hsa-mir-16-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-584     | hsa-mir-584   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-624     | hsa-mir-624   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1179    | hsa-mir-1179  | 0 | 0 | 0 | 0 | 1 | 1 |



|       |                 |                |   |   |   |   |   |   |
|-------|-----------------|----------------|---|---|---|---|---|---|
| CLDN2 | hsa-miR-1285    | hsa-mir-1285-2 | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-15a*    | hsa-mir-15a    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-488*    | hsa-mir-488    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-30e     | hsa-mir-30e    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-23a*    | hsa-mir-23a    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-505     | hsa-mir-505    | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-30b*    | hsa-mir-30b    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-514     | hsa-mir-514-1  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-664*    | hsa-mir-664    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-192*    | hsa-mir-192    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-765     | hsa-mir-765    | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-27b*    | hsa-mir-27b    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-185     | hsa-mir-185    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-187     | hsa-mir-187    | 0 | 0 | 0 | 1 | 0 | 1 |
| CLDN2 | hsa-miR-515-3p  | hsa-mir-515-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1304    | hsa-mir-1304   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-17*     | hsa-mir-17     | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-497*    | hsa-mir-497    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-24      | hsa-mir-24-1   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-331-5p  | hsa-mir-331    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-671-5p  | hsa-mir-671    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-124     | hsa-mir-124-1  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-514     | hsa-mir-514-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-720     | hsa-mir-720    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-190     | hsa-mir-190    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-590-3p  | hsa-mir-590    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-302b    | hsa-mir-302b   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-519b-5p | hsa-mir-519b   | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-453     | hsa-mir-453    | 0 | 0 | 0 | 1 | 0 | 1 |
| CLDN2 | hsa-miR-520g    | hsa-mir-520g   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1305    | hsa-mir-1305   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-20a*    | hsa-mir-20a    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-let-7d      | hsa-let-7d     | 0 | 0 | 0 | 1 | 0 | 1 |
| CLDN2 | hsa-miR-24      | hsa-mir-24-2   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-454     | hsa-mir-454    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-124     | hsa-mir-124-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-514     | hsa-mir-514-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-30c     | hsa-mir-30c-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-484     | hsa-mir-484    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-297     | hsa-mir-297    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-193a-3p | hsa-mir-193a   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-let-7a*     | hsa-let-7a-1   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-302c*   | hsa-mir-302c   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-33b*    | hsa-mir-33b    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-519c-5p | hsa-mir-519c   | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-202     | hsa-mir-202    | 0 | 0 | 0 | 1 | 0 | 1 |

|       |                 |                |   |   |   |   |   |   |
|-------|-----------------|----------------|---|---|---|---|---|---|
| CLDN2 | hsa-miR-218-1*  | hsa-mir-218-1  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-520h    | hsa-mir-520h   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1243    | hsa-mir-1243   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-26b*    | hsa-mir-26b    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-552     | hsa-mir-552    | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-28-3p   | hsa-mir-28     | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-675b    | hsa-mir-675b   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-124     | hsa-mir-124-3  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-514     | hsa-mir-514-3  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1912    | hsa-mir-1912   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-30d     | hsa-mir-30d    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-492     | hsa-mir-492    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-197     | hsa-mir-197    | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-605     | hsa-mir-605    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-7       | hsa-mir-7-3    | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-let-7a*     | hsa-let-7a-3   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-302c    | hsa-mir-302c   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-218-2*  | hsa-mir-218-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-522     | hsa-mir-522    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1246    | hsa-mir-1246   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-220c    | hsa-mir-220c   | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-526a    | hsa-mir-526a-2 | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-338-3p  | hsa-mir-338    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-769-3p  | hsa-mir-769    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-196b    | hsa-mir-196b   | 0 | 0 | 0 | 1 | 0 | 1 |
| CLDN2 | hsa-miR-27a*    | hsa-mir-27a    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-514     | hsa-mir-514-3  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1914    | hsa-mir-1914   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-195*    | hsa-mir-195    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-608     | hsa-mir-608    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-876-3p  | hsa-mir-876    | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-let-7b*     | hsa-let-7b     | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-302d    | hsa-mir-302d   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-649     | hsa-mir-649    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-222*    | hsa-mir-222    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-501-5p  | hsa-mir-501    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-518d-5p | hsa-mir-518d   | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-30a     | hsa-mir-30a    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-450b-3p | hsa-mir-450b   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-103     | hsa-mir-103-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1915*   | hsa-mir-1915   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-578     | hsa-mir-578    | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-10a     | hsa-mir-10a    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-let-7c*     | hsa-let-7c     | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-652     | hsa-mir-652    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-541     | hsa-mir-541    | 0 | 0 | 0 | 0 | 1 | 1 |

|       |                 |               |   |   |   |   |   |   |
|-------|-----------------|---------------|---|---|---|---|---|---|
| CLDN2 | hsa-miR-223*    | hsa-mir-223   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-501-3p  | hsa-mir-501   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1262    | hsa-mir-1262  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-96      | hsa-mir-96    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-890     | hsa-mir-890   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1256    | hsa-mir-1256  | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-143*    | hsa-mir-143   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-545     | hsa-mir-545   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-22*     | hsa-mir-22    | 0 | 0 | 1 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1915    | hsa-mir-1915  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-10b     | hsa-mir-10b   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-193b    | hsa-mir-193b  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1225-3p | hsa-mir-1225  | 1 | 0 | 0 | 0 | 0 | 1 |
|       |                 | hsa-mir-376a- |   |   |   |   |   |   |
| CLDN2 | hsa-miR-376a    | 2             | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-30c     | hsa-mir-30c-1 | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-let-7f-1*   | hsa-let-7f-1  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-373     | hsa-mir-373   | 1 | 0 | 0 | 0 | 0 | 1 |
|       |                 | hsa-mir-548d- |   |   |   |   |   |   |
| CLDN2 | hsa-miR-548d-3p | 1             | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-223     | hsa-mir-223   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-502-3p  | hsa-mir-502   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-96*     | hsa-mir-96    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-875-5p  | hsa-mir-875   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1225-5p | hsa-mir-1225  | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-145     | hsa-mir-145   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-554     | hsa-mir-554   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-34a     | hsa-mir-34a   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1226    | hsa-mir-1226  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-384     | hsa-mir-384   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-302a    | hsa-mir-302a  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-619     | hsa-mir-619   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-let-7f-2*   | hsa-let-7f-2  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-377*    | hsa-mir-377   | 1 | 0 | 0 | 0 | 0 | 1 |
|       |                 | hsa-mir-548d- |   |   |   |   |   |   |
| CLDN2 | hsa-miR-548d-3p | 2             | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-224     | hsa-mir-224   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-548k    | hsa-mir-548k  | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-29b     | hsa-mir-29b-1 | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-190b    | hsa-mir-190b  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-562     | hsa-mir-562   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-520c-5p | hsa-mir-520c  | 0 | 0 | 0 | 0 | 1 | 1 |
|       |                 | hsa-mir-181a- |   |   |   |   |   |   |
| CLDN2 | hsa-miR-181a-2* | 2             | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1234    | hsa-mir-1234  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-654-5p  | hsa-mir-654   | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-411     | hsa-mir-411   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-377     | hsa-mir-377   | 0 | 0 | 0 | 0 | 1 | 1 |

|       |                 |               |   |   |   |   |   |   |
|-------|-----------------|---------------|---|---|---|---|---|---|
| CLDN2 | hsa-miR-1       | hsa-mir-1-2   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-506     | hsa-mir-506   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-302e    | hsa-mir-302e  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-449a    | hsa-mir-449a  | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-744     | hsa-mir-744   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-376b    | hsa-mir-376b  | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-149     | hsa-mir-149   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-1200    | hsa-mir-1200  | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-509-3p  | hsa-mir-509-3 | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-515-3p  | hsa-mir-515-1 | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-125a-3p | hsa-mir-125a  | 0 | 0 | 0 | 0 | 1 | 1 |
| CLDN2 | hsa-miR-624*    | hsa-mir-624   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-21*     | hsa-mir-21    | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-549     | hsa-mir-549   | 1 | 0 | 0 | 0 | 0 | 1 |
| CLDN2 | hsa-miR-30b     | hsa-mir-30b   | 1 | 0 | 0 | 0 | 0 | 1 |

Supplementary table 9. Correlations of IBS symptoms with miRNA/target gene expression in the jejunal mucosa of IBS-D and healthy controls.

|                        | Pain Intensity |          | Pain Frequency |             | Bowel Movements |               | Bristol stool form |               |
|------------------------|----------------|----------|----------------|-------------|-----------------|---------------|--------------------|---------------|
|                        | <i>r</i>       | <i>P</i> | <i>r</i>       | <i>P</i>    | <i>r</i>        | <i>P</i>      | <i>r</i>           | <i>P</i>      |
| <b>hsa-miR-125b-5p</b> | 0.06           | ns       | <b>0.64</b>    | <b>0.01</b> | <b>-0.46</b>    | <b>0.01</b>   | <b>-0.49</b>       | <b>0.007</b>  |
| <b>hsa-miR-16</b>      | 0.31           | ns       | 0.36           | ns          | <b>-0.55</b>    | <b>0.002</b>  | <b>-0.46</b>       | <b>0.009</b>  |
| <b>Cingulin</b>        | -0,36          | ns       | -0,18          | ns          | <b>0,60</b>     | <b>0,0002</b> | <b>0,53</b>        | <b>0,001</b>  |
| <b>Claudin-2</b>       | -0,08          | ns       | -0,07          | ns          | <b>0,58</b>     | <b>0,0002</b> | <b>0,59</b>        | <b>0,0002</b> |

Note: Spearman's correlation rho was applied to the pooled data of healthy controls (HC) and IBS-D patients. Values of  $P < 0.05$  are shown in bold. ns: not significant.

**Supplementary table 10. Correlations of basal stress and depression miRNA/target expression in the jejunal mucosa of IBS-D and healthy controls.**

|                        | Holmes   |          | Cohen        |             | Becks        |             |
|------------------------|----------|----------|--------------|-------------|--------------|-------------|
|                        | <i>r</i> | <i>P</i> | <i>r</i>     | <i>P</i>    | <i>r</i>     | <i>P</i>    |
| <b>hsa-miR-125b-5p</b> | -0.22    | ns       | <b>-0.45</b> | <b>0.01</b> | -0.32        | 0.09        |
| <b>hsa-miR-16</b>      | -0.15    | ns       | <b>-0.40</b> | <b>0.03</b> | <b>-0.37</b> | <b>0.04</b> |
| <b>Cingulin</b>        | -0,07    | ns       | <b>0,40</b>  | <b>0,02</b> | 0,28         | ns          |
| <b>Claudin-2</b>       | 0,01     | ns       | <b>0,38</b>  | <b>0,03</b> | <b>0,37</b>  | <b>0,03</b> |

Note: Spearman's correlation rho was applied to the pooled data of healthy controls (HC) and IBS-D patients. Values of  $P < 0.05$  are shown in bold. ns: not significant.