



## Supplementary Material

### Methods

The validation of serum and CSF EV-rich fractions as collected by size exclusion chromatography was conducted using the following methods.

**Tunable resistive pulse sensing:** Pilot serum and CSF samples from healthy and hospitalized human subjects, respectively, were analyzed on a tunable resistive pulse sensing qNANO platform, following a standardized methodology [60] (Fig. S1A, B). Briefly, an NP100 membrane (Izon Science) was used, and the set-up calibrated using carboxylated particles (diameter = 110 nm). Size and concentration calibrations were performed using CPN100 standards at a concentration of  $10^{10}$  particles/ml. The EV concentration at each size category was determined using a two-points pressure method, with pressures ranging between 0.3–2 kPa. All samples were run in triplicates. Measurements were carried out by Nanotechnology.life laboratories, Loughborough University (Loughborough, UK).

**Transmission electron microscopy (TEM):** Isolated EVs (5  $\mu$ l) were applied onto a freshly glow discharged carbon film grid for 2 min, then washed with distilled de-ionized water and air dried. Negative staining was achieved by a double incubation with 5  $\mu$ l of 1% uranyl acetate. Samples were viewed on a JEOL JEM-1400 TEM with an accelerating voltage of 120 kV. Images were collected using an EMSIS Xarosa digital camera running Radius software (Fig. S1C, D). The procedure was carried out at the Core Biotechnology Services Electron Microscopy Facility, University of Leicester (Leicester, UK).

**Western blotting:** Isolated EVs were lysed in radioimmunoprecipitation assay (RIPA) buffer containing protease inhibitor (cOmplete Mini, Merck). A Pierce BCA Protein Assay (Thermo Fischer) was used to assess protein concentration of individual (Fig. S1E, F) and pooled SEC fractions. Lysates were resolved onto a 12% polyacrylamide precast gel (Criterion TGX, Bio-Rad) using 1x sodium dodecyl sulfate (SDS) running buffer. Samples were then transferred onto a polyvinylidene difluoride (PVDF) membrane for 7 min at 25 V using the Trans-Blot Turbo Transfer system (Bio-Rad). Membranes were rinsed with PBS 1% Tween (PBS-T) and blocked with PBS-T containing 5% non-fat milk powder for 1 h at room temperature before overnight incubation with primary antibody at 4°C. Primary antibodies against the following EV marker proteins were used and at the dilutions indicated: Alix (1:5000, ab186429, Abcam), CD9 (1:2000, ab92726, Abcam), Flotilin-1 (1:1000, 610820, BD Transduction Laboratories), and CD-81 (1:250, MAB4615, R&D Systems). Membranes were then washed in PBS-T (3x 20 min), incubated for 1 h at room temperature with the appropriate horseradish peroxidase-conjugated secondary antibody (1:1000), and finally washed in PBS-T (3x 20 min). Lastly, membranes were incubated with detection solvent (Clarity ECL Western Detection System, Bio-Rad) and images were acquired using Chemidoc MP Imaging system (Bio-Rad) (Fig. S1G, H).

**LDL-cholesterol assay:** The extent of presence of contaminating low-density lipoproteins (LDL) in serum EV preparations was assessed by running 2.5  $\mu$ l EV-rich fractions in the LDL-cholesterol (LDL-C) Assay Kit (Elabscience), according to the manufacturer's instructions (Fig. S1I).

60. Vogel, R.; Coumans, F.A.W.; Maltesen, R.G.; Böing, A.N.; Bonnington, K.E.; Broekman, M.L.; Broom, M.F.; Buzás, E.I.; Christiansen, G.; Hajji, N.; et al. A standardized method to determine the concentration of extracellular vesicles using tunable resistive pulse sensing. *J. Extracell. Vesicles* **2016**, *5*, 31242. <https://doi.org/10.3402/jev.v5.31242>

## Results

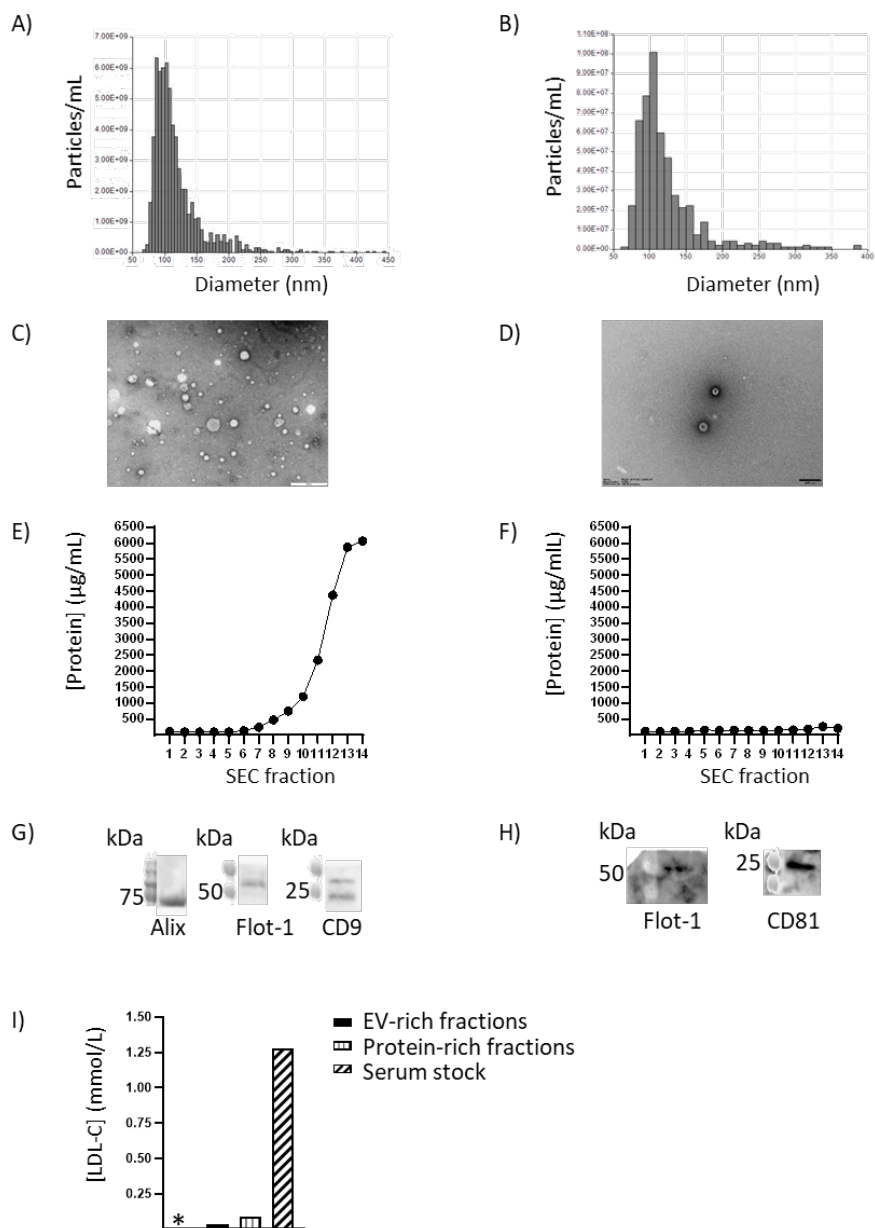


Figure S1. Validation of SEC-isolated serum and CSF EVs. (A, B) TRPS profile of a representative (A) serum EV-rich fraction (concentration:  $6.37 \times 10^{10}$  particles/mL, mean size: 120 nm) and (B) CSF EV-rich fraction (concentration:  $1.43 \times 10^9$  particles/mL, mean size: 127 nm). (C, D) Representative TEM image of (C) serum EVs and (D) CSF EVs; scale bar 200 nm. (E, F) Total protein quantification of individual SEC fractions (1-14) of (E) serum EVs and (F) CSF EVs. (G, H) Western blotting of (G) serum EV-rich fractions for the EV-specific protein markers Alix (75 kDa), Flotilin-1 (47 kDa), and CD9 (22 kDa), 40 µg protein per marker, and of (H) CSF EV-rich fractions for the EV-specific protein markers Flotilin-1 (47 kDa) and CD81 (25 kDa), 6 µg protein per marker. (I) LDL-C concentration for early fractions (1-5), EV-rich fractions (6-10), protein-rich fractions (11-15), and serum stock; \* LDL-C levels in the early fractions were below detection threshold.

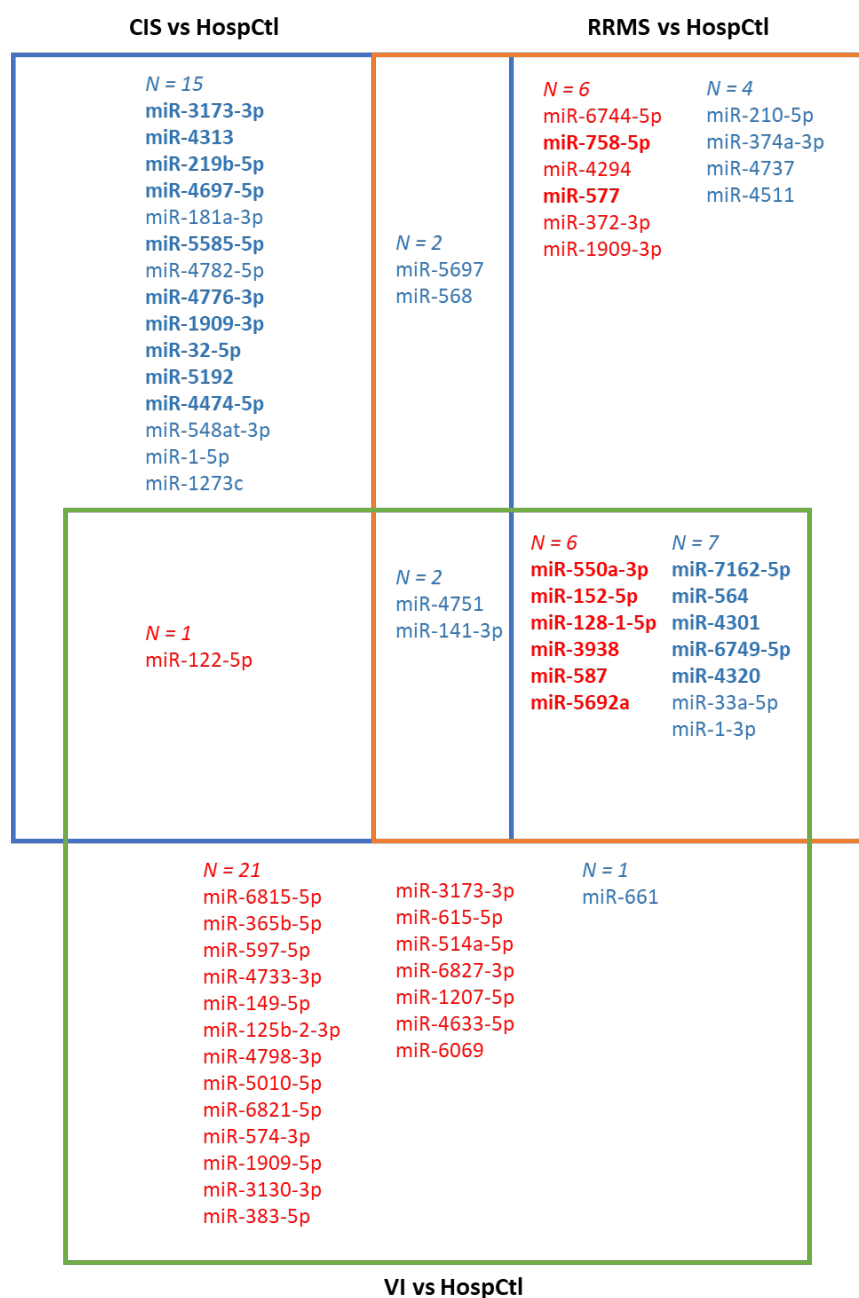
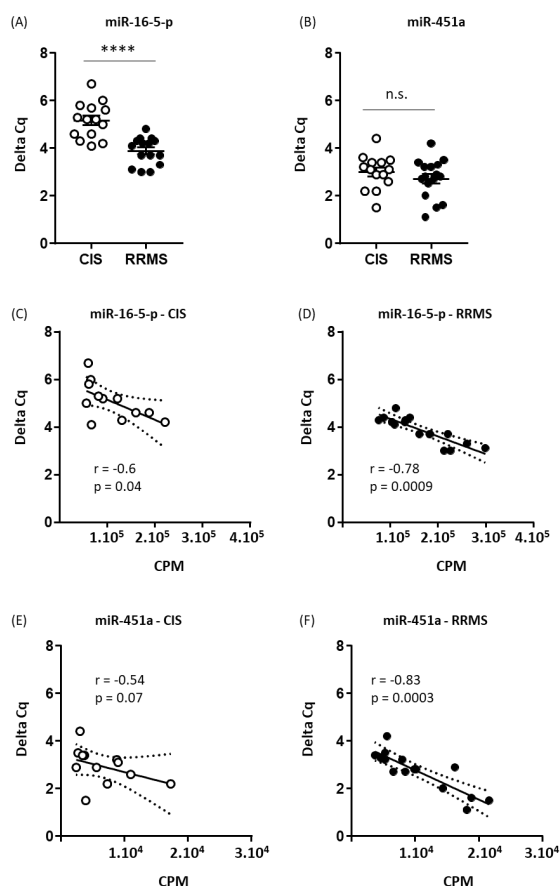


Figure S2. Venn diagram depicting the findings of pair-wise differential expression analysis (DEA) ( $p < 0.01$ ,  $\log_2$  fold change  $\geq 1$  or  $\leq -1$ ) of serum EV miRNomes in different subject groups. As a first step DEA was conducted for CIS vs HospCtl, RRMS vs HospCtl, and VI vs HospCtl. EV miRNAs indicated in blue were down-regulated in the corresponding disease state(s) relative to HospCtl, and miRNAs indicated in red were up-regulated in the corresponding disease state(s) relative to HospCtl. Next, DEA was conducted for CIS vs RRMS. EV miRNAs indicated in blue and bold were down-regulated in RRMS relative to HospCtl and CIS, and miRNAs indicated in red and bold were up-regulated in RRMS relative to HospCtl and CIS. Therefore, 15 down-regulated miRNAs were CIS-remission-specific relative to HospCtl and RRMS-relapse, and 12 miRNAs (6 up-regulated and 6 down-regulated) were RRMS-relapse-specific relative to HospCtl and CIS-remission.

**Table S1.** Comparison between miRNA-Seq and RT-qPCR expression data for two RRMS-specific miRNAs

	hsa-miR-16-5p		hsa-miR-451a	
	CIS	RRMS	CIS	RRMS
miRNA-Seq CPM mean	111182	219829	6627	14634
± SEM	14949	58466	1188	4415
Delta Cq mean	5.2	3.7	3.0	2.7
± SEM	0.20	0.24	0.19	0.21
Spearman's $r$ CPM against Delta Cq	-0.60	-0.78	-0.54	-0.83
Pearson's $r$ p	0.04	0.0009	0.07	0.0003
miRNA-Seq F-test p	0.01		0.007	
miRNA-Seq CPM t-test p	0.1		0.1	
Delta Cq t-test p	< 0.0001		0.3	

CPM: normalized counts per million.  $r$ : Spearman rank-order correlation coefficient.



**Figure S3.** Validation of miRNA-Seq expression values using RT-qPCR. (A) miR-16-5p. (B) miR-451. \*\*\*\* $p < 0.0001$ , two-tailed unpaired Student's  $t$ -test. n.s. = not significant. Individual values, mean and  $\pm$  SEM values are shown. (C-F) Predictive association between miRNA-Seq normalized counts (CPM) and RT-PCR delta Cq values for miR-16-p within (C) CIS subjects and (D) RRMS subjects, and for miR-451a within (E) CIS subjects and (F) RRMS subjects. Scatter plots and the best-fit linear regression line ( $\pm$  95% confidence intervals) are given.

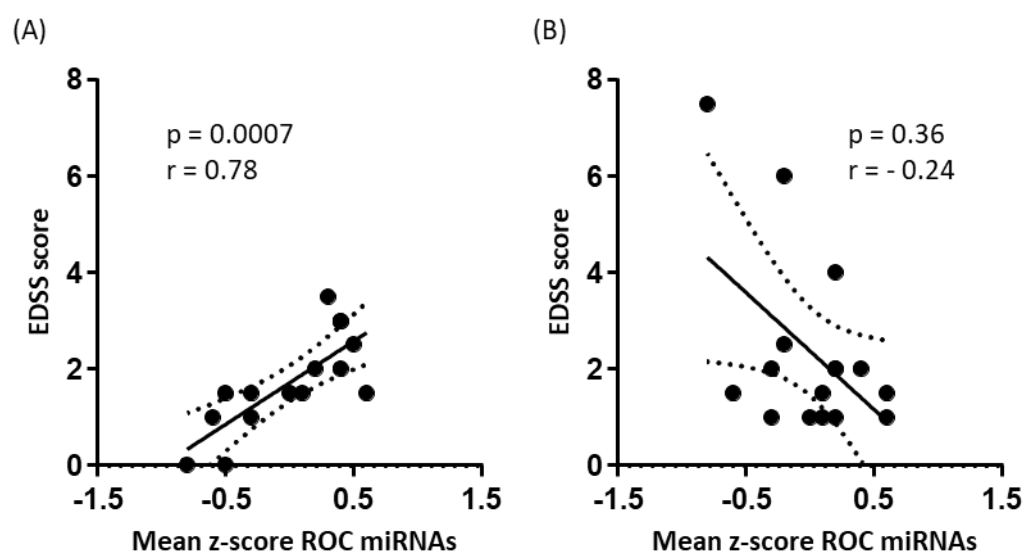


Figure S4. Predictive association between mean z-scores of the CIS-RRMS miRNA predictive panel and EDSS scores. Scatter plots and the best-fit linear regression line ( $\pm$  95% confidence intervals) are given for (A) mean z-score of the CIS-RRMS miRNA predictive panel and EDSS scores of CIS patients and (B) mean z-score of the CIS-RRMS miRNA predictive panel and EDSS scores of RRMS patients.

**Table S2.** Complete list of over-represented pathways identified for validated target genes of the RRMS-specific miRNAs

Pathway	FDR	miRNAs	Target transcripts
Vesicle-mediated transport	$2.14 \times 10^{-8}$	hsa-miR-16-5p	<i>RAB9B, CAPZA2, DCTN5, GALNT1, RAB30, PPP6R3, RAB3IP, SBF1, TBC1D14, KIF2A, RACGAP1, KIF3B, KIF1B, TFRC, COL4A1</i>
		hsa-miR-6840-3p	<i>TRAPPC2, ACTR1A, FZD4, GNS, TBC1D24, GJC1, APOL1</i>
		hsa-miR-6811-3p	<i>RAB13, RAB30, PAFAH1B2, DENND6B</i>
		hsa-miR-5192	<i>CBL, CSNK1D, TBC1D13, SYT2, CALR</i>
		hsa-miR-4476	<i>RAB5B, ACTR2, PACSIN1</i>
		hsa-miR-135b-5p	<i>RAB3GAP2</i>
Membrane trafficking (Vesicle-mediated transport)	$2.14 \times 10^{-8}$	hsa-miR-6840-3p	<i>TRAPPC2, ACTR1A, FZD4, GNS, TBC1D24, GJC1</i>
		hsa-miR-6811-3p	<i>RAB13, RAB30, PAFAH1B2, DENND6B</i>
		hsa-miR-5192	<i>CBL, CSNK1D, TBC1D13, SYT2</i>
		hsa-miR-4476	<i>RAB5B, ACTR2, PACSIN1</i>
		hsa-miR-135b-5p	<i>RAB3GAP2</i>
Post-translational protein modification (Metabolism of proteins)	$1.87 \times 10^{-7}$	hsa-miR-16-5p	<i>RAB9B, CAPZA2, DCTN5, GALNT1, RAB30, PPP6R3, BIRC5, MAP3K7, SOCS2, NUP155, NCOR2, BRCA1, CUL3, FBXL20, B3GNT2, RAB23, GALNT7, ASXL1</i>
		hsa-miR-6840-3p	<i>TRAPPC2, ACTR1A, APOL1, MLEC, RCE1, SUMF2, GGCX, DCAF10, FOXK1, CPM</i>
		hsa-miR-4476	<i>RAB5B, PSMD11, PHC2, TFAP2A, USP12, IGFBP4</i>
		hsa-miR-1909-3p	<i>CANX, TFAP2B, SENP5, DPH2, WAC</i>
		hsa-miR-5192	<i>CSNK1D, CALR, ST6GAL2, RECK</i>

		hsa-miR-6811-3p	<i>RAB13, RAB30, KLHL21, PEX2</i>
		hsa-miR-135b-5p	<i>THBS2</i>
Signaling by Interleukins (Immune system)	$1.87 \times 10^7$	hsa-miR-16-5p	<i>BIRC5, MAP3K7, SOCS2, VEGFA, RPS6KA3, UBE2V1, BCL2, IRAK3, PIM1, HNRNP DL</i>
		hsa-miR-5192	<i>CBL, SOD2, POU2F1, UBE2V1, STX3</i>
		hsa-miR-4476	<i>PSMD11, SOD2, CFL1, IFNLR1</i>
		hsa-miR-1909-3p	<i>CANX, IRAK4, MCL1</i>
		hsa-miR-6840-3p	<i>CRK, IL6R, STAT2</i>
		hsa-miR-135b-5p	<i>STAT6</i>
		hsa-miR-6811-3p	<i>CCR2</i>
Cytokine signalling in immune system (Immune system)	$1.23 \times 10^6$	hsa-miR-16-5p	<i>BIRC5, MAP3K7, SOCS2, VEGFA, RPS6KA3, UBE2V1, BCL2, IRAK3, PIM1, HNRNP DL, NUP155, KRAS, CD44</i>
		hsa-miR-5192	<i>CBL, SOD2, POU2F1, UBE2V1, STX3, EDAR</i>
		hsa-miR-4476	<i>PSMD11, SOD2, CFL1, IFNLR1</i>
		hsa-miR-1909-3p	<i>CANX, IRAK4, MCL1</i>
		hsa-miR-6840-3p	<i>CRK, IL6R, STAT2</i>
		hsa-miR-6811-3p	<i>CCR2, PDE12</i>
		hsa-miR-135b-5p	<i>STAT6</i>
RNA Polymerase II transcription (Transcription)	$7.78 \times 10^6$	hsa-miR-16-5p	<i>BIRC5, VEGFA, NCOR2, BRCA1, KRAS, ANAPC16, TBL1XR1, CCND2, CHEK1, ZC3H 11A, CCNT2, TAF15, PIP4P1, PPM1D, ZNF691</i>
		hsa-miR-4476	<i>PSMD11, SOD2, PHC2, TFAP2A, TNRC6B, TXNIP, TFDP2, RNF111, CHTOP, GATA D2B, HDAC5, ZNF426</i>
		hsa-miR-6811-3p	<i>AGO3, ANAPC16, ZNF716, ZNF770, ZNF490, ZNF154, ZNF175</i>
		hsa-miR-6840-3p	<i>SKIL, OPRK1, INTS3, ZNF100, ZNF716, ZNF589</i>
		hsa-miR-5192	<i>SOD2, POU2F1, E2F6, CCND2, ZC3H11A, FANCC</i>
		hsa-miR-135b-5p	<i>TXNIP</i>
		hsa-miR-1909-3p	<i>TFAP2B</i>
Ca <sup>2+</sup> pathway (Signal transduction - Signaling by Wnt)	$1.15 \times 10^5$	hsa-miR-16-5p	<i>MAP3K7, KRAS</i>
		hsa-miR-4476	<i>TNRC6B</i>
		hsa-miR-6811-3p	<i>AGO3, PRKCA, PDE6A, PDE6B</i>
		hsa-miR-6840-3p	<i>FZD4, GNG4</i>
Innate immune system (Immune system)	$1.65 \times 10^5$	hsa-miR-16-5p	<i>RAB9B, CAPZA2, MAP3K7, RPS6KA3, UBE2V1, BCL2, IRAK3, KRAS, CD44, GOLG A7, VCL, PYGB, PDXK</i>
		hsa-miR-6840-3p	<i>GNS, CRK, MLEC, RHOF, GM2A, RAP2B, POLR1D, SIKE1</i>
		hsa-miR-4476	<i>RAB5B, ACTR2, PSMD11, CFL1, TXNIP, ATOX1, FRK</i>
		hsa-miR-1909-3p	<i>IRAK4, ATOX1, VCL, NFASC</i>
		hsa-miR-6811-3p	<i>PAFAH1B2, CCR2, KLRD1, SVIP</i>
		hsa-miR-135b-5p	<i>STAT6, TXNIP</i>
		hsa-miR-5192	<i>UBE2V1, PKM</i>
Rab regulation of trafficking (Vesicle-mediated transport - Clathrin-mediated endocytosis)	$4.46 \times 10^5$	hsa-miR-16-5p	<i>RAB9B, RAB3IP, SBF1, TBC1D14</i>
		hsa-miR-6811-3p	<i>RAB13, DENND6B</i>
		hsa-miR-6840-3p	<i>TRAPPC2, TBC1D24</i>
		hsa-miR-5192	<i>TBC1D13</i>
		hsa-miR-135b-5p	<i>RAB3GAP2</i>
		hsa-miR-4476	<i>RAB5B</i>

Beta-catenin independent Wnt signaling pathway (Signal transduction - Signaling by Wnt)	0.0002	hsa-miR-6811-3p	AGO3,PRKCA,PDE6A,PDE6B,PRICKLE1
		hsa-miR-16-5p	MAP3K7, KRAS
		hsa-miR-4476	PSMD11, TNRC6B
		hsa-miR-6840-3p	FZD4, GNG4
Cellular responses to external stimuli (Cellular response to stimuli)	0.0002	hsa-miR-16-5p	CAPZA2,DCTN5,VEGFA,RPS6KA3,NUP155,NCOR2,CUL3,ANAPC16,TBL1XR1,RPS24,RPL10,TXN2,HM13,HMGA2,NCOR2,CUL3,TBL1XR1,TXN2,HM13
		hsa-miR-4476	PSMD11,SOD2,PHC2,TNRC6B,TXNIP,TFDP2,ATOX1
		hsa-miR-6811-3p	AGO3,ANAPC16,BAG2
		hsa-miR-135b-5p	TXNIP
		hsa-miR-1909-3p	ATOX1
		hsa-miR-5192	SOD2
		hsa-miR-6840-3p	ACTR1A, RPL28
Adaptive immune system (Immune system)	0.0004	hsa-miR-16-5p	DCTN5,KIF2A,RACGAP1,KIF3B,MAP3K7,UBE2V1,CUL3,FBXL20,KRAS,SEC61A1,ANAPC13,TRIM4,UBE3C,CAPZA2
		hsa-miR-6811-3p	KLHL21,KLRD1,RAET1E
		hsa-miR-6840-3p	ACTR1A,TAP2,RNF14,CD300LG,NCR3LG1,BTN3A2
		hsa-miR-4476	PSMD11, RNF111
		hsa-miR-5192	CALR, UBE2V1
		hsa-miR-1909-3p	CANX
Golgi to ER retrograde transport (Vesicle-mediated transport - Clathrin-mediated endocytosis)	0.0006	hsa-miR-16-5p	CAPZA2,KIF2A,RACGAP1,KIF3B,KIF1B,GALNT1, DCTN5
		hsa-miR-135b-5p	RAB3GAP2
		hsa-miR-6811-3p	PAFAH1B2
		hsa-miR-6840-3p	ACTR1A
Neutrophil degranulation (Immune system - Innate)	0.0007	hsa-miR-16-5p	RAB9B,CD44,GOLGA7,VCL,PYGB,PDXK
		hsa-miR-6840-3p	GNS,MLEC,RHOF,GM2A,RAP2B
		hsa-miR-4476	RAB5B,ACTR2,PSMD11,FRK
		hsa-miR-1909-3p	VCL, NFASC
		hsa-miR-6811-3p	PAFAH1B2, SVIP
		hsa-miR-5192	PKM
Intra-Golgi and retrograde Golgi to ER trafficking (Vesicle-mediated transport - membrane trafficking)	0.0007	hsa-miR-16-5p	RAB9B,CAPZA2,DCTN5,GALNT1,RAB30,KIF2A,RACGAP1,KIF3B,KIF1B
		hsa-miR-6811-3p	RAB30, PAFAH1B2
		hsa-miR-135b-5p	RAB3GAP2
		hsa-miR-6840-3p	ACTR1A
MAPK family signaling cascades (Signal transduction)	0.001	hsa-miR-16-5p	CUL3,KRAS,GOLGA7,VCL,FNTA,ARL2
		hsa-miR-6840-3p	IL6R,RCE1,SPRED1
		hsa-miR-4476	PSMD11, TNRC6B
		hsa-miR-5192	FGFR1, CDC14B

		hsa-miR-6811-3p	AGO3, IGF2BP1
		hsa-miR-1909-3p	VCL
Cell cycle	0.001	hsa-miR-16-5p	PPP6R3, RAB3IP, SBF1, KIF2A, BIRC5, NUP155, BRCA1, ANAPC16, CCND2, CHEK1, TAOK1, ORC4,
		hsa-miR-4476	PSMD11, TFDP2, BUB3, TAOK1, SET
		hsa-miR-5192	CSNK1D, E2F6, CCND2
		hsa-miR-6811-3p	DENND6B, ANAPC16, PRKCA, SPC24, SPAST
		hsa-miR-6840-3p	ACTR1A, ARPP19, CTC1
		hsa-miR-135b-5p	RAB3GAP2
		hsa-miR-4787-5p	CENPO
Rab GEFs exchange GTP for GDP on RABs (Vesicle-mediated transport - membrane trafficking - Rab regulation of trafficking)	0.001	hsa-miR-16-5p	RAB9B, RAB3IP, SBF1
		hsa-miR-6811-3p	RAB13, DENND6B
		hsa-miR-6840-3p	TRAPPC2
		hsa-miR-4476	RAB5B
		hsa-miR-135b-5p	RAB3GAP2
Signaling by Rho GTPases, Miro GTPases and RHOTB3 (Signal transduction)	0.002	hsa-miR-16-5p	CUL3, TAOK1, TXNL1, RAB9B, KIF2A, RACGAP1, TFRC, BIRC5
		hsa-miR-4476	BUB3, TAOK1, DBN1, ACTR2, CFL1
		hsa-miR-6840-3p	RHOF, ACBD5, ARHGAP11A
		hsa-miR-6811-3p	PRKCA, SPC24, EFHD2
		hsa-miR-1909-3p	SRGAP1, WDR81
		hsa-miR-4787-5p	CENPO
		hsa-miR-5192	RALBP1
		hsa-miR-135b-5p	NHS
Metabolism of RNA	0.002	hsa-miR-16-5p	NUP155, ZC3H11A, RPS24, RPL10, RCL1, UTP25, RBM28, EIF4B
		hsa-miR-6840-3p	RPL28, PRORP, RBM28, DCPS, CDKAL1
		hsa-miR-4476	PSMD11, CHTOP, SET, PRORP
		hsa-miR-5192	CSNK1D, ZC3H11A, HNRNPUL1
		hsa-miR-6811-3p	PRKCA, IGF2BP1, EXOSC2, FUS
		hsa-miR-1909-3p	HNRNPA3
Signaling by TGFB family members (Signal transduction)	0.002	hsa-miR-16-5p	NCOR2, CCNT2, ACVR2A
		hsa-miR-4476	TFDP2, RNF111
		hsa-miR-5192	CBL
		hsa-miR-6840-3p	SKIL
		hsa-miR-135b-5p	ACVR1B
COPI-independent Golgi-to-ER retrograde traffic (Vesicle-mediated transport - membrane trafficking)	0.003	hsa-miR-16-5p	CAPZA2, DCTN5, GALNT1
		hsa-miR-6811-3p	PAFAH1B2
		hsa-miR-6840-3p	ACTR1A
		hsa-miR-135b-5p	RAB3GAP2



Cell cycle_Mitotic (Cell cycle)	0.003	hsa-miR-16-5p	KIF2A,BIRC5,NUP155,ANAPC16,CCND2,TAOK1,ORC4
		hsa-miR-4476	PSMD11,TFDP2,BUB3,TAOK1,SET
		hsa-miR-6811-3p	ANAPC16,PRKCA,SPC24,SPAST
		hsa-miR-5192	CSNK1D,E2F6,CCND2
		hsa-miR-4787-5p	CENPO
		hsa-miR-6840-3p	ACTR1A, ARPP19
Signaling by Wnt (Signal transduction)	0.003	hsa-miR-6811-3p	AGO3,PRKCA,PDE6A,PDE6B,PRICKLE1
		hsa-miR-16-5p	MAP3K7,CUL3,KRAS
		hsa-miR-4476	PSMD11,TNRC6B,KREMEN1
		hsa-miR-6840-3p	FZD4,GNG4,PYGO1
IL-4 and IL-13 signaling (Immune system cytokine signaling in immune system)	0.003	hsa-miR-16-5p	GALNT1,VEGFA,NUP155,NCOR2,TBL1XR1,CCNT2,TAF15,RPS24,RPL10
		hsa-miR-135b-5p	STAT6
		hsa-miR-1909-3p	MCL1
		hsa-miR-5192	POU2F1
		hsa-miR-6840-3p	IL6R
Intracellular signaling by second messengers (Signal transduction)	0.005	hsa-miR-4476	PSMD11,PHC2,TNRC6B,GATAD2B,HDAC5,FRK
		hsa-miR-6811-3p	AGO3, PRKCA
		hsa-miR-6840-3p	MTA3
		hsa-miR-135b-5p	PIP5K1A
		hsa-miR-16-5p	PHLPP2
		hsa-miR-1909-3p	IRAK4
		hsa-miR-5192	FGFR1
Cellular response to chemical stress (Cellular response to stress)	0.008	hsa-miR-16-5p	NCOR2, CUL3, TBL1XR1, TXN2, HM13
		hsa-miR-4476	PSMD11,SOD2,TXNIP,ATOX1
		hsa-miR-135b-5p	TXNIP
		hsa-miR-5192	SOD2
		hsa-miR-1909-3p	ATOX1
M Phase (Cell cycle)	0.009	hsa-miR-16-5p	KIF2A,BIRC5,NUP155,ANAPC16,TAOK1
		hsa-miR-4476	PSMD11,BUB3,TAOK1,SET
		hsa-miR-6811-3p	ANAPC16,PRKCA,SPC24,SPAST
		hsa-miR-6840-3p	ACTR1A, ARPP19
		hsa-miR-4787-5p	CENPO
		hsa-miR-5192	CSNK1D
Transcriptional activity of SMAD2/SMAD3:SMAD4 heterodimer (Transcription)	0.009	hsa-miR-16-5p	NCOR2, CCNT2
		hsa-miR-4476	TFDP2, RNF111
		hsa-miR-6840-3p	SKIL
MHC I-mediated antigen processing and presentation (Immune)	0.01	hsa-miR-16-5p	UBE2V1,CUL3,FBXL20,SEC61A1,ANAPC13,TRIM4,UBE3C
		hsa-miR-4476	PSMD11, RNF111
		hsa-miR-5192	CALR, UBE2V1
		hsa-miR-6840-3p	TAP2, RNF14
		hsa-miR-6811-3p	KLHL21

system - <i>Adaptive)</i>		hsa-miR-1909-3p	CANX
Hemostasis	0.01	hsa-miR-6840-3p	CRK,GNG4,IGF1,PDE11A
		hsa-miR-16-5p	BIRC5,VEGFA,BCL2,PIM1
		hsa-miR-6811-3p	PRKCA, IGF1, TBXA2R
		hsa-miR-4476	CFL1,SDC4,SLC7A5
		hsa-miR-1909-3p	VCL
		hsa-miR-5192	FAM3C
NR1H2 and NR1H3- mediated signaling ( <i>Signal transduction - Signaling by nuclear receptors)</i> )	0.01	hsa-miR-16-5p	NCOR2, TBL1XR1
		hsa-miR-4476	TNRC6B
		hsa-miR-6811-3p	AGO3, SCD
Signaling by TGF-beta receptor complex ( <i>Signal transduction - Signaling by TGF-beta family members)</i> )	0.01	hsa-miR-16-5p	NCOR2, CCNT2
		hsa-miR-4476	TFDP2, RNF111
		hsa-miR-5192	CBL
		hsa-miR-6840-3p	SKIL
Organelle biogenesis and mainainance	0.01	hsa-miR-6840-3p	ACTR1A,SSTR3,CEP89,GABPB1,ATP5F1A
		hsa-miR-16-5p	RAB3IP,KIF3B,TBL1XR1,ARL3
		hsa-miR-5192	CSNK1D, SOD2
		hsa-miR-6811-3p	GABPB1
		hsa-miR-4476	UNC119B
PTEN regulation ( <i>Signal transduction - intracellular signaling by second messenger - PIP3 activates AKT signaling)</i> )	0.01	hsa-miR-4476	PSMD11,PHC2,TNRC6B,GATAD2B,HDAC5,FRK
		hsa-miR-6811-3p	AGO3
		hsa-miR-6840-3p	MTA3
Infectious disease ( <i>Disease)</i> )	0.01	hsa-miR-6840-3p	CRK,IL6R,STAT2,GNG4,RPL28,MTA3,VAMP1
		hsa-miR-16-5p	GALNT1, VEGFA, NUP155, NCOR2, TBL1XR1, CCNT2, TAF15, RPS24, RPL10
		hsa-miR-4476	ACTR2,PSMD11,TXNIP,GATAD2B
		hsa-miR-5192	CBL,SYT2,CALR
		hsa-miR-135b-5p	TXNIP
		hsa-miR-1909-3p	CANX

Rab regulation of trafficking ( <i>Vesicle-mediated transport - Clathrin-mediated endocytosis</i> )	4.46E-05	miR-16-5p	RAB9B, RAB3IP, SBF1, TBC1D14
		miR-6811-3p	RAB13, DENND6B
		miR-6840-3p	TRAPPC2, TBC1D24
		miR-5192	TBC1D13
		miR-135b-5p	RAB3GAP2
Beta-catenin independent Wnt signaling pathway ( <i>Signal transduction - Signaling by Wnt</i> )	0.0002	miR-6811-3p	AGO3, PRKCA, PDE6A, PDE6B, PRICKLE1
		miR-16-5p	MAP3K7, KRAS
		miR-4476	PSMD11, TNRC6B
		miR-6840-3p	FZD4, GNG4
Cellular responses to external stimuli ( <i>Cellular response to stimuli</i> )	0.0002	miR-16-5p	CAPZA2, DCTN5, VEGFA, RPS6KA3, NUP155, NCOR2, CUL3, ANAPC16, TBL1XR1, RPS24, RPL10, TXN2, HM13, HMGA2, NCOR2, CUL3, TBL1XR1, TXN2, HM13
		miR-4476	PSMD11, SOD2, PHC2, TNRC6B, TXNIP, TFD2, ATOX1
		miR-6811-3p	AGO3, ANAPC16, BAG2
		miR-135b-5p	TXNIP
		miR-1909-3p	ATOX1
		miR-5192	SOD2
Adaptive immune system ( <i>Immune system</i> )	0.0004	miR-6840-3p	ACTR1A, RPL28
		miR-16-5p	DCTN5, KIF2A, RACGAP1, KIF3B, MAP3K7, UBE2V1, CUL3, FBXL20, KRAS, SEC61A1, ANAPC13, TRIM4, UBE3C, CAPZA2
		miR-6811-3p	KLHL21, KLRD1, RAET1E
		miR-6840-3p	ACTR1A, TAP2, RNF14, CD300LG, NCR3LG1, BTN3A2
		miR-4476	PSMD11, RNF111
Golgi to ER retrograde transport ( <i>Vesicle-mediated transport - Clathrin-mediated endocytosis</i> )	0.0006	miR-5192	CALR, UBE2V1
		miR-1909-3p	CANX
		miR-16-5p	CAPZA2, KIF2A, RACGAP1, KIF3B, KIF1B, GALNT1, DCTN5
		miR-135b-5p	RAB3GAP2
Neutrophil degranulation ( <i>Immune system - Innate</i> )	0.0007	miR-6811-3p	PAFAH1B2
		miR-6840-3p	ACTR1A
		miR-16-5p	RAB9B, CD44, GOLGA7, VCL, PYGB, PDXK
		miR-6840-3p	GNS, MLEC, RHOF, GM2A, RAP2B
		miR-4476	RAB5B, ACTR2, PSMD11, FRK
Intra-Golgi and retrograde Golgi to ER trafficking ( <i>Vesicle-mediated transport - membrane trafficking</i> )	0.0007	miR-1909-3p	VCL, NFASC
		miR-6811-3p	PAFAH1B2, SVIP
		miR-5192	PKM
		miR-16-5p	RAB9B, CAPZA2, DCTN5, GALNT1, RAB30, KIF2A, RACGAP1, KIF3B, KIF1B
MAPK family signaling cascades ( <i>Signal transduction</i> )	0.001	miR-6811-3p	RAB30, PAFAH1B2
		miR-135b-5p	RAB3GAP2
		miR-6840-3p	ACTR1A
		miR-16-5p	CUL3, KRAS, GOLGA7, VCL, FNTA, ARL2
		miR-6840-3p	IL6R, RCE1, SPRED1
Cell cycle	0.001	miR-4476	PSMD11, TNRC6B
		miR-5192	FGFR1, CDC14B
		miR-6811-3p	AGO3, IGF2BP1
		miR-1909-3p	VCL
		miR-16-5p	PPP6R3, RAB3IP, SBF1, KIF2A, BIRC5, NUP155, BRCA1, ANAPC16, CCND2, CHEK1, TAOK1, ORC4
		miR-4476	PSMD11, TFD2, BUB3, TAOK1, SET
Rab GEFs exchange GTP for GDP on RABs ( <i>Vesicle-mediated transport - membrane trafficking - Rab regulation of trafficking</i> )	0.001	miR-5192	CSNK1D, E2F6, CCND2
		miR-6811-3p	DENND6B, ANAPC16, PRKCA, SPC24, SPAST
		miR-6840-3p	ACTR1A, ARPP19, CTC1
		miR-135b-5p	RAB3GAP2
		miR-4787-5p	CENPO
Signaling by Rho GTPases, Miro GTPases and RHOBTB3 ( <i>Signal transduction</i> )	0.002	miR-16-5p	RAB9B, RAB3IP, SBF1
		miR-6811-3p	RAB13, DENND6B
		miR-6840-3p	TRAPPC2
		miR-4476	RAB5B
		miR-135b-5p	RAB3GAP2
		miR-16-5p	CUL3, TAOK1, TXNL1, RAB9B, KIF2A, RACGAP1, TFRC, BIRC5
		miR-4476	BUB3, TAOK1, DBN1, ACTR2, CFL1
	0.002	miR-6840-3p	RHOF, ACBD5, ARHGAP11A
		miR-6811-3p	PRKCA, SPC24, EFHD2
		miR-1909-3p	SRGAP1, WDR81
		miR-4787-5p	CENPO
		miR-5192	RALBP1
		miR-135b-5p	NHS

Metabolism of RNA	0.002	miR-16-5p	NUP155,ZC3H11A,RPS24,RPL10,RCL1,UTP25,RBM28,EIF4B
		miR-6840-3p	RPL28,PRORP,RBM28,DCPS,CDKAL1
		miR-4476	PSMD11,CHTOP,SET,PRORP
		miR-5192	CSNK1D,ZC3H11A,HNRNPUL1
		miR-6811-3p	PRKCA,IGF2BP1,EXOSC2,FUS
		miR-1909-3p	HNRNPA3
Signaling by TGFβ family members (Signal transduction)	0.002	miR-16-5p	NCOR2,CCNT2,ACVR2A
		miR-4476	TFDP2, RNF111
		miR-5192	CBL
		miR-6840-3p	SKIL
		miR-135b-5p	ACVR1B
COPI-independent Golgi-to-ER retrograde traffic (Vesicle-mediated transport - membrane trafficking)	0.003	miR-16-5p	CAPZA2,DCTN5,GALNT1
		miR-6811-3p	PAFAH1B2
		miR-6840-3p	ACTR1A
		miR-135b-5p	RAB3GAP2
Cell cycle_Mitotic (Cell cycle)	0.003	miR-16-5p	KIF2A,BIRC5,NUP155,ANAPC16,CCND2,TAOK1,ORC4
		miR-4476	PSMD11,TFDP2,BUB3,TAOK1,SET
		miR-6811-3p	ANAPC16,PRKCA,SPC24,SPAST
		miR-5192	CSNK1D,E2F6,CCND2
		miR-4787-5p	CENPO
		miR-6840-3p	ACTR1A, ARPP19
Signaling by Wnt (Signal transduction)	0.003	miR-6811-3p	AGO3,PRKCA,PDE6A,PDE6B,PRICKLE1
		miR-16-5p	MAP3K7,CUL3,KRAS
		miR-4476	PSMD11,TNRC6B,KREMEN1
		miR-6840-3p	FZD4,GNG4,PYGO1
IL-4 and IL-13 signaling (Immune system - cytokine signaling in immune system)	0.003	miR-16-5p	GALNT1,VEGFA,NUP155,NCOR2,TBL1XR1,CCNT2,TAF15,RPS24,RPL10
		miR-135b-5p	STAT6
		miR-1909-3p	MCL1
		miR-5192	POU2F1
		miR-6840-3p	IL6R
Intracellular signaling by second messengers (Signal transduction)	0.005	miR-4476	PSMD11,PHC2,TNRC6B,GATAD2B,HDAC5,FRK
		miR-6811-3p	AGO3, PRKCA
		miR-6840-3p	MTA3
		miR-135b-5p	PIP5K1A
		miR-16-5p	PHLPP2
		miR-1909-3p	IRAK4
		miR-5192	FGFR1
Cellular response to chemical stress (Cellular response to stress)	0.008	miR-16-5p	NCOR2, CUL3, TBL1XR1, TXN2, HM13
		miR-4476	PSMD11,SOD2,TXNIP,ATOX1
		miR-135b-5p	TXNIP
		miR-5192	SOD2
		miR-1909-3p	ATOX1
M Phase (Cell cycle)	0.009	miR-16-5p	KIF2A,BIRC5,NUP155,ANAPC16,TAOK1
		miR-4476	PSMD11,BUB3,TAOK1,SET
		miR-6811-3p	ANAPC16,PRKCA,SPC24,SPAST
		miR-6840-3p	ACTR1A, ARPP19
		miR-4787-5p	CENPO
		miR-5192	CSNK1D
Transcriptional activity of SMAD2/SMAD3:SMAD4 heterodimer (Transcription)	0.009	miR-16-5p	NCOR2, CCNT2
		miR-4476	TFDP2, RNF111
		miR-6840-3p	SKIL
MHC I-mediated antigen processing and presentation (Immune system - Adaptive)	0.01	miR-16-5p	UBE2V1,CUL3,FBXL20,SEC61A1,ANAPC13,TRIM4,UBE3C
		miR-4476	PSMD11, RNF111
		miR-5192	CALR, UBE2V1
		miR-6840-3p	TAP2, RNF14
		miR-6811-3p	KLHL21
		miR-1909-3p	CANX
Hemostasis	0.01	miR-6840-3p	CRK,GNG4,IGF1,PDE11A
		miR-16-5p	BIRC5,VEGFA,BCL2,PIM1
		miR-6811-3p	PRKCA, IGF1, TBXA2R
		miR-4476	CFL1,SDC4,SLC7A5
		miR-1909-3p	VCL
		miR-5192	FAM3C

NR1H2 and NR1H3-mediated signaling (Signal transduction - Signaling by nuclear receptors)	0.01	miR-16-5p	NCOR2, TBL1XR1
		miR-4476	TNRC6B
		miR-6811-3p	AGO3, SCD
Signaling by TGF-beta receptor complex (Signal transduction - Signaling by TGF-beta family members)	0.01	miR-16-5p	NCOR2, CCNT2
		miR-4476	TFDP2, RNF111
		miR-5192	CBL
Organelle biogenesis and maintenance	0.01	miR-6840-3p	SKIL
		miR-6840-3p	ACTR1A, SSTR3, CEP89, GABPB1, ATP5F1A
		miR-16-5p	RAB3IP, KIF3B, TBL1XR1, ARL3
		miR-5192	CSNK1D, SOD2
		miR-6811-3p	GABPB1
PTEN regulation (Signal transduction - intracellular signaling by second messenger - PIP3 activates AKT)	0.01	miR-4476	UNC119B
		miR-4476	PSMD11, PHC2, TNRC6B, GATAD2B, HDAC5, FRK
		miR-6811-3p	AGO3
Infectious disease (Disease)	0.01	miR-6840-3p	MTA3
		miR-6840-3p	CRK, IL6R, STAT2, GNG4, RPL28, MTA3, VAMP1
		miR-16-5p	GALNT1, VEGFA, NUP155, NCOR2, TBL1XR1, CCNT2, TAF15, RPS24, RPL10
		miR-4476	ACTR2, PSMD11, TXNIP, GATAD2B
		miR-5192	CBL, SYT2, CALR
		miR-135b-5p	TXNIP
		miR-1909-3p	CANX