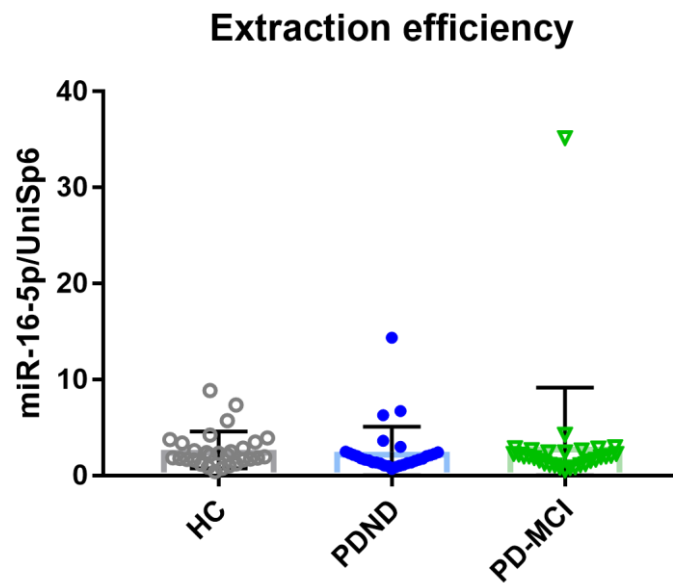


Supplementary Materials



Supplementary Figure 1. The RNA extraction efficiency examination by the ratio of miR-16-5p/UniSp6. The external spike-in UniSp6 (0.5 μ l) was added to the lysis buffer before RNA extraction. The expression of miR-16-5p and UniSp6 were examined by ddPCR. The ratio of miR-16-5p/UniSp6 was analyzed using Kruskal-Wallis test followed by Dunn's multiple comparisons test (post-hoc test) among the groups of HC (n=29), PDND (n=30) and PD-MCI (n=30). Data are shown as Mean \pm SD.

Supplementary Table 1. The multivariate logistic regression model for detecting PDD.

Covariate	Coefficient	Estimated Standard Error	z value	p-value
Intercept	-25.42314	8.42341	-3.018	<0.01
N203*	0.22671	0.08279	2.738	<0.01
Age	0.23692	0.09185	2.579	<0.01
UPDRS_III	0.19145	0.05594	3.422	<0.001

*N203: the ratio of miR-203a-3p/miR16-5p.

Supplementary Table 2. The 95% confidence interval of specificity, sensitivity and accuracy for regression model by test dataset in a five-fold cross validation.

Variables	AUC (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Accuracy (95% CI)
N203	0.7593 (0.5370-0.9383)	0.7222 (0.5000-0.9444)	0.7777 (0.5528 -1.0000)	0.7407 (0.5917-0.8889)
Age	0.7654 (0.5617-0.929)	0.6667 (0.4444-0.8889)	0.7778 (0.4444-1.0000)	0.7037 (0.5185-0.8889)
UPDRS III	0.7932 (0.5709-0.9691)	0.7778 (0.5556-0.9444)	0.8889 (0.6667-1.0000)	0.8148 (0.6667-0.9630)
N203 + Age	0.8642 (0.6914-0.9877)	0.8333 (0.6667-1.0000)	0.7778 (0.5528-1.0000)	0.8148 (0.6667-0.9630)
N203 + UPDRS III	0.8827 (0.7344-0.9815)	0.8333 (0.6667-1.0000)	0.7778 (0.4444-1.0000)	0.8148 (0.6667-0.9630)
Age + UPDRS III	0.8272 (0.6049-0.9815)	0.7222 (0.5000-0.8889)	0.8889 (0.6667-1.0000)	0.7778 (0.6296- 0.9259)
N203 + Age + UPDRS III	0.8827 (0.7282-0.9938)	0.8889 (0.7222-1.0000)	0.7778 (0.4444-1.0000)	0.8519 (0.7037-0.9630)

*N203: the ratio of miR-203a-3p/miR16-5p.

Supplementary Table 3. The experimental-based predicted pathways and target genes of miR-203a-3p via KEGG database analysis.

Pathway	p-value	Target genes
Hepatitis B	2.73E-09	AKT2,BIRC5,CDK6,CREB1,CXCL8,E2F1,E2F3,IL6,JUN,MAPK8,MAPK9,MYD88,PIK3CA,PRKCA,SMAD4,SRG,STAT1,TBK1,TNF
Pathways in cancer	5.04E-07	ABL1,AKT2,BIRC5,CDH1,CDK6,CXCL8,E2F1,E2F3,EGLN1,FGF2,FZD2,GSK3B,IGF1R,IL6,JUN,MAPK8,MAPK9,MMP1,NCOA4,PIK3CA,PRKCA,SMAD2,SMAD4,STAT1,VEGFA
Pancreatic cancer	3.68E-06	AKT2,CDK6,E2F1,E2F3,MAPK8,MAPK9,PIK3CA,SMAD2,SMAD4,STAT1,VEGFA
Chagas disease (American trypanosomiasis)	2.75E-05	AKT2,CALR,CXCL8,GNAS,IL6,JUN,MAPK8,MAPK9,MYD88,PIK3CA,SMAD2,TNF
Ras signaling pathway	3.09E-05	ABL1,AKT2,EXOC2,FGF2,IGF1R,MAPK8,MAPK9,PIK3CA,PLD2,PRKACB,PRKCA,RAP1A,RASA2,RASAL2,RGL2,TBK1,VEGFA
Influenza A	4.16E-05	AKT2,CXCL8,GSK3B,IL6,JUN,MAPK8,MAPK9,MYD88,PIK3CA,PRKCA,SOC3,STAT1,TBK1,TNF
Toll-like receptor signaling pathway	4.16E-05	AKT2,CXCL8,IL6,JUN,MAPK8,MAPK9,MYD88,PIK3CA,STAT1,TBK1,TNF
Colorectal cancer	6.55E-05	AKT2,BIRC5,GSK3B,JUN,MAPK8,MAPK9,PIK3CA,SMAD2,SMAD4
MicroRNAs in cancer	6.55E-05	ABL1,ATM,BCL2L2,BMI1,CDK6,E2F1,E2F3,PIK3CA,PRKCA,TP63,TRIM71,VEGFA,ZEB1,ZEB2
Prolactin signaling pathway	9.75E-05	AKT2,GSK3B,MAPK8,MAPK9,PIK3CA,SOC3,SOC6,SRG,STAT1
Focal adhesion	1.11E-04	AKT2,CAV1,GSK3B,IGF1R,JUN,MAPK8,MAPK9,PIK3CA,PPP1CB,PRKCA,RAP1A,RAPGEF1,ROCK2,SRG,VEGFA
HTLV-I infection	1.23E-04	AKT2,ATM,CALR,CREB1,E2F1,E2F3,FZD2,GSK3B,IL6,JUN,MAPK8,PIK3CA,PRKACB,RAN,SMAD2,SMAD4,TNF
Hepatitis C	1.63E-04	AKT2,CXCL8,GSK3B,IFIT1,MAPK8,MAPK9,PIK3CA,SOC3,STAT1,TBK1,TNF
Wnt signaling pathway	2.27E-04	CXXC4,FZD2,GSK3B,JUN,MAPK8,MAPK9,PRICKLE2,PRKACB,PRKCA,ROCK2,SMAD4,WIF1
Dopaminergic synapse	3.00E-04	AKT2,CLOCK,CREB1,GNAS,GSK3B,KIF5B,MAPK8,MAPK9,PPP1CB,PRKACB,PRKCA
FoxO signaling pathway	3.56E-04	AKT2,ATM,G6PC,IGF1R,IL6,MAPK8,MAPK9,PIK3CA,SMAD2,SMAD4,SOD2
ErbB signaling pathway	5.16E-04	ABL1,AKT2,GSK3B,JUN,MAPK8,MAPK9,PIK3CA,PRKCA,SRG
Melanoma	5.30E-04	AKT2,CDH1,CDK6,E2F1,E2F3,FGF2,IGF1R,PIK3CA

Herpes simplex infection	6.53E-04	<i>CLOCK,IFIT1,IL6,JUN,MAPK8,MAPK9,MYD88,PPP1CB,SOC S3,STAT1,TBK1,TNF</i>
Bladder cancer	8.25E-04	<i>CDH1, CXCL8,E2F1,E2F3,MMP1,VEGFA</i>
Endocytosis	8.64E-04	<i>ASAP1,CAV1,CCR5,IGF1R,PARD6B,PIP5K1A,PLD2,RAB22A, RNF41,SH3GLB1,SMAD2,SMURF2,SRC</i>
Proteoglycans in cancer	8.64E-04	<i>AKT2,CAV1,FGF2,FZD2,IGF1R,PIK3CA,PPP1CB,PRKACB,PR KCA,ROCK2,SMAD2,SRC,TNF,VEGFA</i>
Osteoclast differentiation	0.001	<i>AKT2,CREB1,JUN,MAPK8,MAPK9,PIK3CA,SOCS3,STAT1,SY K,TNF</i>
TNF signaling pathway	0.001	<i>AKT2,CREB1,IL6,JUN,MAPK8,MAPK9,PIK3CA,SOCS3,TNF</i>
Tuberculosis	0.001	<i>AKT2,CREB1,IL6,MAPK8,MAPK9,MYD88,NFYA,SRC,STAT1, SYK,TNF</i>
Adherens junction	0.002	<i>CDH1, IGF1R,SMAD2,SMAD4,SNAI1,SNAI2,SRC</i>
Fc epsilon RI signaling pathway	0.002	<i>AKT2, MAPK8,MAPK9,PIK3CA,PRKCA,SYK,TNF</i>
Glioma	0.002	<i>AKT2, CDK6,E2F1,E2F3,IGF1R,PIK3CA,PRKCA</i>
GnRH signaling pathway	0.002	<i>GNAS,JUN,MAPK8,MAPK9,PLD2,PRKACB,PRKCA,SRC</i>
Insulin signaling pathway	0.002	<i>AKT2,G6PC,GSK3B,MAPK8,MAPK9,PIK3CA,PPP1CB,PRKAC B,RAPGEF1,SOCS3</i>
Neurotrophin signaling pathway	0.002	<i>ABL1,AKT2,GSK3B,JUN,MAPK8,MAPK9,PIK3CA,RAP1A,RA PGEF1</i>
Non-alcoholic fatty liver disease (NAFLD)	0.002	<i>AKT2,CXCL8,GSK3B,IL6,JUN,MAPK8,MAPK9,PIK3CA,SOCS 3,TNF</i>
Pertussis	0.002	<i>CXCL8, IL6,JUN,MAPK8,MAPK9,MYD88,TNF</i>
Rap1 signaling pathway	0.002	<i>AKT2,CDH1,FGF2,GNAS,IGF1R,PARD6B,PIK3CA,PRKCA,RA P1A,RAPGEF1,SRC,VEGFA</i>
Renal cell carcinoma	0.002	<i>AKT2,EGLN1,JUN,PIK3CA,RAP1A,RAPGEF1,VEGFA</i>
Chronic myeloid leukemia	0.003	<i>ABL1, AKT2,CDK6,E2F1,E2F3,PIK3CA,SMAD4</i>
Non-small cell lung cancer	0.003	<i>AKT2, CDK6,E2F1,E2F3,PIK3CA,PRKCA</i>
Amphetamine addiction	0.004	<i>CREB1, GNAS,JUN,PPP1CB,PRKACB,PRKCA</i>

HIF-1 signaling pathway	0.004	<i>AKT2,EGLN1,IGF1R,IL6,LDHA,PIK3CA,PRKCA,VEGFA</i>
Hippo signaling pathway	0.004	<i>BIRC5,BMPR1A,CDH1,FZD2,GSK3B,PARD6B,PPP1CB,SMAD2,SMAD4,SNAI2</i>
Salmonella infection	0.004	<i>CXCL8, IL6,JUN,MAPK8,MAPK9,MYD88,ROCK2</i>
Shigellosis	0.004	<i>ABL1, CXCL8,MAPK8,MAPK9,ROCK2,SRC</i>
TGF-beta signaling pathway	0.004	<i>ACVR2B,BMPR1A,SMAD2,SMAD4,SMAD9,SMURF2,TNF</i>
Fc gamma R-mediated phagocytosis	0.005	<i>AKT2,ASAP1,PIK3CA,PIP5K1A,PLD2,PRKCA,SYK</i>
Prostate cancer	0.005	<i>AKT2, CREB1,E2F1,E2F3,GSK3B,IGF1R,PIK3CA</i>
Toxoplasmosis	0.005	<i>AKT2,CCR5,MAPK8,MAPK9,MYD88,PIK3CA,STAT1,TNF</i>
Adipocytokine signaling pathway	0.006	<i>AKT2, G6PC,MAPK8,MAPK9,SOCS3,TNF</i>
Chemokine signaling pathway	0.006	<i>AKT2,CCR5,CXCL8,GSK3B,PIK3CA,PRKACB,RAP1A,ROCK2, SRC,STAT1</i>
Type II diabetes mellitus	0.006	<i>MAPK8, MAPK9,PIK3CA,SOCS3,TNF</i>
Measles	0.007	<i>AKT2,CDK6,GSK3B,IL6,MYD88,PIK3CA,STAT1,TBK1</i>
African trypanosomiasis	0.008	<i>IL6, MYD88,PRKCA,TNF</i>
Cell cycle	0.008	<i>ABL1,ATM,CDK6,E2F1,E2F3,GSK3B,SMAD2,SMAD4</i>
Estrogen signaling pathway	0.008	<i>AKT2, CREB1,GNAS,JUN,PIK3CA,PRKACB,SRC</i>
Jak-STAT signaling pathway	0.008	<i>AKT2, IL24,IL6,IL7,LIFR,PIK3CA,SOCS3,STAT1</i>
Amoebiasis	0.009	<i>CXCL8, GNAS,IL6,PIK3CA,PRKACB,PRKCA,TNF</i>
Cytokine-cytokine receptor interaction	0.009	<i>ACVR2B,BMPR1A,CCR5,CXCL8,IL24,IL6,IL7,LIFR,TNF,TNFR SF9,VEGFA</i>
Pathogenic Escherichia coli infection	0.009	<i>ABL1, CDH1,NCL,PRKCA,ROCK2</i>
Epstein-Barr virus infection	0.01	<i>AKT2,GSK3B,JUN,MAPK8,MAPK9,PIK3CA,PRKACB,RAN,SY K,TBK1</i>

MAPK signaling pathway	0.01	<i>AKT2,DUSP5,FGF2,JUN,MAP3K13,MAPK8,MAPK9,PRKACB,PRKCA,RAP1A,RASA2,TNF</i>
NOD-like receptor signaling pathway	0.01	<i>CXCL8, IL6,MAPK8,MAPK9,TNF</i>
Rheumatoid arthritis	0.01	<i>CXCL8, IL6,JUN,MMP1,TNF,VEGFA</i>
Apoptosis	0.011	<i>AKT2, ATM,MYD88,PIK3CA,PRKACB,TNF</i>
Progesterone-mediated oocyte maturation	0.011	<i>AKT2, IGF1R,MAPK8,MAPK9,PIK3CA,PRKACB</i>
Inflammatory bowel disease (IBD)	0.012	<i>IL6, JUN,SMAD2,STAT1,TNF</i>
RIG-I-like receptor signaling pathway	0.012	<i>CXCL8, MAPK8,MAPK9,TBK1,TNF</i>
VEGF signaling pathway	0.012	<i>AKT2, PIK3CA,PRKCA,SRC,VEGFA</i>
mTOR signaling pathway	0.012	<i>AKT2, PIK3CA,PRKCA,TNF,VEGFA</i>
Thyroid hormone signaling pathway	0.014	<i>AKT2,GSK3B,PIK3CA,PRKACB,PRKCA,SRC,STAT1</i>
Malaria	0.016	<i>CXCL8, IL6,MYD88,TNF</i>
Cocaine addiction	0.017	<i>CREB1, GNAS,JUN,PRKACB</i>
Epithelial cell signaling in Helicobacter pylori infection	0.017	<i>CXCL8, JUN,MAPK8,MAPK9,SRC</i>
PI3K-Akt signaling pathway	0.017	<i>AKT2,CDK6,CREB1,FGF2,G6PC,GSK3B,IGF1R,IL6,IL7,PIK3CA,PRKCA,SYK,VEGFA</i>
Melanogenesis	0.022	<i>CREB1, FZD2,GNAS,GSK3B,PRKACB,PRKCA</i>
B cell receptor signaling pathway	0.024	<i>AKT2, GSK3B,JUN,PIK3CA,SYK</i>
Serotonergic synapse	0.024	<i>ALOX15,GABRB1,GNAS,HTR2A,PRKACB,PRKCA</i>
Cholinergic synapse	0.027	<i>AKT2, CREB1,KCNJ2,PIK3CA,PRKACB,PRKCA</i>
T cell receptor signaling pathway	0.027	<i>AKT2, GSK3B,JUN,MAPK9,PIK3CA,TNF</i>
Adrenergic signaling in cardiomyocytes	0.03	<i>AKT2,CREB1,GNAS,PIK3CA,PPP1CB,PRKACB,PRKCA</i>

Vascular smooth muscle contraction	0.03	<i>EDNRA, GNAS,PPP1CB,PRKACB,PRKCA,ROCK2</i>
Vibrio cholerae infection	0.031	<i>GNAS, PRKACB,PRKCA,TJP2</i>
Viral carcinogenesis	0.031	<i>CCR5,CDK6,CREB1,JUN,PIK3CA,PRKACB,RASA2,SRC,SYK</i>
Circadian rhythm	0.033	<i>CLOCK, CREB1,FBXL3</i>
Endometrial cancer	0.033	<i>AKT2, CDH1,GSK3B,PIK3CA</i>
GABAergic synapse	0.033	<i>GABRB1, PRKACB,PRKCA,SLC12A5,SRC</i>
Transcriptional misregulation in cancer	0.037	<i>ATM, BMI1,CXCL8,IGF1R,IL6,RUNX2,SIX1,ZEB1</i>
Legionellosis	0.039	<i>CXCL8, IL6,MYD88,TNF</i>
Morphine addiction	0.041	<i>GABRB1, GNAS,PDE7A,PRKACB,PRKCA</i>
NF-kappa B signaling pathway	0.041	<i>ATM, CXCL8,MYD88,SYK,TNF</i>
Prion diseases	0.041	<i>IL6, PRKACB,PRNP</i>
Small cell lung cancer	0.041	<i>AKT2, CDK6,E2F1,E2F3,PIK3CA</i>
Gap junction	0.042	<i>GNAS, HTR2A,PRKACB,PRKCA,SRC</i>
Inositol phosphate metabolism	0.042	<i>IPMK, PI4K2B,PIK3CA,PIP5K1A</i>
Tight junction	0.042	<i>AKT2, CASK,PARD6B,PRKCA,SRC,TJP2</i>
Antigen processing and presentation	0.046	<i>CALR, CREB1,NFYA,TNF</i>