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Research article

Downregulation of CDC14B in 5218 breast cancer patients: A novel prognosticator for triple-negative breast cancer

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Abstract: Breast cancer is the most common female malignancy worldwide and the prognosis of triple-negative breast cancer (TNBC) and advanced breast cancer patients is unsatisfying. The exploration of novel prognostic indicators and appropriate targets is crucial for improving the treatment outcomes of breast cancer patients. The cell division cycle protein 14B (CDC14B) is known for its roles in cell cycle control, but its expression status and molecular function in breast cancer is unknown. This study explores the expression patterns and clinical values of CDC14B in breast cancer tissues. For this research, the authors downloaded gene microarrays and RNA sequencing datasets to examine the expression levels of CDC14B in 5218 breast cancer tissues, comparing them to the expression levels in 1176 normal breast tissues. The relationships between CDC14B and clinicopathologic characteristics of breast cancer were also addressed. The mutation conditions of CDC14B were then clarified using cBioPortal. Finally, differentially expressed genes and co-expressed genes related to CDC14B were filtered using the Limma-Voom package. These genes were intersected to conduct functional annotations and to construct a protein-protein interaction network. It was observed that CDC14B was significantly downregulated in breast cancer tissues but not in normal breast tissues (standardized mean difference= −1.17 [−1.50–−0.85], area under the curve = 0.88). In addition, CDC14B downregulation was correlated with the poor prognosis of TNBC patients (hazard ratios < 1; $p < 0.05$). Amplification was detected to be the most frequent alteration of CDC14B. The presence of this alteration forecasted unfavourable overall

survival outcomes in breast cancer patients ($p < 0.05$). Dysregulated genes that co-expressed with CDC14B were pivotal in cell cycle (namely mitotic-nuclear division and DNA packaging complex) and cancer-related signaling pathways (namely the peroxisome proliferators activated receptor [PPAR] signalling pathway and the AMP-activated protein kinase [AMPK] signalling pathway). Moreover, the genes ADIPOQ and CCNE2 were identified as two promising prognostic factors in breast cancer. In summary, CDC14B was downregulated in breast cancer tissue and may be a promising hallmark in TNBC patients. The dysregulated genes co-expressed with CDC14B may play an important role in the development of breast cancer through PPAR and AMPK signalling pathways.

Keywords: CDC14B; breast cancer; microarray; RNA sequencing; clinical utility; genetic mutation; signaling pathway

Supplementary

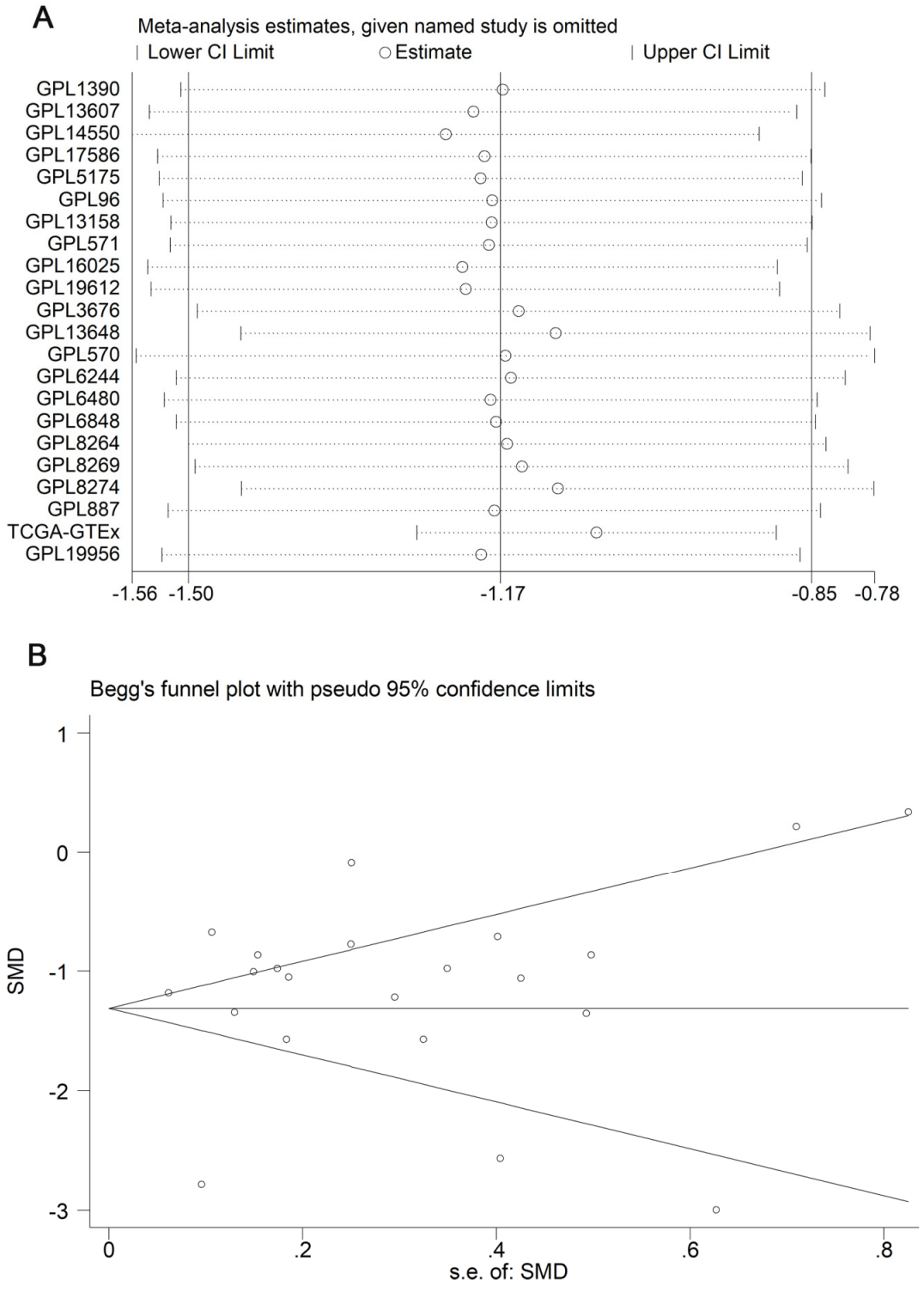


Figure S1. Sensitive analysis and Begg's funnel plot. A: Differences between data sets can be ignored because they are not the source of high degree of heterogeneity. B: A symmetrical funnel plot indicates no significant publication bias.

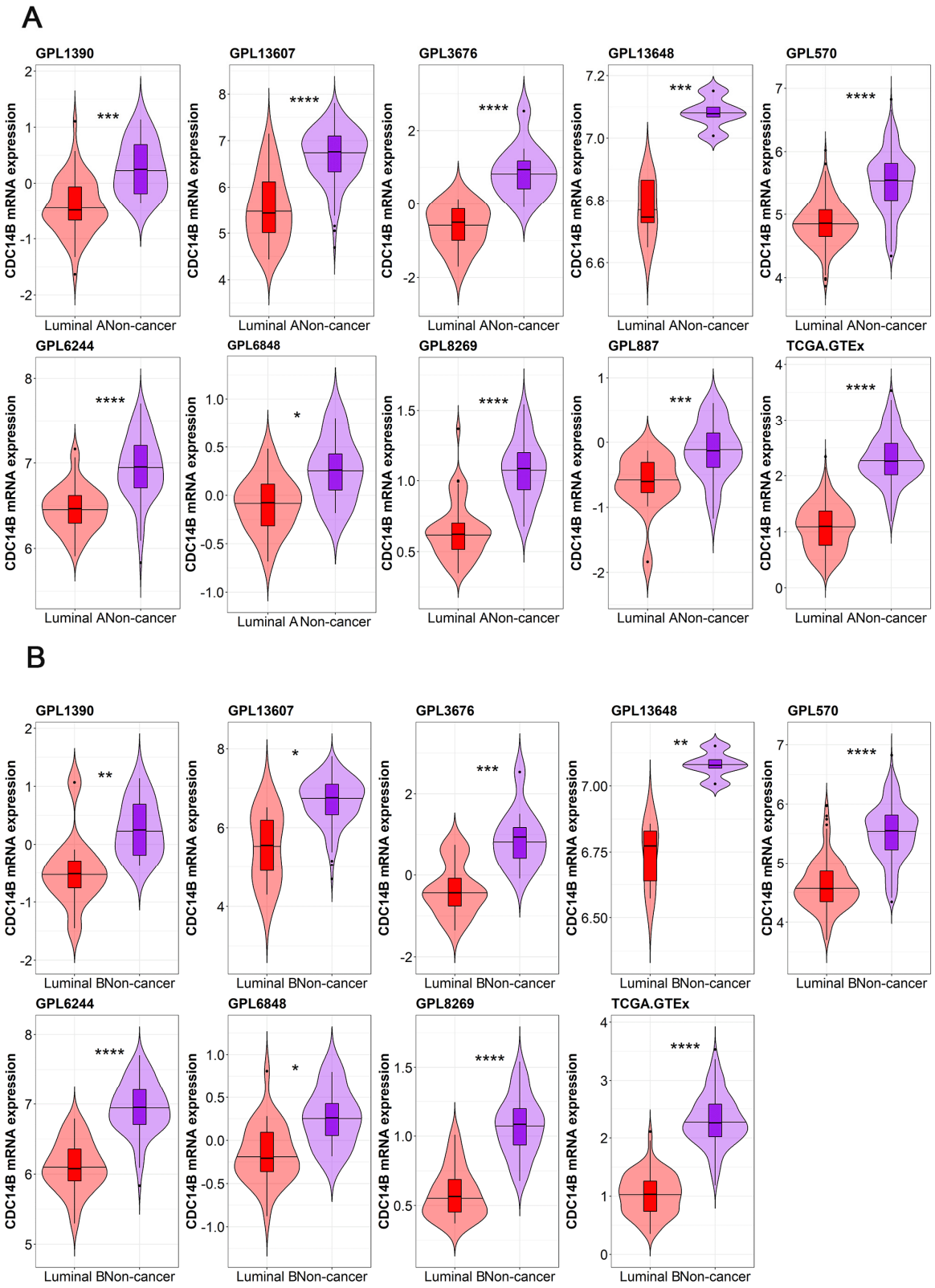


Figure S2. Expression levels of CDC14B in breast cancer. CDC14B expression levels are significantly decreased in luminal A (A) and luminal B (B) breast cancer tissues when compared to normal breast tissues.

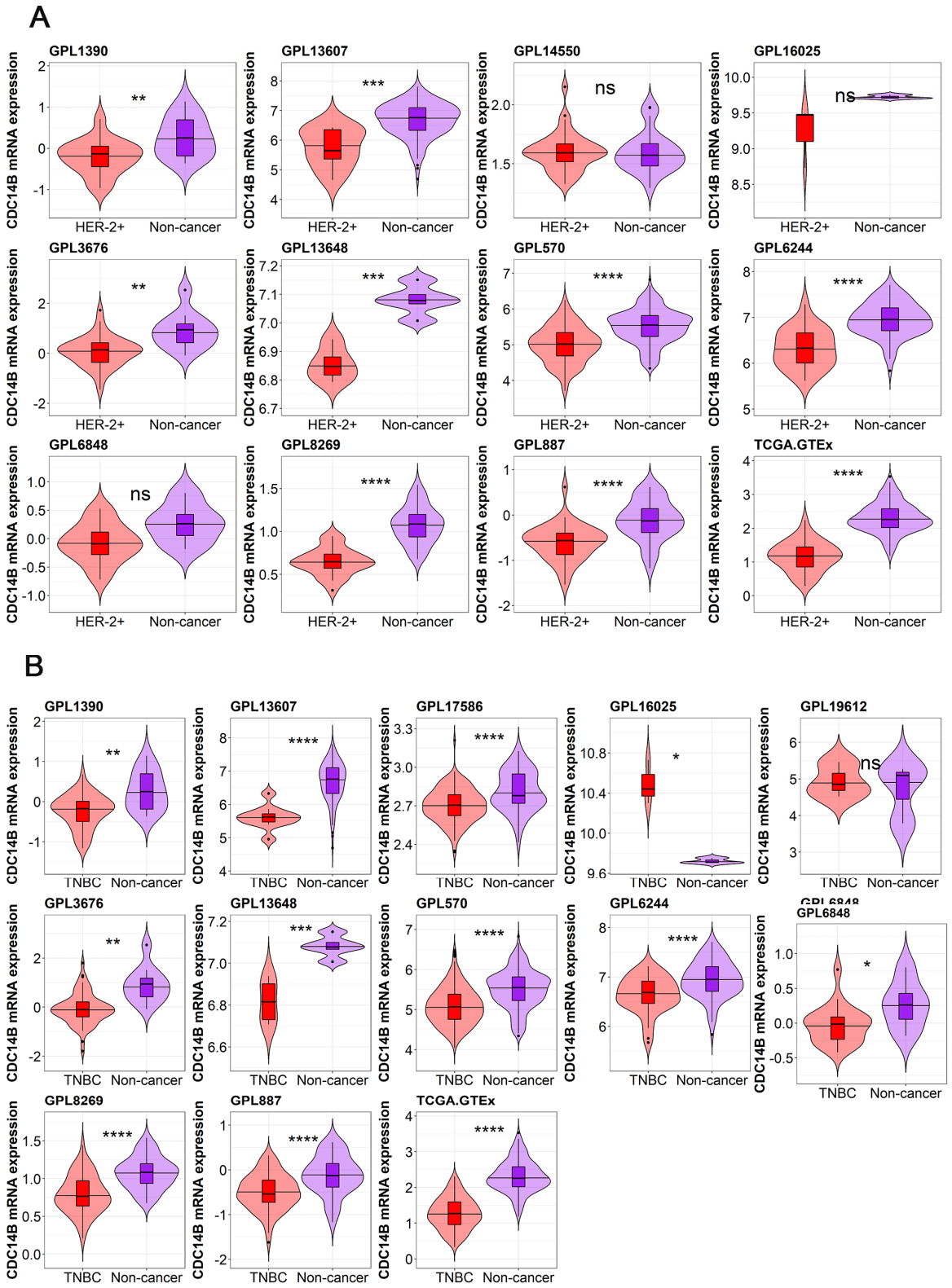


Figure S3. Expression levels of CDC14B in breast cancer. CDC14B expression levels are significantly decreased in HER-2+ (A) and triple-negative breast cancer (B) tissues when compared to normal breast tissues.

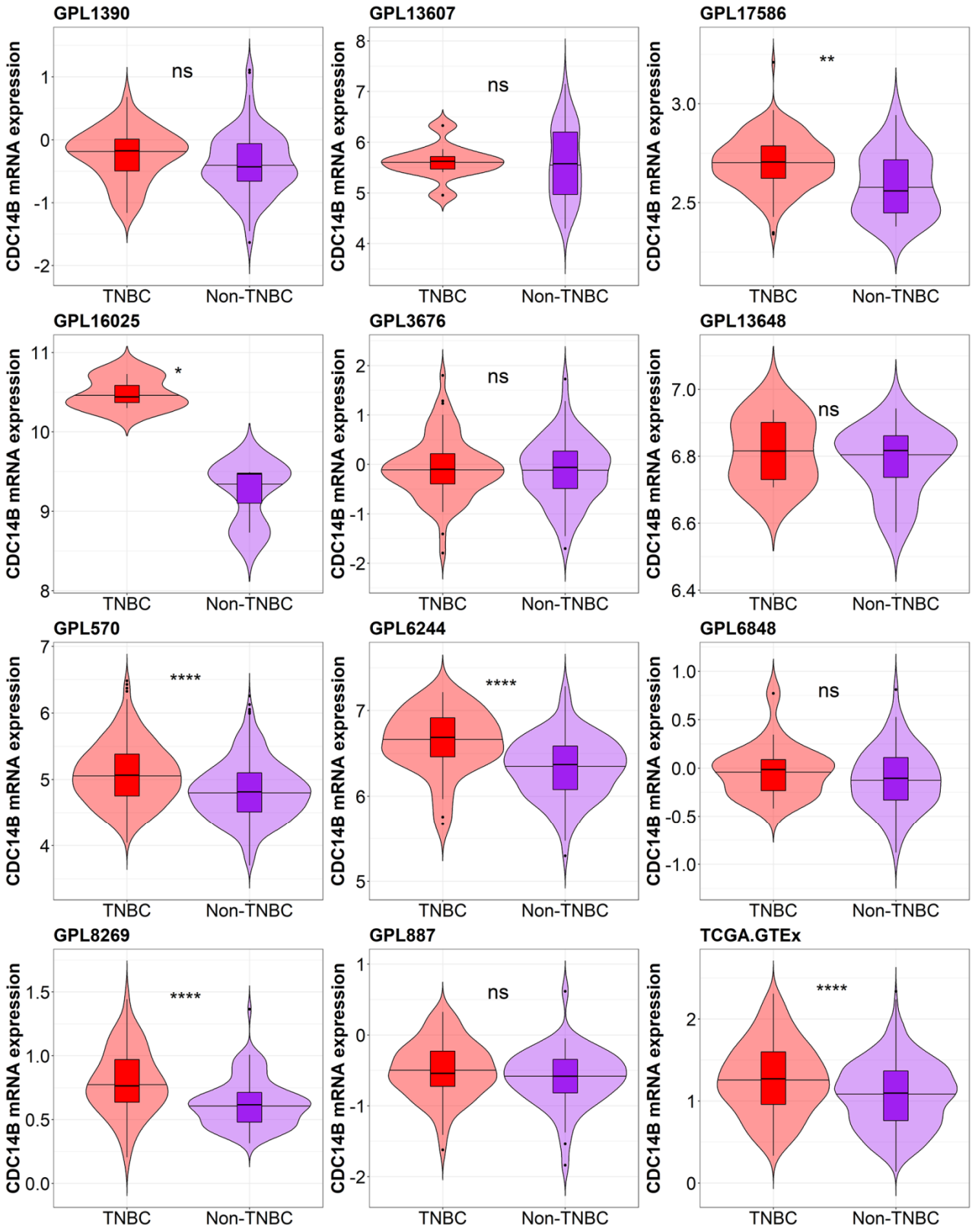


Figure S4. Expression levels of CDC14B in breast cancer. CDC14B expression levels are significantly decreased in non-triple-negative breast cancer (TNBC) tissues when compared to TNBC tissues.

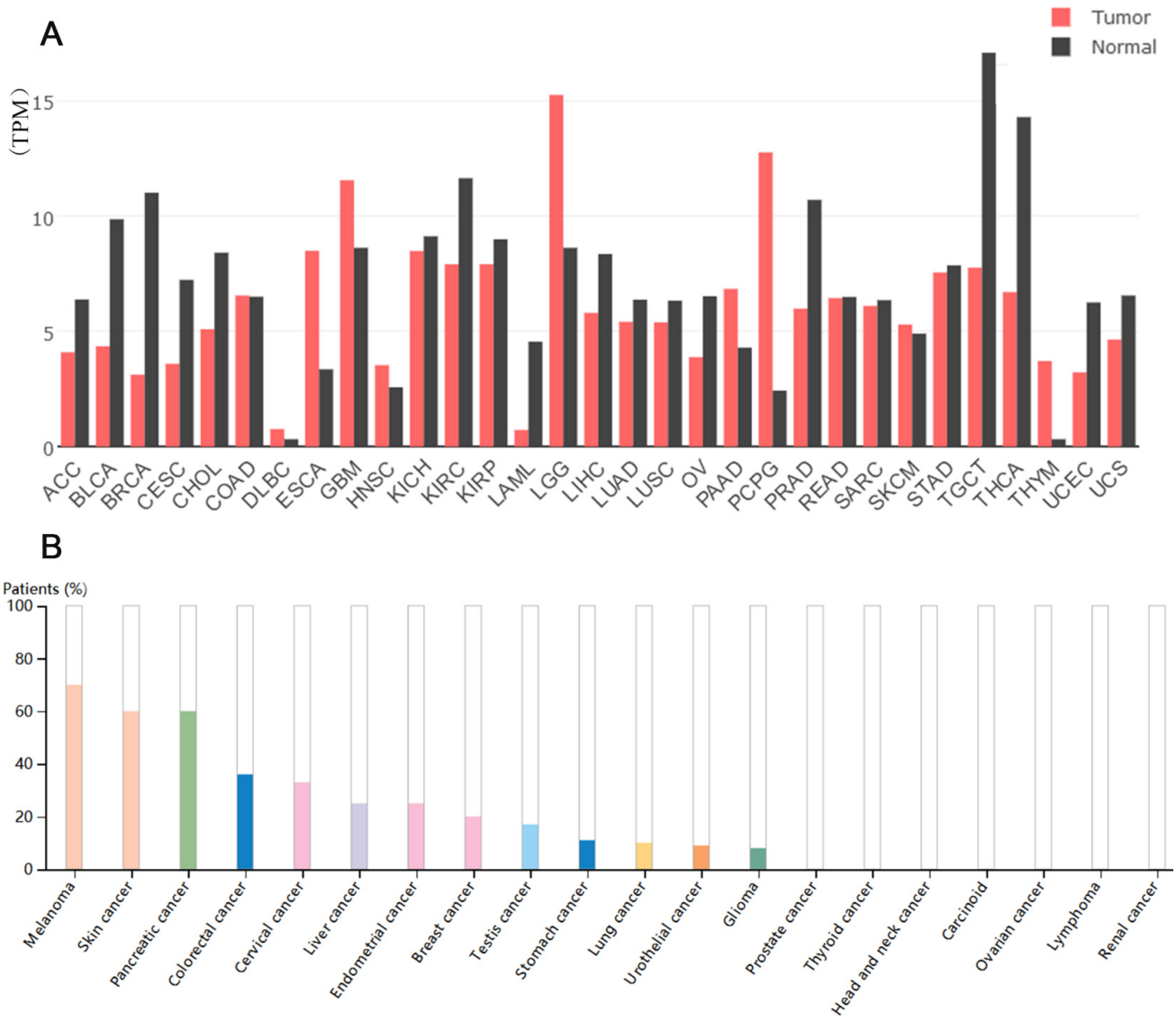


Figure S5. CDC14B expression levels in various types of cancers. A: CDC14B mRNA level as expressed by transcripts per million reads (TPM) based on RNA sequencing data provided by Gene Expression Profiling Interactive Analysis (GEPIA). B: CDC14B protein level based on immunohistochemistry provided by The Human Protein Atlas (THPA).

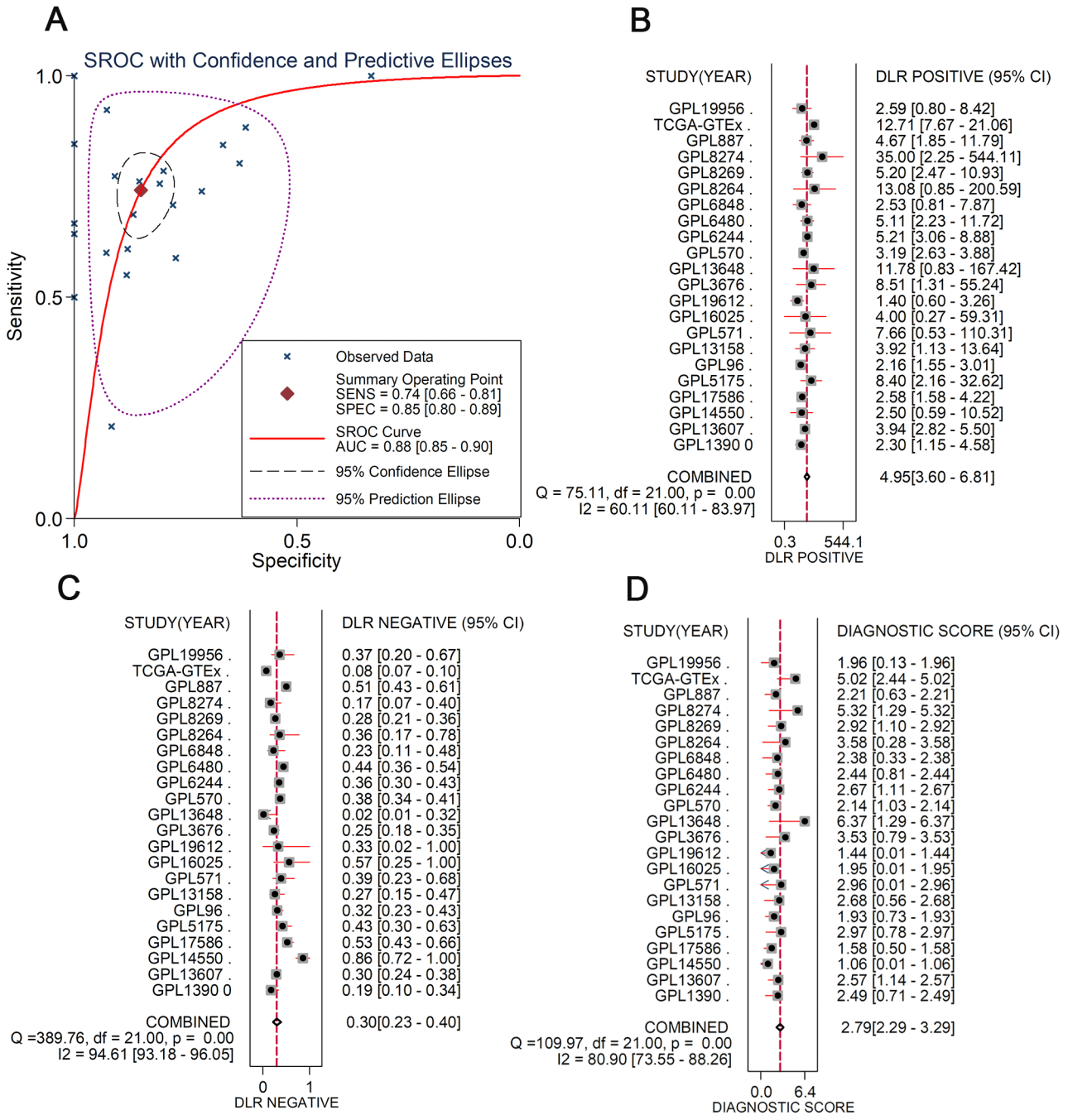


Figure S6. The discriminatory ability of CDC14B in breast cancer tissues and normal breast tissues. A–D: CDC14B exhibits a moderate capability in differentiating between breast cancer tissues and normal breast tissues.

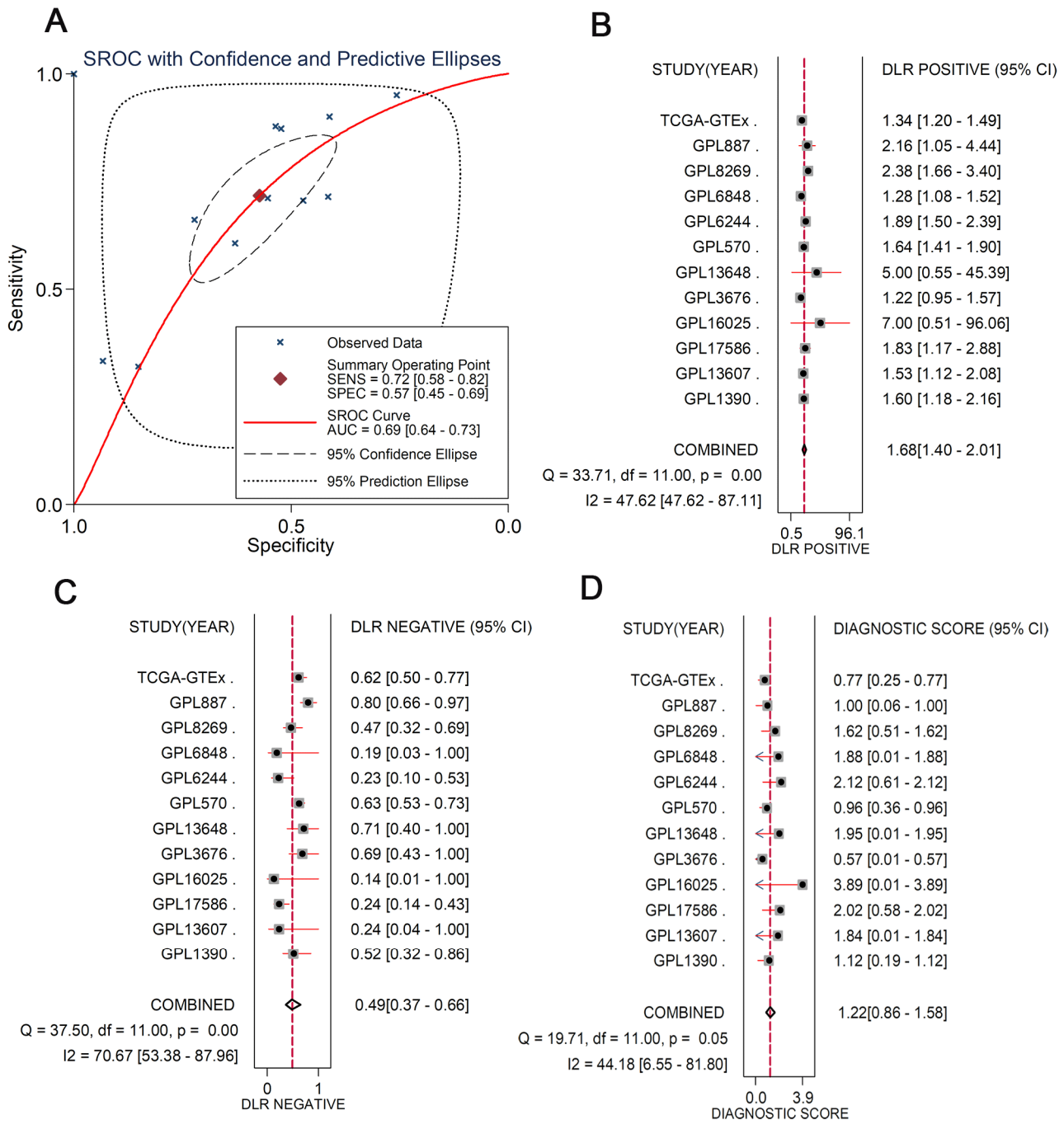


Figure S7. The discriminatory ability of CDC14B in triple-negative breast cancer (TNBC) tissues and non-TNBC tissues. A-D: CDC14B exhibits a weak capability in differentiating between TNBC tissues and non-TNBC tissues (covering luminal A, luminal B, and HER-2+).

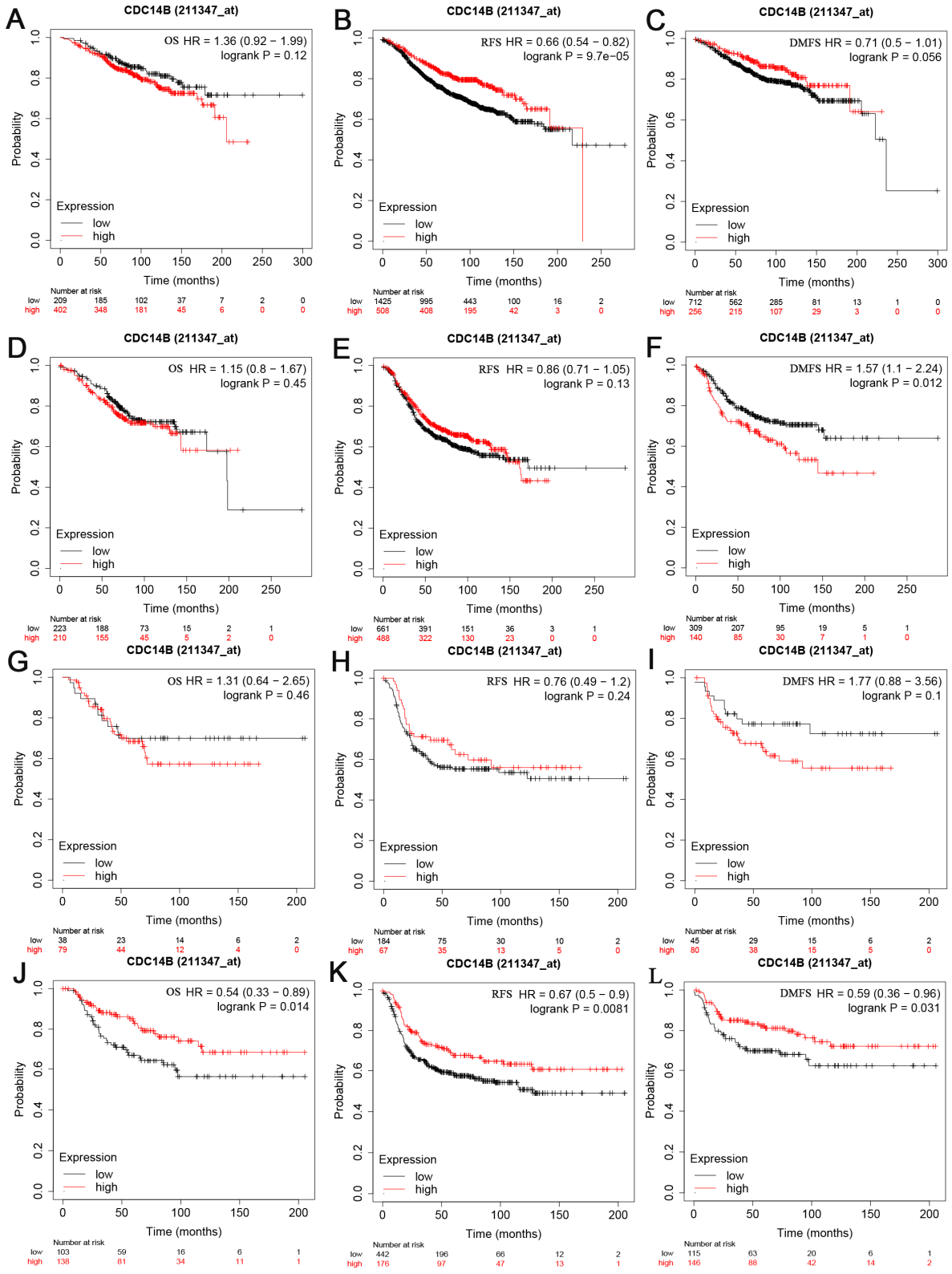
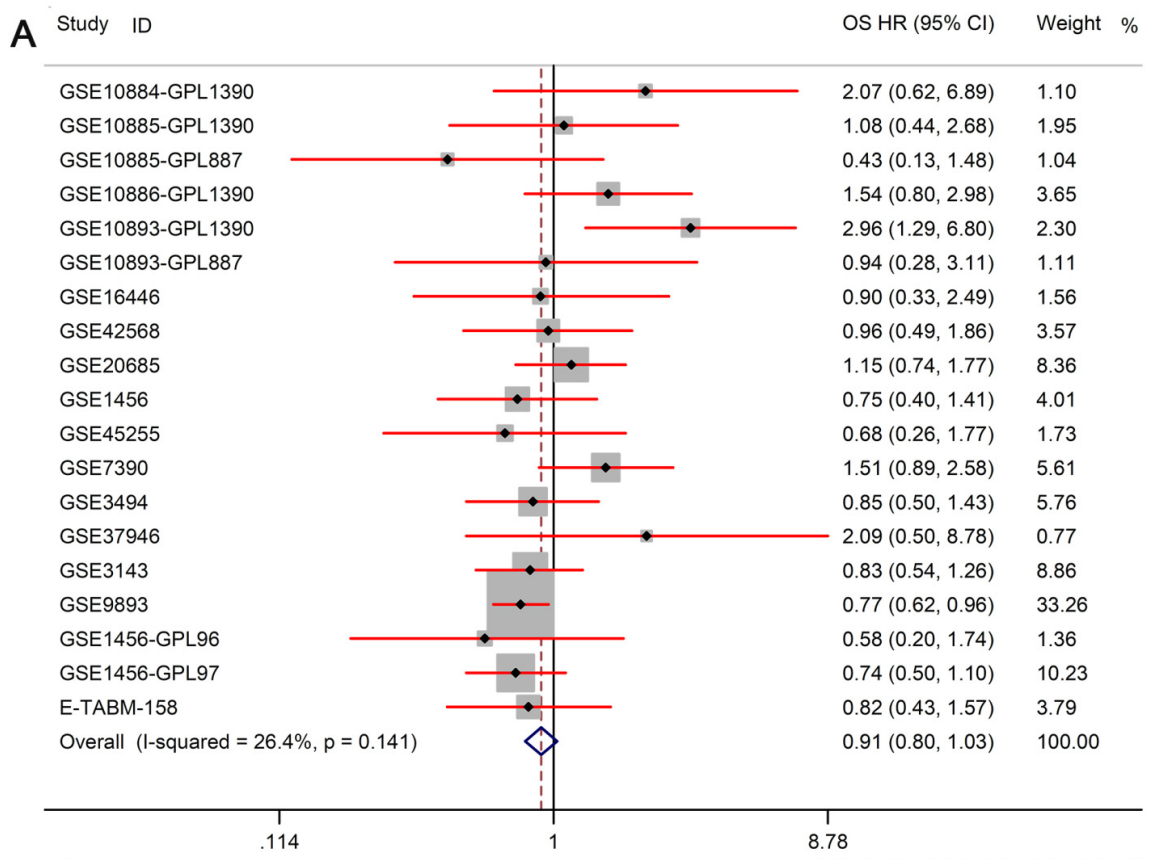


Figure S8. Prognostic value of CDC14B across different intrinsic subtypes in breast cancer. The prognostic value of CDC14B was presented in Luminal A (A–C), Luminal B (D–F), HER-2+ (G–I), TNBC (J–L). CDC14B was a prognostic factor in the overall survival; relapse-free survival; distal-metastasis-free survival of TNBC patients. TNBC, triple-negative breast cancer.



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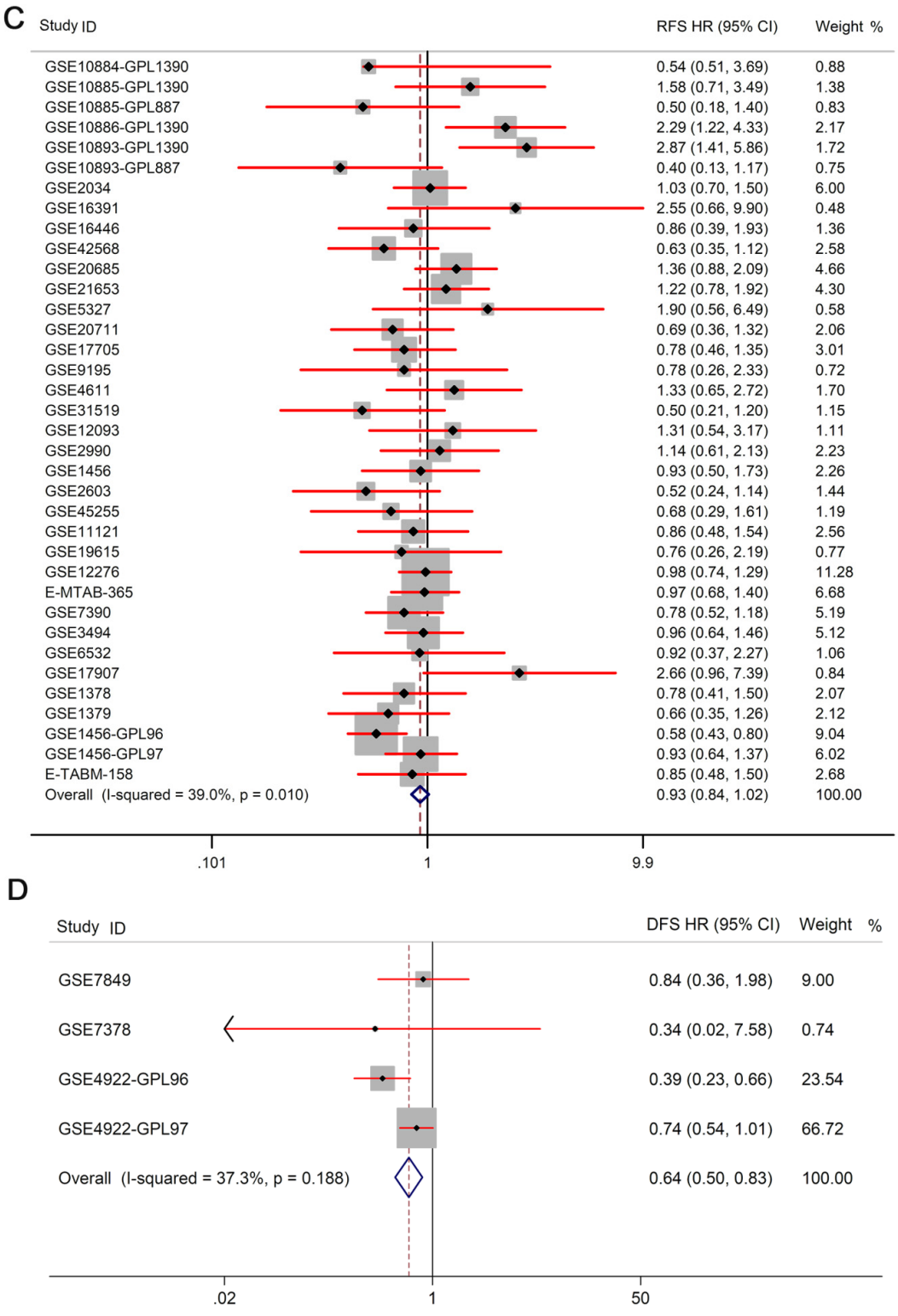

Figure S9. Prognostic capacity of CDC14B in breast cancer patients. A–C: Prognostic values of CDC14B in overall survival, distal-metastasis-free survival, and relapse-free survival of breast cancer patients are not significant; D: CDC14B could be an independent protective prognostic factor in disease-free survival of breast cancer patients.

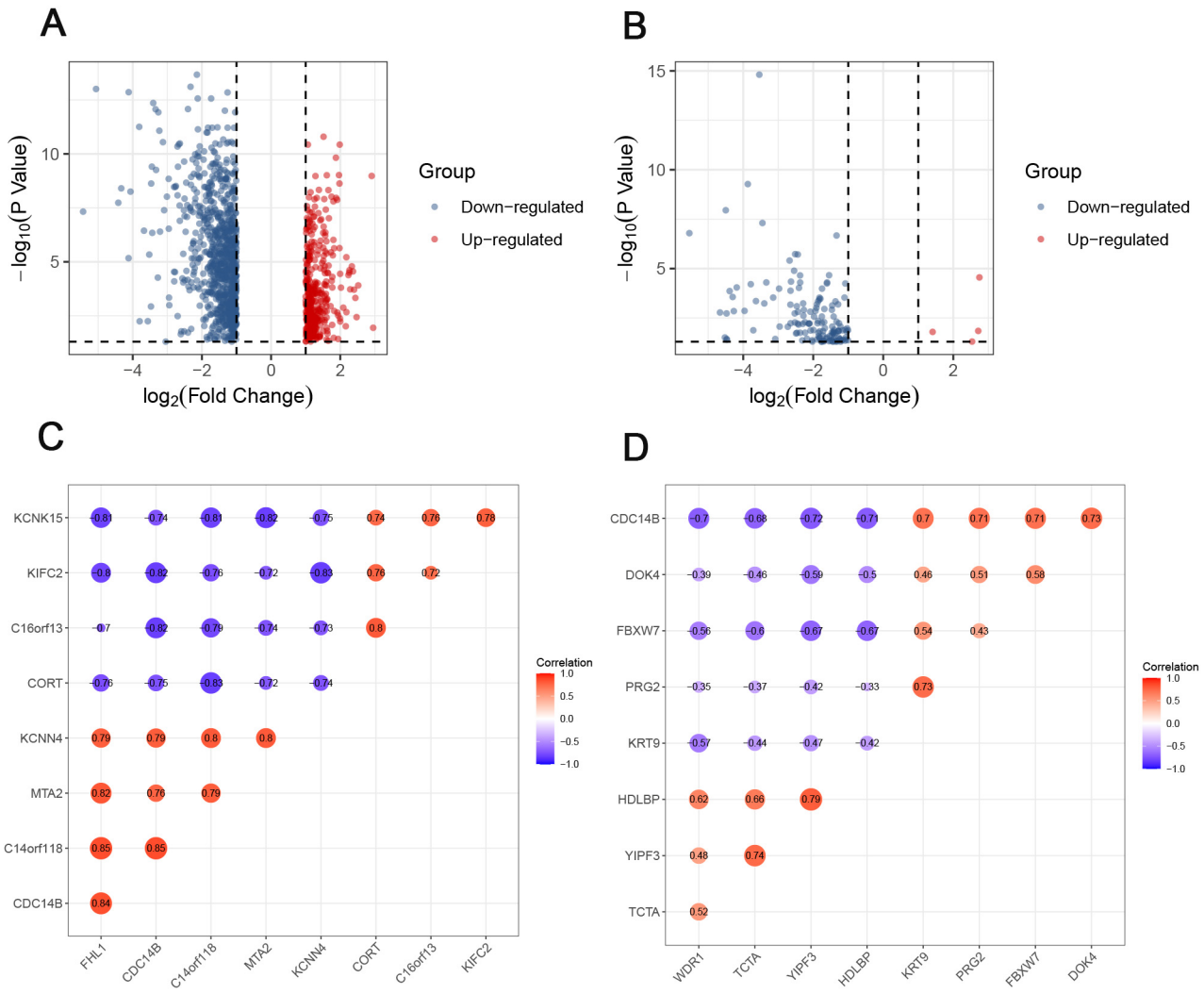

Figure S10. Identification of differentially expressed genes in breast cancer and co-expressed genes of CDC14B. A–D: Volcano plot and correlation diagram are based on two platforms: GPL13648 (GSE50428) and GPL571 (GSE10797). Only the most related genes of CDC14B in breast cancer are presented in correlation diagram.

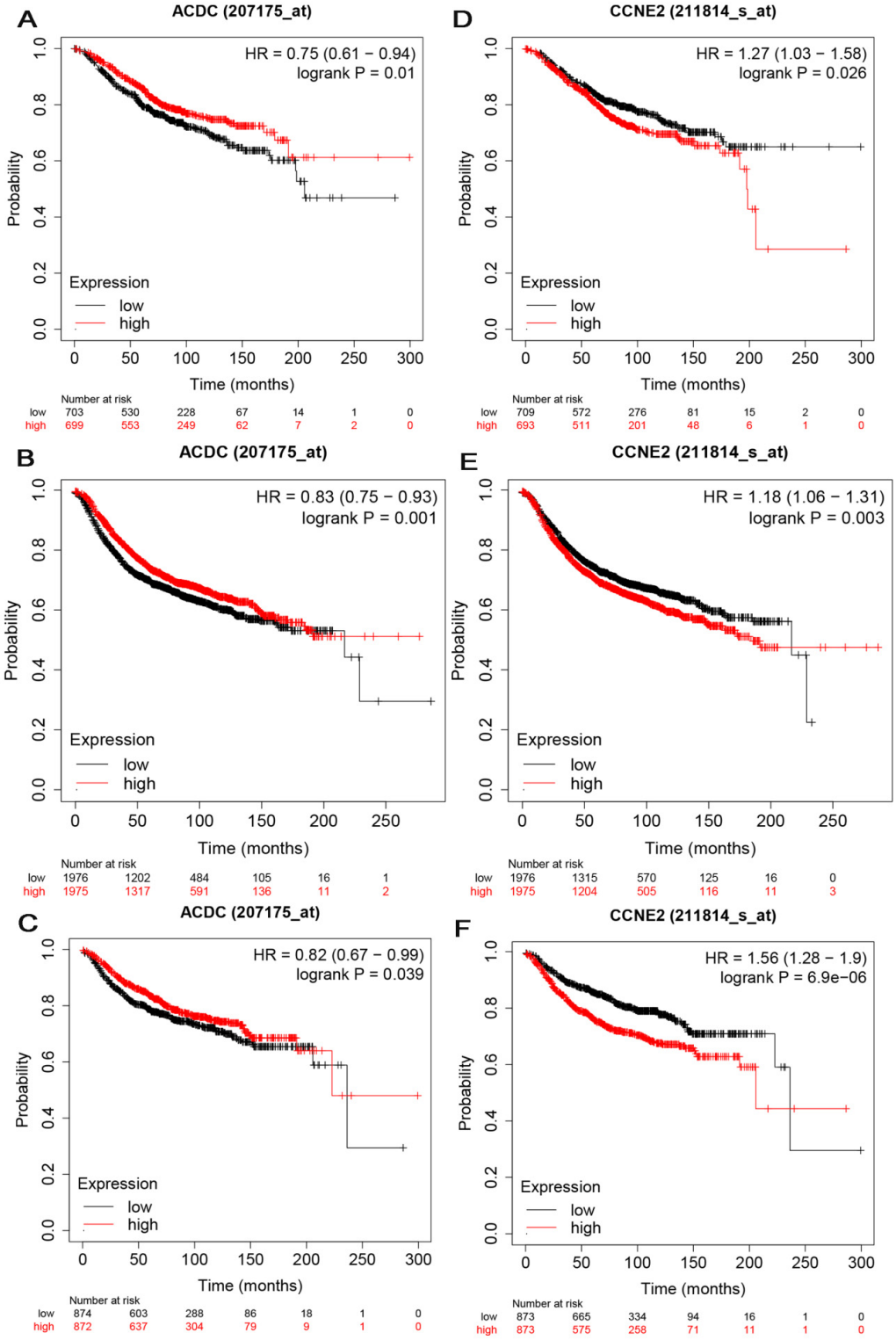

Figure S11. Prognostic value of ADIPOQ and CCNE2 in breast cancer achieved from Kaplan–Meier plotter. The prognostic value of ADIPOQ (or ACDC) and CCNE2 in breast cancer patients: overall survival (n = 1402, A and D); relapse-free survival (RFS, n = 3951, B and E); distal-metastasis-free survival (n = 1746, C and F). ADIPOQ and CCNE2 were two prognostic factors in breast cancer.

Table S1. Association between CDC14B mRNA expression levels and clinicopathological information of breast cancer patients.

Clinicopathological features	mRNA expression level of CDC14B			
	N	M	SD	*p*
Age（years）				
≥50	784	1.1039	0.4297	0.1852
<50	293	1.1425	0.4125	
Race				
Asian	61	1.1521	0.4143	0.5265
Non-Asian	923	1.1170	0.4201	
Race				
Asian	61	1.1521	0.4143	0.2782
Black or African American	743	1.1269	0.4220	
White	179	1.0756	0.4121	
Ethnicity				
Hispanic or Latino	37	1.1033	0.4034	0.5797
Not Hispanic or Latino	870	1.1152	0.4249	
Tumor status				
With tumor	92	1.0644	0.3870	0.2323
Tumor free	863	1.1200	0.4276	
Menopause status				
Premenopause	225	1.1215	0.4070	0.9602
Perimenopause	39	1.1094	0.3736	
Postmenopause	701	1.1127	0.4284	
Pathologic stage				
Stage I	181	1.1458	0.4029	0.6858
Stage II	610	1.1093	0.4361	
Stage III	244	1.1020	0.4064	
Stage IV	19	1.1573	0.4077	
T stage				
T1	278	1.1458	0.4366	0.4198
T2	620	1.1022	0.4205	
T3	137	1.1271	0.4119	
T4	39	1.0584	0.4661	
N stage				
N0	509	1.1192	0.4098	0.8366
N1	354	1.1218	0.4627	
N2	119	1.0859	0.4168	
N3	75	1.1370	0.3702	

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Clinicopathological features	mRNA expression level of CDC14B			
	N	M	SD	*p*
M stage				
M0	21	1.1738	0.3908	0.5581
M1	896	1.1189	0.4258	
Pathological molecular classification				
Luminal A	562	1.0945	0.4327	0.3907
Luminal B	95	1.1189	0.4005	
HER-2+	38	1.1078	0.3821	
TNBC	227	1.1524	0.4310	
ER status				
Positive	790	1.1021	0.4242	0.3830
Negative	237	1.1294	0.4220	
PR status				
Positive	683	1.0982	0.4284	0.2811
Negative	341	1.1285	0.4159	
HER status				
Positive	160	1.1080	0.4014	0.8884
Negative	554	1.1133	0.4287	

Table S2. Results of Gene Ontology analysis based on intersection of downregulated genes in breast cancer and co-expressed genes of CDC14B. Mitotic nuclear division is the most clustered biological process.

Terms	ID	Description	*p*.adjust	Gene
BP	GO:0140014	mitotic nuclear division	7.3E−08	CAV2/CDKN1C/RACGAP1/MYBL2/ZWINT/CENPF/PLK1/KIF4A/TPX2/IGF1/KIF11/KIF23/NEK2/AURKA/NUSAP1/UBE2C/CDCA8/BUB1B/CCNB1/CDC25C/UBE2S/KIF2C/PRC1/MKI67/SPAG5/SMC4/PKMYT1
BP	GO:0001101	response to acid chemical	7.71E−07	EGFR/RBP4/PID1/TGFBR3/GSN/AKR1C3/FOXO1/NTRK2/LPL/PPARG/CDO1/KRT8/SFRP1/OSR1/ADIPOQ/AQP1/FZD4/BMP6/AKR1C1/CD36/PDGFD/KLF4/LEP/PDK4/CCNB1/DGAT2/PCNA/PCK1/E2F1/EGR1
BP	GO:0000280	nuclear division	1.34E−05	CAV2/CDKN1C/RACGAP1/CKS2/MYBL2/ZWINT/CENPF/PLK1/KIF4A/TPX2/IGF1/KIF11/KIF23/NEK2/AURKA/TOP2A/NUSAP1/UBE2C/CDCA8/BUB1B/CCNB1/CDC25C/UBE2S/KIF2C/PRC1/MKI67/SPAG5/SMC4/PKMYT1
CC	GO:0062023	collagen-containing extracellular matrix	1.68E−07	ADAMTS5/SRPX/ANXA1/PRELP/MFAP4/ITIH5/FBLN5/CLEC3B/SOD3/FREM1/SFRP1/DST/ECM2/DPT/TNXB/DCN/ADIPOQ/MYOC/CXCL12/MATN2/F3/ADAMTS1/GPC3/F12/GDF10/LAMA2/LAMC2/SPARCL1/RARRES2/SULF1/COL6A6/COL10A1
CC	GO:0044815	DNA packaging complex	8.13E−07	HIST1H2BD/HIST1H3F/HIST1H2BK/HIST1H2BF/HIST1H3H/HIST1H2AI/HIST1H2BH/HIST2H2BE/HIST1H2BM/HIST1H4H/HIST1H2AM/HIST1H2BJ/HIST1H2BO/SMC4/HIST1H2BI/HIST1H3B
CC	GO:0000786	nucleosome	1.83E−06	HIST1H2BD/HIST1H3F/HIST1H2BK/HIST1H2BF/HIST1H3H/HIST1H2AI/HIST1H2BH/HIST2H2BE/HIST1H2BM/HIST1H4H/HIST1H2AM/HIST1H2BJ/HIST1H2BO/HIST1H2BI/HIST1H3B
MF	GO:0046982	protein heterodimerization activity	8.70E−06	EGFR/CAV1/RBP4/PAFAH1B3/CAV2/TPD52/HIST1H2BD/PPARG/JAM2/AOC3/TBX15/KCNB1/EPAS1/FZD4/BMP6/HIST1H3F/HIST1H2BK/AURKA/HIST1H2BF/TOP2A/HIST1H3H/MID1/HIST1H2AI/HIST1H2BH/HIST2H2BE/HIST1H2BM/HIST1H4H/HIST1H2AM/HIST1H2BJ/SOX17/HIST1H2BO/SMC4/HIST1H2BI/HIST1H3B/NR4A1
MF	GO:1901681	sulfur compound binding	0.002046	ADAMTS5/TGFBR3/PCOLCE2/CD34/LPL/FGF2/CLEC3B/SOD3/SFRP1/TNXB/ACACB/ADAMTS1/SAA1/LAMC2/HPSE2/CFH/ACADL/RSPO3
MF	GO:0008201	heparin binding	0.002652	ADAMTS5/TGFBR3/PCOLCE2/LPL/FGF2/CLEC3B/SOD3/SFRP1/TNXB/ADAMTS1/SAA1/LAMC2/CFH/RSPO3

Table S3. Results of Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis based on intersection of downregulated genes in breast cancer and co-expressed genes of CDC14B.

ID	Description	*p*.adjust	Gene
hsa05034	Alcoholism	3.52E−05	HIST1H2BD/NTRK2/CREB5/GNG11/HIST1H3F/GNAI1/HIST1H2BK/HIST1H2BF/HIST1H3H/HIST1H2AI/HIST1H2BH/HIST2H2BE/HIST1H2BM/HIST1H4H/HIST1H2AM/FOSB/HIST1H2BJ/HIST1H2BO/HIST1H2BI/MAOA/HIST1H3B
hsa03320	PPAR signaling pathway	0.000305	SORBS1/LPL/PPARG/ADIPOQ/CD36/AQP7/FABP4/PLTP/PLIN1/PCK1/ACADL/OLR1
hsa05322	Systemic lupus erythematosus	0.000958	HIST1H2BD/HIST1H3F/HIST1H2BK/HIST1H2BF/HIST1H3H/HIST1H2AI/HIST1H2BH/HIST2H2BE/HIST1H2BM/HIST1H4H/HIST1H2AM/HIST1H2BJ/HIST1H2BO/HIST1H2BI/HIST1H3B
hsa04110	Cell cycle	0.001083	CDKN1C/MCM4/PLK1/CDKN2C/BUB1B/CCNB1/CDC25C/CCNB2/PCNA/BUB1/E2F1/CCNE2/PKMYT1/PTTG1
hsa00350	Tyrosine metabolism	0.003167	AOC3/ADH1C/ADH1A/ADH1B/AOX1/MAOA/IL4I1
hsa04152	AMPK signaling pathway	0.008182	LEPR/FOXO1/PPARG/LIPE/CREB5/ADIPOQ/CD36/IGF1/LEP/ACACB/SLC2A4/PCK1
hsa04923	Regulation of lipolysis in adipocytes	0.008182	NPR1/LIPE/ADRB2/AQP7/GNAI1/FABP4/PLIN1/PDE3B
hsa04914	Progesterone-mediated oocyte maturation	0.021777	PLK1/IGF1/GNAI1/AURKA/PDE3B/CCNB1/CDC25C/CCNB2/BUB1/PKMYT1
hsa00360	Phenylalanine metabolism	0.029416	AOC3/GLYAT/MAOA/IL4I1
hsa04512	ECM-receptor interaction	0.029416	ITGA7/FREM1/TNXB/CD36/RELN/LAMA2/LAMC2/COL6A6/SDC1

Table S4. Results of Disease Ontology analysis based on intersection of downregulated genes in breast cancer and co-expressed genes of CDC14B.

ID	Description	p.adjust	Gene
DOID:3996	urinary system cancer	3.79E−07	EGFR/CAV1/EDNRB/ANXA1/TGFBR2/TGFBR3/AKR1C3/MME/IGFBP6/CD34/LEPR/DLC1/PPARG/AP1M2/FGF2/SPINT2/HOXA5/SFRP1/ID4/MYBL2/ADIPOQ/EPAS1/AQP1/TK1/BMP6/CXCL12/IGF1/LEP/ANGPT1/ADM/NR3C2/KRT18/AURKA/FABP4/BIRC5/AVPR2/FAM107A/EZH2/ID1/CCNB1/SNCG/UBE2S/MKI67/ESRP1/NDRG2/E2F1/EGR1/MUC1
DOID:4451	renal carcinoma	1.56E−06	EGFR/CAV1/EDNRB/TGFBR2/TGFBR3/AKR1C3/MME/IGFBP6/CD34/DLC1/PPARG/AP1M2/FGF2/SPINT2/HOXA5/SFRP1/ADIPOQ/EPAS1/AQP1/TK1/BMP6/CXCL12/IGF1/LEP/ANGPT1/ADM/NR3C2/KRT18/BIRC5/AVPR2/FAM107A/EZH2/CCNB1/UBE2S/MKI67/ESRP1/NDRG2/E2F1/MUC1
DOID:4450	renal cell carcinoma	7.73E−06	EGFR/CAV1/EDNRB/TGFBR2/TGFBR3/AKR1C3/MME/IGFBP6/CD34/DLC1/PPARG/AP1M2/FGF2/SPINT2/HOXA5/SFRP1/ADIPOQ/EPAS1/AQP1/TK1/CXCL12/IGF1/LEP/NR3C2/KRT18/BIRC5/FAM107A/EZH2/CCNB1/UBE2S/MKI67/ESRP1/NDRG2/E2F1/MUC1
DOID:263	kidney cancer	1.25E−05	EGFR/CAV1/EDNRB/TGFBR2/TGFBR3/AKR1C3/MME/IGFBP6/CD34/DLC1/PPARG/AP1M2/FGF2/SPINT2/HOXA5/SFRP1/ADIPOQ/EPAS1/AQP1/TK1/BMP6/CXCL12/IGF1/LEP/ANGPT1/ADM/NR3C2/KRT18/BIRC5/AVPR2/FAM107A/EZH2/CCNB1/UBE2S/MKI67/ESRP1/NDRG2/E2F1/EGR1/MUC1
DOID:2994	germ cell cancer	1.39E−05	EGFR/PLAGL1/CAV1/ITIH5/CDKN1C/MCAM/KRT8/SFRP1/ID4/AQP1/PLK1/PDGFD/CXCL12/KLF4/IGF1/LEP/GPRC5A/NEK2/KPNA2/GPC3/KRT18/BIRC5/KRT19/PITX1/CDKN2C/ID1/LAMC2/CCNB1/SNCG/RRM2/MKI67/PCNA/SOX17/HPSE2/RAD51/NDRG2/MUC1/SDC1
DOID:5844	myocardial infarction	1.39E−05	NPR1/GSN/F10/CD34/CDKN1C/LPL/PPARG/TFPI/FGF2/SOD3/S100B/MB/ADH1C/ADRB2/ADIPOQ/CD36/CXCL12/IGF1/F3/PTGIS/ADM/KRT18/ADH1B/F12/ALDH2/CLDN5/CFH/OLR1/PARP1/RAMP1
DOID:3393	coronary artery disease	1.67E−05	NPR1/GSN/F10/CD34/CDKN1C/LPL/PPARG/TFPI/FGF2/SOD3/S100B/MB/ADH1C/ADRB2/ADIPOQ/CD36/CXCL12/IGF1/LEP/F3/PTGIS/ADM/KRT18/FABP4/ADH1B/PLTP/F12/CX3CL1/ALDH2/CLDN5/CFH/OLR1/PARP1/RAMP1
DOID:688	embryonal cancer	2.54E−05	EGFR/PLAGL1/CAV1/ITIH5/CDKN1C/MCAM/KRT8/SFRP1/ID4/PLK1/PDGFD/CXCL12/IGF1/LEP/GPRC5A/NEK2/KPNA2/KRT18/BIRC5/KRT19/PITX1/CDKN2C/ID1/LAMC2/CCNB1/SNCG/RRM2/MKI67/PCNA/SOX17/HPSE2/RAD51/NDRG2/MUC1/SDC1
DOID:3908	non-small cell lung carcinoma	3.29E−05	EGFR/CAV1/SRPX/DDR2/TGFBR2/TGFBR3/GSN/SPRY2/BMX/NTRK2/LPL/DLC1/PPARG/KRT8/SFRP1/ADRB2/EPAS1/CXCL12/IGF1/LEP/F3/ADAMTS1/KPNA2/GPC3/KRT18/TOP2A/BIRC5/SAA1/KRT19/UBE2C/CCNB1/NNAT/RRM2/MKI67/CCNB2/PCNA/E2F1/MUC1
DOID:5082	liver cirrhosis	3.66E−05	EGFR/CAV1/RBP4/CAV2/TGFBR2/PPARG/KRT8/FGF2/ADIPOQ/AQP1/CXCL12/IGF1/MATN2/LEP/F3/CDKN3/GPC3/KRT18/SLC2A4/RELN/BIRC5/KRT19/RGN/MKI67/PCNA

Table S5. Results of Reactome pathway analysis based on intersection of downregulated genes in breast cancer and co-expressed genes of CDC14B.

ID	Description	p.adjust	Gene
R-HSA-2299718	Condensation of Prophase Chromosomes	1.96E−07	HIST1H2BD/HIST1H3F/PLK1/HIST1H2BK/HIST1H2BF/HIST1H3H/HIST1H2BH/HIST2H2BE/CCNB1/HIST1H2BM/HIST1H4H/HIST1H2BJ/HIST1H2BO/SMC4/HIST1H2BI/HIST1H3B
R-HSA-9006931	Signaling by Nuclear Receptors	2.62E−07	EGFR/CAV1/CAV2/AKR1C3/HIST1H2BD/GNG11/RDH5/ADH1C/ADH1A/HIST1H3F/CXCL12/GPAM/ALDH1A1/GNAI1/PDK4/HIST1H2BK/KPNA2/HIST1H2BF/HIST1H3H/HIST1H2BH/KANK1/HIST2H2BE/HIST1H2BM/FOSB/HIST1H2BJ/HIST1H2BO/HIST1H2BI/HIST1H3B
R-HSA-5625740	RHO GTPases activate PKNs	4.04E−07	HIST1H2BD/PPP1R14A/HIST1H3F/PPP1R12B/HIST1H2BK/HIST1H2BF/HIST1H3H/HIST1H2BH/HIST2H2BE/HIST1H2BM/HIST1H4H/CDC25C/HIST1H2BJ/HIST1H2BO/HIST1H2BI/HIST1H3B/MYL9
R-HSA-5334118	DNA methylation	7.07E−07	HIST1H2BD/HIST1H3F/HIST1H2BK/HIST1H2BF/UHRF1/HIST1H3H/HIST1H2BH/HIST2H2BE/HIST1H2BM/HIST1H4H/HIST1H2BJ/HIST1H2BO/HIST1H2BI/HIST1H3B
R-HSA-195258	RHO GTPase Effectors	8.18E−07	WASF3/HIST1H2BD/PPP1R14A/NUF2/ZWINT/HIST1H3F/CENPF/PLK1/PAK3/PPP1R12B/HIST1H2BK/HIST1H2BF/BIRC5/HIST1H3H/HIST1H2BH/CDCA8/BUB1B/HIST2H2BE/SPC25/HIST1H2BM/HIST1H4H/CDC25C/KIF2C/HIST1H2BJ/HIST1H2BO/BUB1/HIST1H2BI/HIST1H3B/MYL9/CENPM
R-HSA-212300	PRC2 methylates histones and DNA	2.32E−06	HIST1H2BD/HIST1H3F/HIST1H2BK/HIST1H2BF/HIST1H3H/HIST1H2BH/EZH2/HIST2H2BE/HIST1H2BM/HIST1H4H/HIST1H2BJ/HIST1H2BO/HIST1H2BI/HIST1H3B
R-HSA-73728	RNA Polymerase I Promoter Opening	2.50E−06	HIST1H2BD/HIST1H3F/HIST1H2BK/HIST1H2BF/HIST1H3H/HIST1H2BH/HIST2H2BE/HIST1H2BM/HIST1H4H/HIST1H2BJ/HIST1H2BO/HIST1H2BI/HIST1H3B
R-HSA-69620	Cell Cycle Checkpoints	2.50E−06	HIST1H2BD/NUF2/MCM4/ZWINT/CENPF/PLK1/HIST1H2BK/HIST1H2BF/BIRC5/HIST1H2BH/UBE2C/CDCA8/BUB1B/HIST2H2BE/SPC25/CCNB1/HIST1H2BM/HIST1H4H/CDC25C/KIF2C/CCNB2/HIST1H2BJ/HIST1H2BO/HIST1H2BI/CCNE2/PKMYT1/CENPM

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ID	Description	p.adjust	Gene
R-HSA-194315	Signaling by Rho GTPases	2.93E−06	WASF3/ARHGAP20/HIST1H2BD/DLC1/PPP1R14A/RHOJ/RACGAP1/NUF2/ZWINT/HIST1H3F/CENPF/PLK1/PAK3/PPP1R12B/FAM13A/HIST1H2BK/HIST1H2BF/BIRC5/HIST1H3H/HIST1H2BH/CDCA8/BUB1B/HIST2H2BE/HIST1H2BM/HIST1H4H/CDC25C/KIF2C/PRC1/HIST1H2BJ/HIST1H2BO/BUB1/HIST1H2BI/HIST1H3B/MYL9/CENPM
R-HSA-68886	M Phase	2.93E−06	HIST1H2BD/NUF2/ZWINT/HIST1H3F/CENPF/PLK1/HIST1H2BK/KIF20A/KIF23/NEK2/HIST1H2BF/BIRC5/HIST1H3H/HIST1H2BH/LMNB1/UBE2C/CDCA8/BUB1B/HIST2H2BE/SPC25/CCNB1/HIST1H2BM/HIST1H4H/CCNB2/HIST1H2BJ/HIST1H2BO/BUB1/SMC4/HIST1H2BI/HIST1H3B/PTTG1/CENPM