Bioinformatics analysis of potential therapeutic targets among *ARHGAP* genes in breast cancer

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Abstract. GTPase activating proteins (RhoGAPs) serve significant roles in multiple aspects of tumor biology. Genes encoding RhoGAPs (*ARHGAP*), which switch off Rho-like GTPases, are responsible for breast cancer biogenesis. However, the identification of suitable and novel biomarkers for precision treatment and prognosis remains challenging. The present study aimed to evaluate the expression of ARHGAP family genes in breast cancer and investigate the survival data using the Oncomine, Kaplan-Meier Plotter, bcGenExMiner and cBioPortal online databases. The results demonstrated low expression of *ARHGAP6*, *7*, *10*, *14*, *19*, *23* and *24* and high expression of *ARHGAP9*, *11*, *15*, *18* and *30* in patients with breast cancer compared with that in healthy individuals. The survival analysis revealed that low expression levels of *ARHGAP6*, *7* and *19* were associated with poor relapse-free survival (RFS) and overall survival (OS), whereas high expression levels of *ARHGAP9*, *15* and *30* were associated with preferable RFS and OS. Metastatic relapse data demonstrated that higher expression of *ARHGAP9*, *15*, *18*, *19*, *25* and *30* were associated with better prognosis and increased expression of *ARHGAP11A* and *14* exerted negative effects on patient prognosis. The overlapping genes *ARHGAP9*, *15*, *19* and *30* obtained from these bioinformatics analysis tools exhibited significant association with clinical parameters including age, the presence of estrogen receptor, progesterone receptor and epidermal growth factor receptor-2, Scarff-Bloom-Richardson grade and Nottingham prognostic index. In conclusion, bioinformatics analysis revealed that *ARHGAP9*, *15*, *19* and *30*, but not other ARHGAP family genes may be promising targets with prognostic value and biological function for precision treatment of breast cancer.

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Introduction

Breast cancer is the most common malignant tumor and a leading cause of cancer-related death among females worldwide. Cases in China account for 12.2% of newly diagnosed breast cancers and 9.6% of breast cancer-associated deaths worldwide in 2014 (1). Although advances have been achieved in early diagnosis and systemic therapy, the prognosis of patients with breast cancer remains poor. The identification of new sensitive and specific biomarkers for the prognosis of patients with breast cancer is therefore urgently needed.

Rho/Rac/cell division cycle 42-like (Rho-like) GTPases are key regulators of multiple cell functions, including cell polarity control, membrane transport, transcriptional regulation, survival, adhesion and proliferation (2,3). Rho-like GTPases are inactive in GDP-bound form and active in GTP-bound form. GTPase activating proteins (RhoGAPs) are negative regulators of Rho-like GTPases, which exert their functions by catalyzing the conversion of the active GTP-bound state to the inactive GDP-bound state. A family of genes encoding RhoGAPs (*ARHGAP*) switch off Rho-like GTPases. Genetic alterations of ARHGAP family genes are responsible for cancer biogenesis through the dysregulation of Rho-like GTPases (2,3). Low expression of *ARHGAP7* is associated with poor prognosis in patients with estrogen receptor (ER)-positive breast cancer with further decrease in survival in patients with metastatic lesions (4). *ARHGAP15* is an androgen-induced gene and has anti-tumor roles associated with the Rac1 pathway (5). *ARHGAP18* expression is associated with improved patient outcomes in invasive breast cancer (6). Thus, researchers and clinicians are increasingly considering *ARHGAP* expression levels as a source of important clinical and predictive therapeutic information.

Although previous studies have reported a general expression profile of *ARHGAP* family genes in breast cancer,

several challenges remain in the identification of suitable and novel biomarkers for precision treatment and prognosis. The present study aimed to perform bioinformatics analysis of the clinicopathological parameters and survival data associated with *ARHGAP* family genes in patients with breast cancer by pooling and analyzing several large online databases.

Materials and methods

Oncomine. Oncomine (http://www.oncomine.org) is an online database that incorporates 715 datasets and 86,733 samples and aims to compute gene expression signatures and extract biological insights from the data for cancer research (7). All the mentioned *ARHGAP* genes were queried in the database and the results were filtered by selecting 'breast cancer' and 'cancer' vs. 'normal' analysis with the threshold of fold change ≥2, $P \leq 1x10^{-4}$, and gene rank ≥ top 10%.

Kaplan-Meier plotter. The Kaplan Meier Plotter (http://kmplot.com/analysis/) provides a powerful platform for assessing the biological relationships between gene expression levels and survival information including relapse-free survival (RFS) and overall survival (OS) in patients with breast cancer (8). P-values, hazard ratios and 95% confidence intervals according to the mRNA expression level (low or high) of each ARHGAP gene were obtained.

bcGenExMiner. The Breast Cancer Gene-Expression Miner v4.1 (bcGenExMiner v4.1; http://bcgenex.centregauducheau.fr/BC-GEM) is a mining tool of published annotated genomics data (9,10). The selected *ARHGAP* family genes were analyzed with clinical parameters such as age, nodal status, the presence of estrogen receptor (*ER*), progesterone receptor (*PR*) and epidermal growth factor receptor-2 (*HER-2*), Scarff-Bloom-Richardson (SBR) grade and Nottingham prognostic index (NPI). Prognostic values of metastatic relapse event and *ARHGAP* genes were calculated using the prognostic module (9,10).

cBioPortal. The cBioPortal (http://www.cbioportal.org) database offers visualization, analysis and download of large-scale cancer genomics datasets (11,12). To analyze the ARHGAP-centered regulation system, a network of the *ARHGAP* family and the neighboring genes was generated in cBioPortal.

Statistical analysis. According to protocols of the aforementioned tools, mRNA levels of ARHGAP in breast cancer and normal tissues in each individual dataset were analyzed using Student's t-test. Kaplan-Meier survival analysis was performed to compare patient survival based on *ARHGAP* expression levels by log-rank test. Global significant difference between groups of clinical parameters was assessed by Welch's and Dunnett-Tukey-Kramer's tests. Data are presented as the mean ± standard error of mean (SEM). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Dysregulated expression of ARHGAP genes in patients with breast cancer. The expression of *ARHGAP* family genes in were evaluated in 20 common types of cancer, and their levels were compared to normal individuals using the Oncomine database. Lower expression levels (blue) of *ARHGAP6*, *7*, *10*, *14*, *19*, *23* and *24* and higher expression levels (red) of *ARHGAP9*, *11*, *15*, *18* and *30* were observed in breast cancer samples compared with normal tissues. *ARHGAP4*, *8*, *25* and *29* were neither upregulated nor downregulated in patients with breast cancer compared with healthy individuals (Fig. 1).

Dysregulated ARHGAP genes in RFS and OS of patients with breast cancer. The survival data of ARHGAP family genes were analyzed using the Kaplan-Meier Plotter. The Kaplan-Meier curves demonstrated that reduced *ARHGAP6*, *7*, *10*, *14*, *19* and *24* mRNA levels were significantly associated with poor RFS (Table I; Fig. 2A). Patients with high expression levels of *ARHGAP9*, *15* and *30* exhibited favorable RFS (Table I; Fig. 2B). In addition, low expression of *ARHGAP6*, *7* and *19* was associated with poor OS (Table II; Fig. 3A), whereas high expression of *ARHGAP9*, *15* and *30* were associated with preferable OS (Table II; Fig. 3B). To further verify the role of *ARHGAP* family genes in breast cancer prognosis, the bc-GenExMiner online software was used; *ARHGAP15* exhibited the most significant positive effect on patient metastatic relapse-free survival, and the expression levels of *ARHGAP9*, *19* and *30* were associated with improved metastatic relapse-free survival compared with patients in the respective low expression groups (Table III).

ARHGAP genes and clinicopathological characteristics of patients with breast cancer. By comparing the aforementioned databases, the expression levels of the overlapped genes *ARHGAP9*, *15*, *19* and *30* were analyzed between different patient groups based on clinicopathological characteristics. The SBR grade, which evaluates tubule formation, nuclear characteristics of pleomorphism and mitotic index, is an important prognostic factor in breast cancer (13). Patients with high grade (SBR3) tumors tended to express high levels of *ARHGAP9* and *30* and low levels of *ARHGAP19* than lower grade (SBR1) tumors (Fig. 4A). The NPI is based on histopathological factors and is used to stratify patients with breast cancer into prognostic groups (14); low expression of *ARHGAP19* was associated with NPI (Fig. 4B). No significant differences were observed between the ≤51 and >51 years groups, with an exception for *ARHGAP19*, which was expressed at low levels in the >51 years group. Patients with ER-positive or PR-positive breast cancer exhibited lower expression levels of *ARHGAP9*, *15* and *30* compared with patients with ER-negative or PR-negative status. Patients with HER-2-positive status exhibited higher expression levels of *ARHGAP9* and *30* compared with patients with HER-2-negative status. In addition, *ARHGAP9*, *15*, *19* and *30* expression levels were significantly elevated in patients with triple-negative breast cancer compared with patients without triple-negative breast cancer. No significant association was observed between nodal status and *ARHGAP9*, *15*, *19* and *30* expression levels (Fig. 5).

Construction of the ARHGAP gene network. To better visualize the potential genes interacting with *ARHGAP9*, *15*, *19* and *30*, a gene network was constructed using the

Table I. Prognostic association between *ARHGAP* family gene expression in breast cancer and relapse-free survival based on Kaplan-Meier Plotter analysis.

Gene name	Cut-off value	Expression (range of probe)	P-value	HR (95% CI)	N
ARHGAP4	125	6-1003	>0.0001	0.75 (0.67-0.83)	3,951
ARHGAP6	136	3-2602	0.0003	0.82 (0.73-0.91)	3,951
ARHGAP7	901	26-10898	0.0350	0.89 (0.80-0.99)	3,951
ARHGAP8	867	6-8528	0.0004	0.82 (0.74-0.91)	3,951
ARHGAP9	398	24-4139	>0.0001	0.60 (0.51-0.70)	1,764
ARHGAP10	271	16-1124	0.0015	0.84 (0.75-0.94)	3,951
ARHGAP11A	45	1-806	0.1300	1.09 (0.97-1.21)	3,951
ARHGAP14	221	6-1787	>0.0001	0.70 (0.63-0.78)	3,951
ARHGAP15	316	4-4586	>0.0001	0.67 (0.60-0.75)	3,951
ARHGAP18	157	3-1189	0.0010	0.77 (0.66-0.90)	1,764
ARHGAP19	246	12-1183	0.0170	0.88 (0.79-0.98)	3,951
ARHGAP23	237	9-5617	0.0070	0.81 (0.69-0.94)	1,764
ARHGAP24	110	3-1758	>0.0001	0.72 (0.65-0.81)	3,951
ARHGAP25	171	3-4021	0.0051	0.86 (0.77-0.95)	3,951
ARHGAP29	112	1-1992	>0.0001	0.57 (0.49-0.67)	1,764
ARHGAP30	441	21-3316	>0.0001	0.67 (0.57-0.78)	1,764

ARHGAP, Rho GTPase-activating protein; HR, hazard ratio; 95% CI, 95% confidence interval.

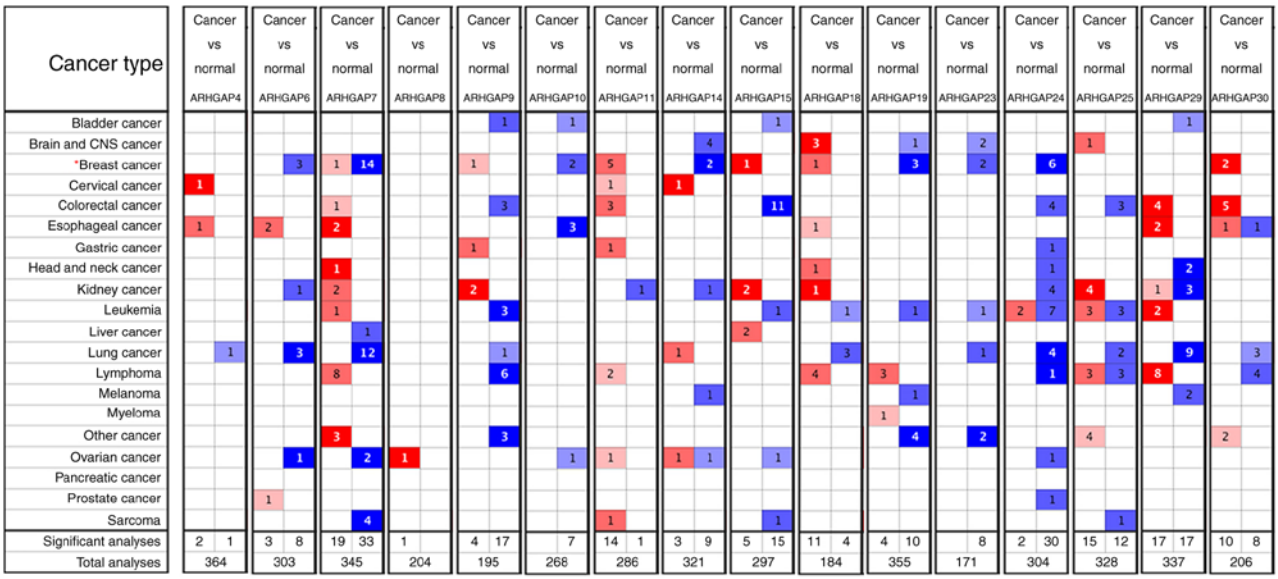

Figure 1. Expression of *ARHGAP* family genes in 20 common types of cancer vs. corresponding normal tissues in the Oncomine database. P≤0.0001, fold change ≥2, gene rank ≥ top 10%. Red and blue represent the numbers of datasets with statistically significantly (P<0.05) upregulated or downregulated *ARHGAP* family gene mRNA expression, respectively. *ARHGAP*, Rho GTPase-activating protein.

cBioPortal online database. *ARHGAP23* and *39* were connected to *ARHGAP9*, *15*, *19* and *30*. Of note, *ARHGAP9*, *15* and *19* also interacted with *ARHGAP30* (Fig. 6).

Discussion

Rho-like GTPases are involved in various cell functions and are negative regulators of Rho proteins; RhoGAPs serve significant roles in multiple aspects of tumor biology including gene expression, cell cycle, survival, migration and invasion (3,6). *ARHGAP*, a group of family genes encoding RhoGAPs that switch off Rho-like GTPases, have been extensively studied since the discovery that genetic alterations of *ARHGAP* family genes are responsible for breast cancer biogenesis (2,3). However, several challenges remain regarding the identification of suitable and novel biomarkers for precision treatment and prognosis. To best of our knowledge, this is the first report to characterize specific *ARHGAP* genes with prognostic value

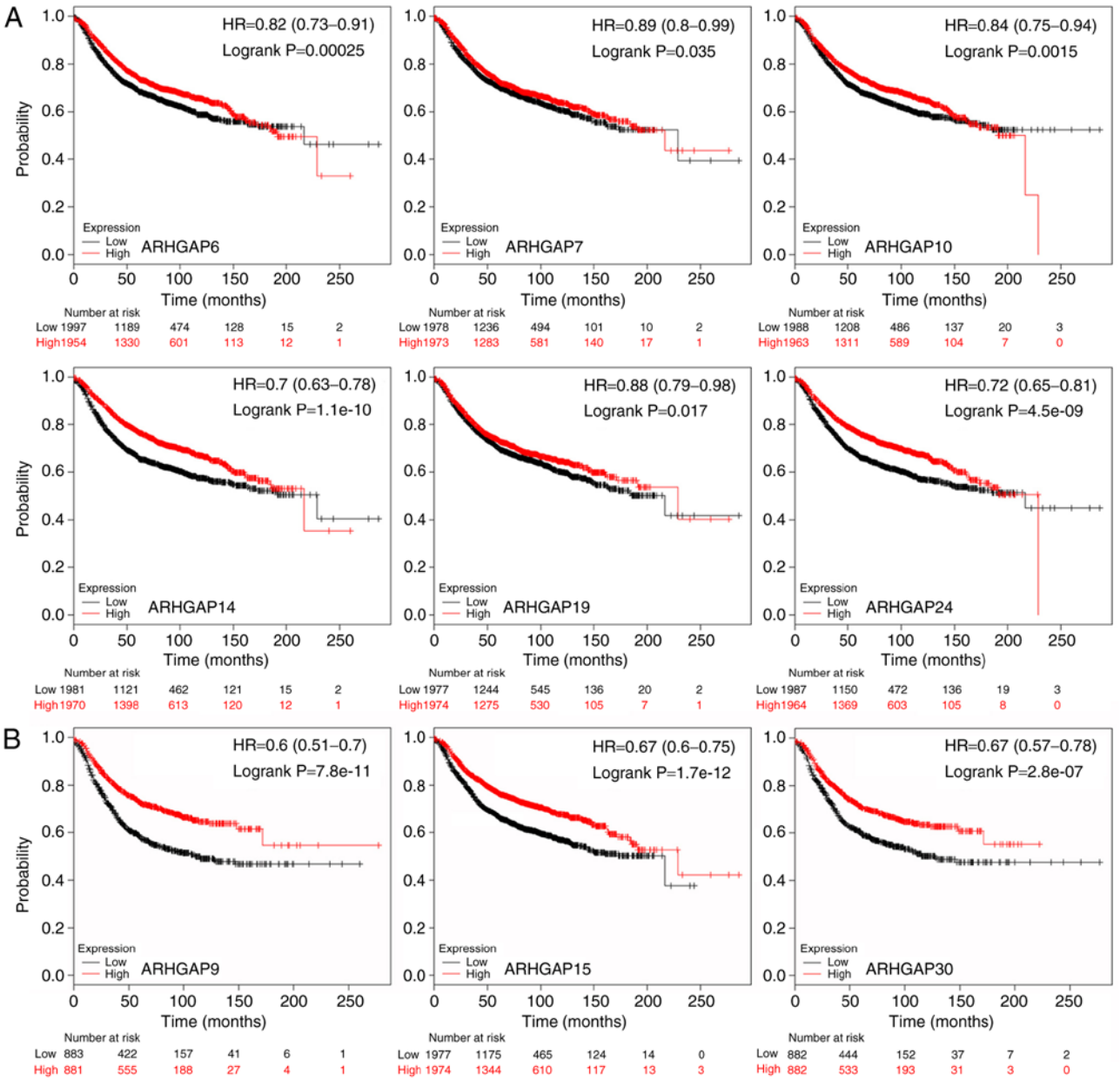

Figure 2. Kaplan-Meier curves of RFS based on *ARHGAP* family gene mRNA levels. (A) Patients with breast cancer with low expression (black) of *ARHGAP6*, *7*, *10*, *14*, *19* and *24* exhibited worse RFS compared with patients in the respective high expression groups. (B) Patients with breast cancer with high expression (red) of *ARHGAP9*, *15* and *30* exhibited better RFS compared with patients in the respective low expression groups. RFS, relapse-free survival; *ARHGAP*, Rho GTPase-activating protein; HR, hazard ratio.

and biological function in breast cancer using bioinformatics analysis.

Although the involvement of ARHGAP in cancer progression is becoming increasingly apparent, the association between *ARHGAP* expression and most cancer types has not been fully characterized. Therefore, a thorough study to determine the expression of *ARHGAP* in different types of cancer is needed. Researchers and clinicians are increasingly regarding *ARHGAP* family genes as important clinical and predictive therapeutic information. In the present study, a total of 16 ARHGAP family genes were evaluated in breast cancer samples and compared with those in normal tissues using the Oncomine database; the results demonstrated that *ARHGAP6*, *7*, *10*, *14*, *19*, *23* and *24* were downregulated, *ARHGAP9*, *11*, *15*, *18* and *30* were upregulated, and *ARHGAP4*, *8*, *25* and *29* exhibited no dysregulation. The number of significant unique analyses was small for *ARHGAP6*, *9*, *10*, *14*, *15*, *23* and *30* or even zero in *ARHGAP4*, *8*, *25* and *29*; however, bioinformatics analysis was performed using all genes to identify several suitable and novel biomarkers among *ARGHAP* family genes. The results of the Kaplan-Meier survival analysis demonstrated that reduced *ARHGAP6*, *7* and *19* were associated with poor RFS and OS, whereas increased *ARHGAP9*, *15* and *30* were associated with preferable RFS and OS. In addition, bc-GenExMiner online software provided metastatic relapse data, which revealed that*ARHGAP9*, *15*, *18*, *19*, *25* and *30* were associated with favorable prognosis, whereas high expression levels of *ARHGAP11A* and *14* exerted negative effects on patient prognosis. Therefore, *ARHGAP9*, *15*, *19* and *30* were identified as potential prognostic targets for

Table II. Prognostic association between *ARHGAP* family gene expression in breast cancer and overall survival based on Kaplan-Meier Plotter analysis.

Gene name	Cut-off value	Expression (range of probe)	P-value	HR (95% CI)	N
ARHGAP4	120	10-699	0.0670	0.82 (0.66-1.01)	1,402
ARHGAP6	157	3-3919	0.0150	0.77 (0.62-0.95)	1,402
ARHGAP7	1,031	37-10272	0.0100	0.76 (0.61-0.94)	1,402
ARHGAP8	850	7-8528	0.6000	1.06 (0.85-1.31)	1,402
ARHGAP9	414	41-3927	0.0072	0.65 (0.47-0.89)	626
ARHGAP10	298	21-1124	0.6300	1.05 (0.85-1.31)	1,402
ARHGAP11A	46	1-806	0.7200	1.04 (0.84-1.29)	1,402
ARHGAP14	216	6-1540	0.0550	0.81 (0.65-1.00)	1,402
ARHGAP15	363	4-4586	>0.0001	0.61 (0.49-0.76)	1,402
ARHGAP18	170	5-1189	0.0660	0.75 (0.55-1.02)	626
ARHGAP19	235	16-1078	0.0003	0.67 (0.54-0.83)	1,402
ARHGAP23	219	9-4750	0.1300	1.27 (0.93-1.74)	626
ARHGAP24	115	5-1758	0.4500	0.92 (0.74-1.14)	1,402
ARHGAP25	172	7-2335	0.0006	0.68 (0.55-0.85)	1,402
ARHGAP29	126	2-1388	0.0250	0.70 (0.51-0.96)	626
ARHGAP30	470	21-2542	0.0016	0.60 (0.44-0.83)	626

ARHGAP, Rho GTPase-activating protein; HR, hazard ratio; 95% CI, 95% confidence interval.

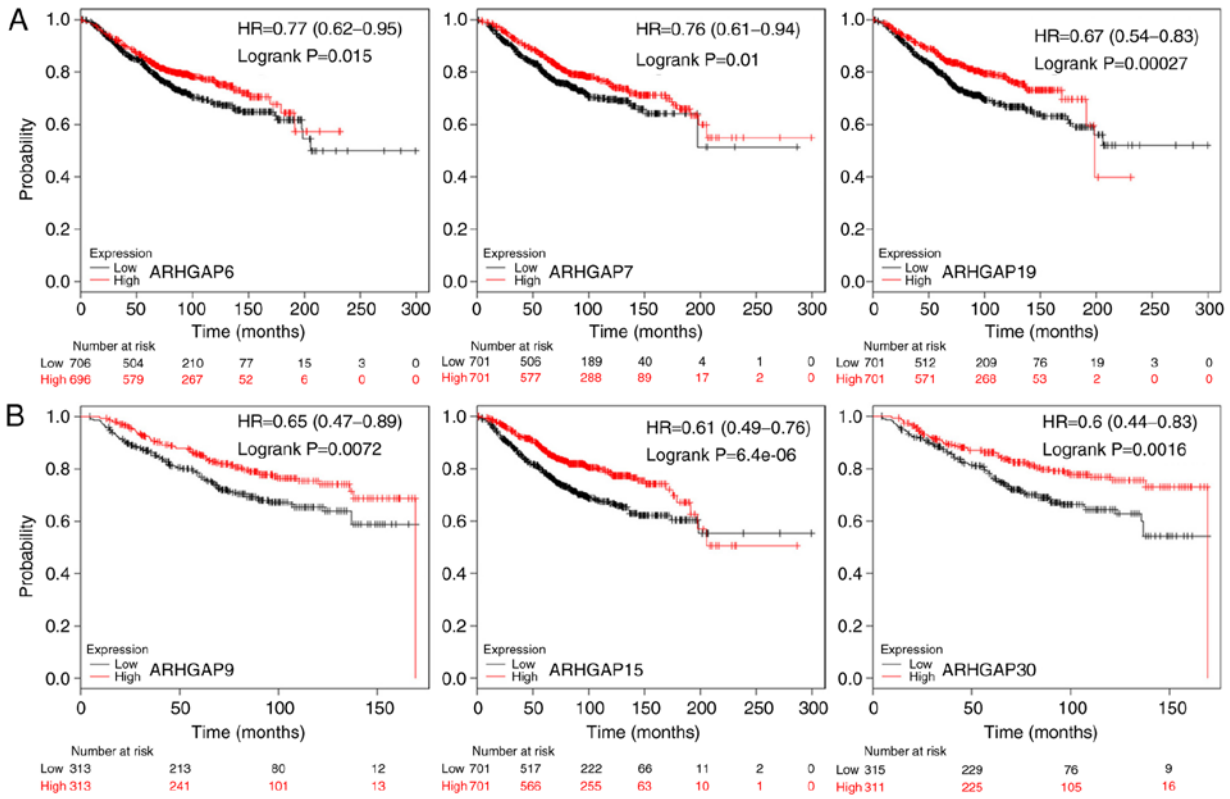

Figure 3. Kaplan-Meier curves of OS based on *ARHGAP* family gene mRNA levels. (A) Patients with breast cancer with low expression (black) of *ARHGAP6*, *7*, *10*, *14*, *19* and *24* exhibited worse OS compared with patients in the respective high expression groups. (B) Patients with breast cancer with high expression (red) of *ARHGAP9*, *15* and *30* exhibited better OS compared with patients in the respective low expression groups. OS, overall survival; *ARHGAP*, Rho GTPase-activating protein; HR, hazard ratio.

breast cancer by comparing databases and the overlapped genes.

ARHGAP9, which is a mitogen-activated protein kinase-docking protein, inhibits mitogen-activated protein kinase 1

Table III. Prognostic association *ARHGAP* family gene expression in breast cancer between and metastatic relapse based on bc-GenExMiner analysis.

Gene name	P-value	HR	95% CI	N	Metastatic relapse
ARHGAP4	0.4483	0.98	0.92-1.04	3,825	993
ARHGAP6	0.4608	0.97	0.89-1.06	3,500	907
ARHGAP7	0.1422	0.94	0.87-1.02	3,924	1,023
ARHGAP8	0.1410	1.09	0.97-1.21	1,345	340
ARHGAP9	0.0244	0.89	0.81-0.99	1,721	438
ARHGAP10	0.3605	1.03	0.96-1.11	3,456	878
ARHGAP11A	0.0099	1.09	1.02-1.17	3,826	993
ARHGAP14	<0.0001	1.20	1.11-1.29	3,610	911
ARHGAP15	<0.0001	0.84	0.79-0.89	3,701	966
ARHGAP18	<0.0001	0.82	0.75-0.90	2,016	539
ARHGAP19	0.0006	0.89	0.84-0.95	3,923	1,023
ARHGAP23	0.0574	1.15	1.00-1.33	1,425	358
ARHGAP24	0.1126	0.94	0.88-1.01	3,845	1,006
ARHGAP25	0.0009	0.89	0.83-0.95	3,826	993
ARHGAP29	0.0649	0.94	0.88-1.00	3,925	1,023
ARHGAP30	0.0490	0.90	0.81-1.00	1,862	491

ARHGAP, Rho GTPase-activating protein; HR, hazard ratio; 95% CI, 95% confidence interval.

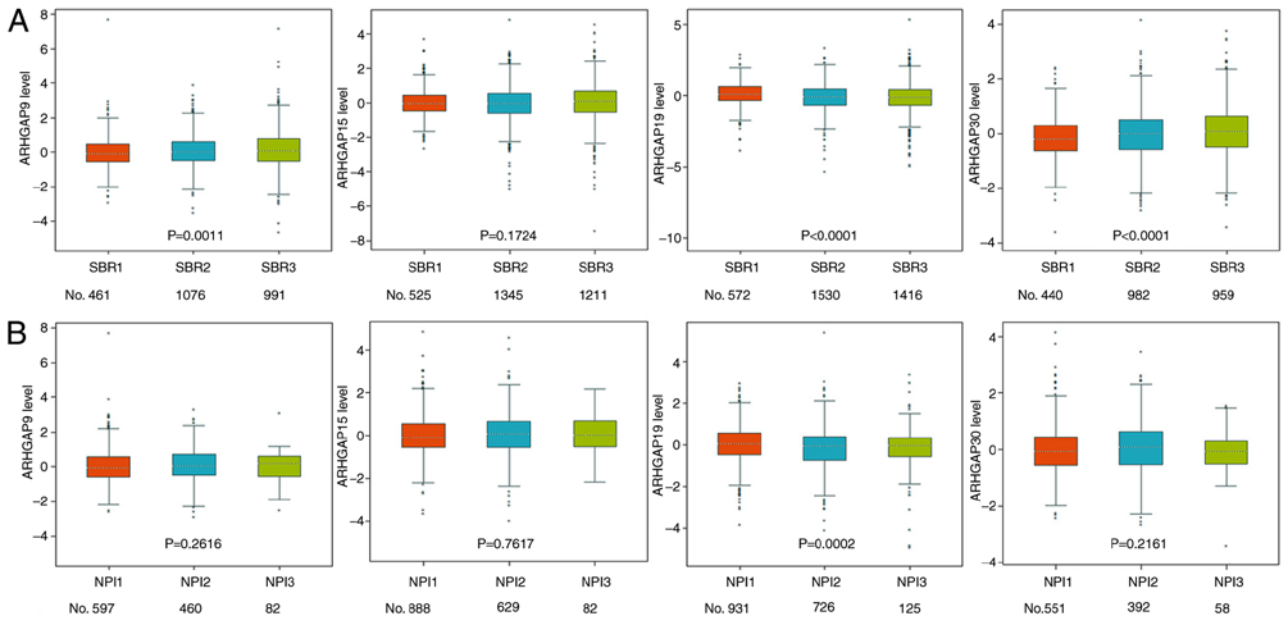

Figure 4. ARGHAP family gene expression in patients with different SBR grades and NPI values. The association between mRNA expression levels of *ARHGAP915*, *19* and *30* and (A) SBR or (B) NPI value based on the bc-GenExMineronline software. *ARHGAP*, Rho GTPase-activating protein; SBR, Scarff-Bloom-Richardson grade; NPI, Nottingham prognostic index.

and p38α activation through WW domain binding (15,16). *ARHGAP9* has been demonstrated to suppress the migration and invasion of hepatocellular carcinoma cells by upregulating forkhead box J2 and E-cadherin (17). In addition, down-regulated *ARHGAP9* is associated with breast cancer risk and suppresses the proliferation, migration and invasion of breast cancer cells (18). The present study also demonstrated that high levels of *ARHGAP9* were associated with RFS and OS advantages in patients with breast cancer patients and may be a promising prognostic factor.

ARHGAP15, a Rac-specific RhoGAP described in 2003, serves a dual role in inhibiting small GTPase signaling (19,20). A previous study has demonstrated that decreased expression of *ARHGAP15* promotes the development of colorectal cancer through the PTEN/AKT/forkhead box protein O1 axis (21). In addition, *ARHGAP15* is an androgen-induced

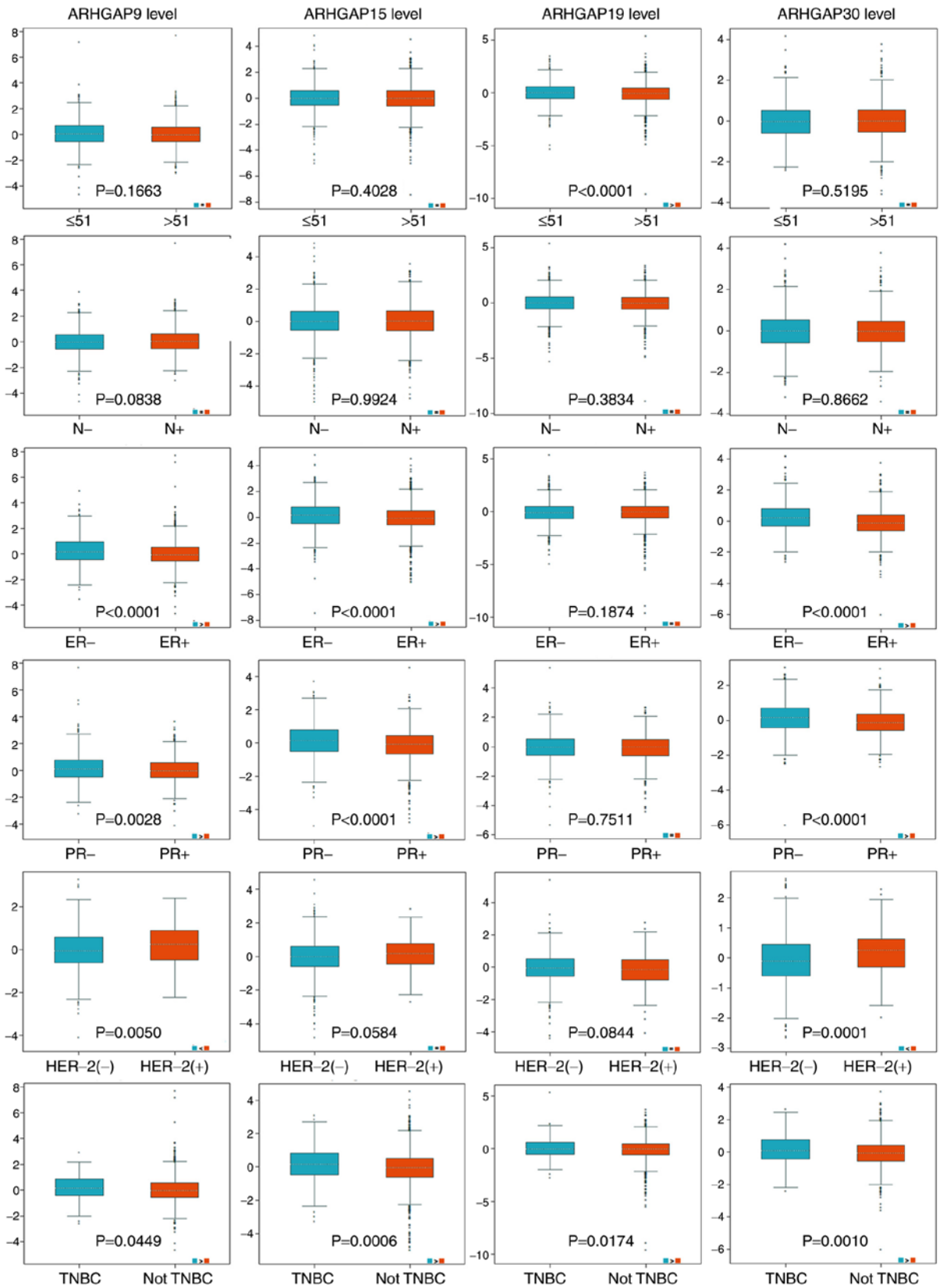

Figure 5. The association between mRNA expression of *ARHGAP9*, *15*, *19* and *30* and clinicopathological characteristics of patients with breast cancer based on the bc-GenExMiner online software. *ARHGAP*, Rho GTPase-activating protein; N, node status; ER, estrogen receptor; PR, progesterone receptor; HER2, epidermal growth factor receptor-2; TNBC, triple-negative breast cancer.

gene and serves an antitumor function associated with the Rac1 pathway (5). These results, along with the results of the survival analysis based on *ARHGAP15* expression levels in the present study, suggested that *ARHGAP15* may serve as a tumor suppressor during breast cancer progression and metastasis.

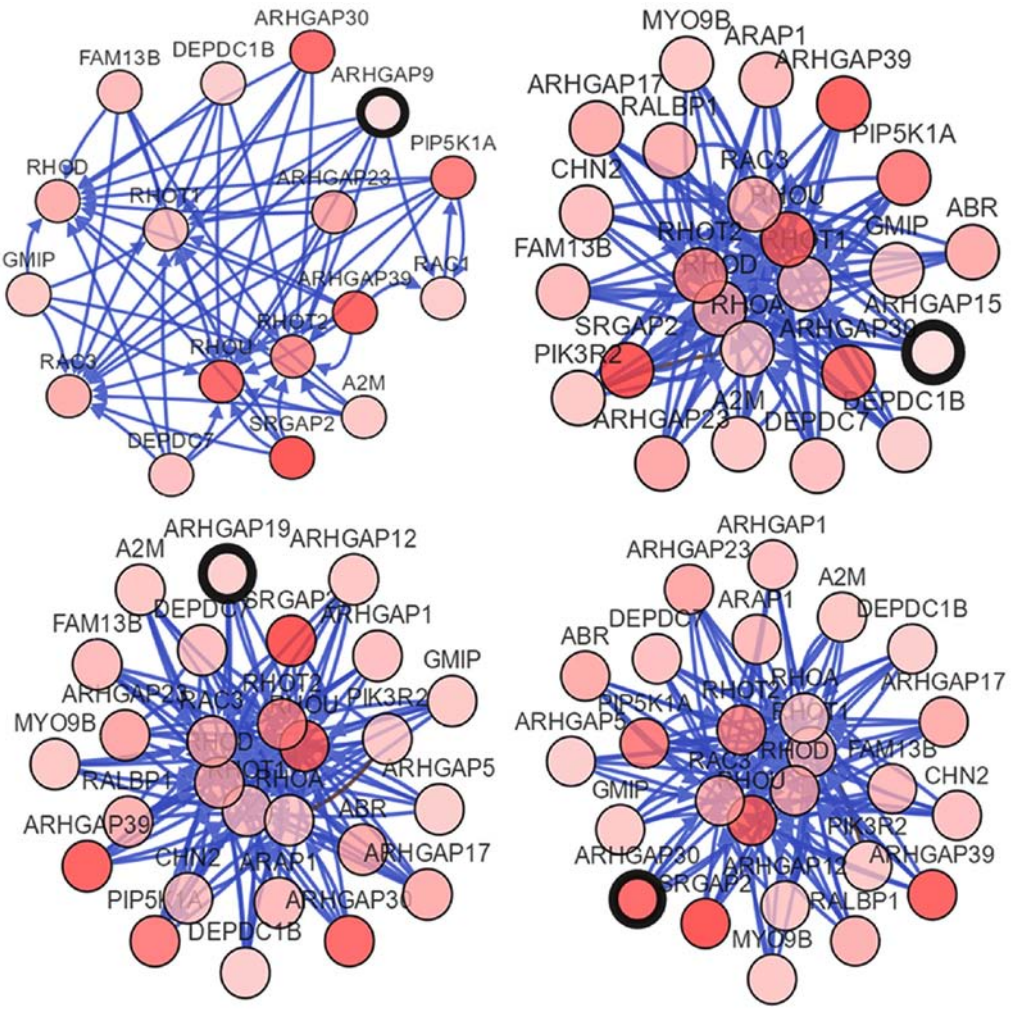

Figure 6. Gene networks of *ARHGAP9*, *15*, *19* and *30* constructed using the cBioPortal online database.

ARHGAP30, a Rac1- and RhoA-specific RhoGAP, is a Wrch-1-interacting protein involved in actin dynamics and cell adhesion (22). *ARHGAP30* is required for p53 acetylation and functional activation in colorectal cancer; ectopic expression of *ARHGAP30* induced p53 activation and efficiently suppressed tumor growth in an *in vivo* xenograft study (23). Therefore, *ARHGAP30* may be a prognostic marker and a potential therapeutic target for cancer, which is consistent with the results of the bioinformatics analysis in the present study.

ARHGAP19 is predominantly expressed in hematopoietic cells and controls cytokinesis and chromosome segregation in T lymphocytes (24). In the present study, low *ARHGAP19* expression levels were associated with poor RFS and OS. In addition, bc-GenExMiner software provided metastatic relapse data, which demonstrated that high *ARHGAP19* expression was associated with favorable metastatic relapse-free survival. These results, along with the observation of decreased *ARHGAP19* expression in patients with high-grade tumors compared with patients with low-grade tumors, opposed the result that *ARHGAP19* expression levels were elevated in patients with triple-negative breast cancer. Since there is limited information on *ARHGAP19* expression in breast cancer, further studies are necessary to determine how *ARHGAP19* is involved in breast cancer biology and progression.

Patients with ER- or PR-positive breast cancer are often treated with drugs that block estrogen effects and generally exhibit good prognosis with compared with ER- or PR-negative patients. The results of the present study demonstrated that *ARHGAP9*, *15* and *30* exhibited lower expression in ER- or PR-positive cancer compared with ER- or PR-negative cases, which contradicted the earlier conclusion that *ARHGAP9*, *15* and *30* acts as tumor suppressors. This difference may be due to the *ARHGAP* expression profiles in the dataset being primarily from RNA sequences, as well as due to differences in the clinical samples and experimental conditions. Further investigations are required to precisely elucidate the physiological relevance of *ARHGAP9*, *15*, *19* and *30*.

In conclusion, the results of the present study suggested that *ARHGAP9*, *15*, *19* and *30*, compared with other ARHGAP family genes, might be promising targets with prognostic value and biological function for precision treatment in patients with breast cancer. Further experiments and clinical trials are required to validate the value of these genes.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WXC, ML, LC, YLZ and HD conceived and designed the experiments. WXC, LC and QQ performed the experiments. QQ, LYX and LS analyzed the data. YLZ and HD contributed to reagents, materials and analysis tools. WXC and ML wrote the manuscript. HD gave final approval of the version to be published.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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