JBUON 2020; 25(6): 2537-2545
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Detection of critical genes associated with poor prognosis in breast cancer via integrated bioinformatics analyses

Donghua Liu[1,2], Jinfeng Zhang[1,2], Liang Li[1,2], Qiuming Wang[1,2], Yongquan Lan[1,2]

[1]Department of Medical Oncology 3, The Meizhou People's Hospital, Meizhou, China. [2]Guangdong Provincial Key Laboratory of Precision Medicine and Clinical Translation Research of Hakka Population, Meizhou, China.

Summary

Purpose: *To explore the potential prognostic differentially expressed genes (DEGs) in breast cancer (BC) via bioinformatic analysis and elucidate possible mechanisms underlying the effects on BC progression.*

Methods: *Three datasets (GSE21422, GSE31192 and GSE42568) were extracted from Gene Expression Omnibus (GEO) information bank. The GEO2R tool and Venn diagram softwares were used for data filtration, GO (Gene Ontology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) analysis method were used to functionally annotate the selected DEGs. Protein-protein interaction (PPI) network of the selected DEGs was visualized by Cytoscape. Lastly, Kaplan–Meier (KM) plotter and Profiling Interactive Analysis (GEPIA) were employed to validate the values of the DEGs.*

Results: *A total of 46 up-regulated and 65 down-regulated DEGs were identified. Of these, up-regulated DEGs were enriched in pathways related to cancer, p53 signaling pathway, ECM-receptor interaction, PI3K-Akt signaling pathway, while down-regulated DEGs were enriched in pathways involved in PPAR signaling pathway, proteoglycans in cancer, focal adhesion. 24 genes were selected from the PPI network analysis by Molecular Complex Detection (MCODE), and 20 vital genes were found to be correlated to poorer overall survival (OS) rates in BC. The prognostic values of these genes were validated by both KM and GEPIA. Finally, the CCNE2, CCNB1 and RRM2 genes were found to be markedly enriched in the p53 signaling pathway through the DAVID analysis.*

Conclusion: *This study revealed that the p53 signaling pathway could be an important pathway in BC progression. The three p53-related genes CCNE2, CCNB1 and RRM2 may represent candidate therapeutic gene targets for the treatment of BC.*

Key words: *breast cancer, differentially expressed genes, overall survival, bioinformatics*

Introduction

Breast cancer (BC) remains the leading cause of cancer in females across the globe. 2018 saw a total of 2.1 million new BC cases. BC also represents the primary cause of cancer-related mortality in females in more than one hundred countries [1]. BC is a genetically heterogeneous disease. Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2(HER-2)are well known factors that are predictive for response to treatment and prognosis in BC. Significant variation has been demonstrated between different molecular subtypes of BC in terms of disease prognosis and treatment efficacy [2,3]. However, despite the availability of molecular analysis techniques, not all women have benefited equally [4]. A striking divergence in mortality trend has already appeared and continues to widen, especially between black and white women [5]. Hence, more dependable prognostic factors should be investigated in order to offer an individual precise and effective treatment.

Gene chips have been proven to be a practical and highly specific genetic testing tool that works

Corresponding author: Jinfeng Zhang, MD. [1]Department of Medical Oncology 3, The Meizhou People's Hospital, Meizhou, China. [2]Guangdong Provincial Key Laboratory of Precision Medicine and Clinical Translation Research of Hakka Population, Meizhou, China.
Tel: +86 0753-2131710, Email: jfzhang1980@hotmail.com
Received: 04/03/2020; Accepted: 11/04/2020

through identification of pre-selected deferentially expressed genes [6]. Gene chips specific to a myriad of human cancers have already been developed [7-9]. Bioinformatic technology is the incorporation of computer and biological software, and is increasingly used to predict molecules or pathways directly related to BC, which may enhance the rates of early diagnosis in BC.

In this study, GEO-derived gene microarray datasets are subjected to bioinformatic screening to determine to search for potential genes and underlying pathways related to BC progression. The results of our study suggested that three genes (CCNE2, CCNB1 and RRM2) may function as candidate biomarkers for therapeutic and prognostic purposes in BC.

Methods

Microarray data information and processing

Three datasets (GSE21422, GSE31192 and GSE42568) were extracted from the GPL570 platform. GEO2R analysis with the GEO database (https://www.ncbi.nlm.nih.gov/geo/) was used to contrast differences in mRNA expression between BC and normal breast tissues. Each dataset contained 14 BC tissues and 5 normal breast tissues, 20 BC tissues and 13 control breast tissues and 104 BC tissues and 17 normal breast tissues, respectively.

DEGs between BC and normal breast tissues were grouped as those that were up-regulated and those that were down-regulated based on cutoff thresholds of $|logFC| > 2$ and p value < 0.05. An online Venn diagram software (http://bioinformatics.psb.ugent.be/webtools/Venn/) was used to illustrated DEGs that were common across all 3 datasets.

GO and KEGG analysis

Gene ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were used to explore the biological properties and potential signaling pathways that the DEGs were involved in. DAVID (https://david.ncifcrf.gov/), an online bioinformatic tool, was used to illustrate the functional enrichment analyses [10]. $P<0.05$ was determined as significant.

Human PPI analysis

A DEG PPI was constructed using the Search Tool for the Retrieval of Interacting Genes (STRING, https://

Table 1. Down or up regulated genes in breast cancer tissues compared to normal controls

DEGs	*Genes name*
Up-regulated	IQGAP3 TPX2 S100P CCNB1 HMGB3 ASPM INHBA IFI6 KNL1 ANLN BIRC5 UBE2C CDK1 CEP55 RRM2 SLC35F6///CENPA TOP2A GJB2 COMP CCNE2 FGFR3 AURKA FN1 DLGAP5 CXCL10 LEF1 DTL SULF1 SPP1 GPRC5A COL10A1 LRRC15 MELK COL11A1 CTHRC1 UHRF1 KIAA0101 NUF2 PRR11 NEK2 CENPF NUSAP1 CKS2 ECT2 MMP9 MMP11
Down-regulated	IGF1 PPP1R14A ITIH5 BTNL9 HOXA10-HOXA9///MIR196B///HOXA9 MEOX1 GHR CRYAB CD36 TF DCLK1 PCDH18 PIR-FIGF///FIGF HLF SPRY2 TSHZ2 FHL1 PLAGL1 TMEM47 SEMA3G PDGFD EDNRB EGFLAM CD300LG S100B RBP7 MME LOC100506558///MATN2 MAGI2-AS3 COPG2IT1 ARHGAP20 NR3C2 SCARA5 IGSF10 NTRK2 SDPR SORBS1 LIFR PALMD LDB2 CAV1 ITM2A SRPX ABCA9 TWIST2 APCDD1 FMO2 MIR548F5///MAB21L1 RBMS3 TGFBR3 MEST LPL FABP4 GPC3 DMD NOVA1 CAV2 GSTM5 SOBP MAMDC2 ADAMTS5 C2orf40 SFRP1 COL6A6 GULP1

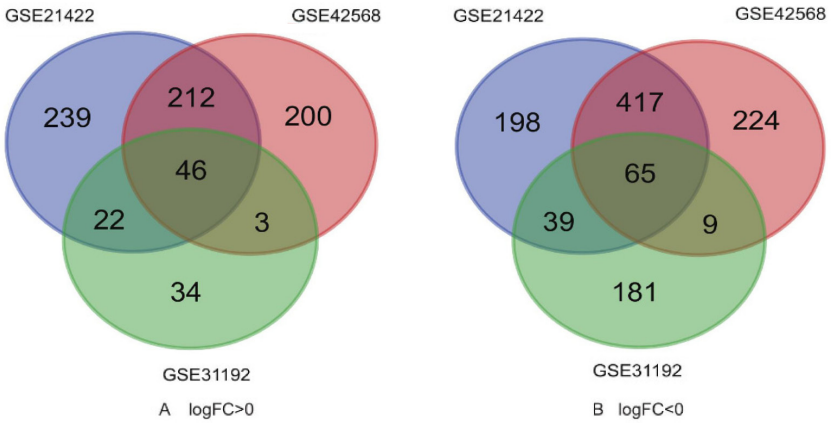

Figure 1. The Venn diagrams of three datasets including 46 shared up-regulated DEGs and 65 shared down-regulated DEGs.

string-db.org/) database, which is an online tool that works by highlighting interacting genes and proteins. Cytoscape was performed used for protein-protein interaction (PPI) network visualization, and the MCODE plug in Cytoscape was used to identify key clustering modules.

Survival analysis

The association between DEGs and BC overall survival was analyzed with Kaplan-Meier plots (https://kmplot.com/analysis/) that included hazard ratios (HRs) and 95% confidence intervals. The GEPIA website(http://gepia.cancer-pku.cn/) was used to validate key DEGs, with a log rank p value of less than 0.05, used as the threshold of statistical significance.

Results

Identification of DEGs in BC

A total of 138 breast tumor tissues as well as 35 non-cancer tissues were analyzed in our study,

Table 2. GO analysis of DEGs in breast cancer.

Expression	*category*	*Term*	*Count*	*%*	*p value*	*FDR*
Up-regulated	GOTERM_BP_DIRECT	GO:0035987~endodermal cell differentiation	4	0.05	5.94E-05	0.08
	GOTERM_BP_DIRECT	GO:0051726~regulation of cell cycle	4	0.05	1.00E-02	1.4
	GOTERM_BP_DIRECT	GO:0090307~mitotic spindle assembly	3	0.03	2.00E-02	3.56
	GOTERM_BP_DIRECT	GO:0043154~negative regulation of cysteine-type endopeptidase activity involved in apoptosis process	3	0.03	3.90E-02	5.41
	GOTERM_BP_DIRECT	GO:0021873~forebrain neuroblast division	2	0.02	6.00E-03	8.08
	GOTERM_BP_DIRECT	GO:0007155~cell adhesion	4	0.05	9.00E-03	11.89
	GOTERM_CC_DIRECT	GO:0030496~midbody	4	0.06	8.72E-05	0.09
	GOTERM_CC_DIRECT	GO:0005876~spindle Microtubule	4	0.05	1.11E-04	0.11
	GOTERM_CC_DIRECT	GO:0005578~proteinaceous extracellular matrix	5	0.06	1.00E-03	1.35
	GOTERM_CC_DIRECT	GO:0005634~nucleus	16	0.21	2.00E-03	2.18
	GOTERM_MF_DIRECT	GO:0008301~DNA binding, bending	3	0.03	3.26E-04	0.33
	GOTERM_MF_DIRECT	GO:0003682~chromatin Binding	5	0.06	8.00E-03	8.07
	GOTERM_MF_DIRECT	GO:0008201~heparin Binding	3	0.04	2.30E-02	21.6
Down-regulated	GOTERM_BP_DIRECT	GO:0031623~receptor internalization	3	0.03	8.00E-03	12.3
	GOTERM_BP_DIRECT	GO:0007275~multicellular organism development	7	0.07	6.00E-03	9.92
	GOTERM_BP_DIRECT	GO:0046326~positive regulation of glucose import	3	0.03	4.00E-03	6.29
	GOTERM_BP_DIRECT	GO:0008284~positive regulation of cell proliferation	7	0.07	4.00E-03	5.92
	GOTERM_BP_DIRECT	GO:0007517~muscle organ development	4	0.04	3.00E-03	4.54
	GOTERM_BP_DIRECT	GO:0001954~positive regulation of cell-matrix adhesion	3	0.03	2.00E-03	3.44
	GOTERM_CC_DIRECT	GO:0009986~cell surface	11	0.11	7.20E-06	0.008
	GOTERM_CC_DIRECT	GO:0045121~membrane Raft	7	0.07	4.81E-05	0.05
	GOTERM_CC_DIRECT	GO:0043235~receptor Complex	5	0.05	7.13E-04	0.82
	GOTERM_CC_DIRECT	GO:0005615~extracellular space	13	0.13	7.13E-04	1.07
	GOTERM_CC_DIRECT	GO:0005887~integral component of plasma membrane	13	0.13	1.00E-03	1.64
	GOTERM_CC_DIRECT	GO:0005578~proteinaceous extracellular matrix	6	0.06	1.00E-03	1.84
	GOTERM_CC_DIRECT	GO:0005576~extracellular Region	12	0.12	1.10E-02	12.73
	GOTERM_MF_DIRECT	GO:0008201~heparin Binding	4	0.04	1.10E-02	13.38
	GOTERM_MF_DIRECT	GO:0050998~nitric-oxide synthase binding	2	0.02	4.00E-02	39.44
	GOTERM_MF_DIRECT	GO:0004222~ metalloendopeptidase activity	3	0.03	4.40E-02	42.04

and 1238, 1176 and 181 DEGs were extracted from GSE21422, GSE42568 and GSE31192 datasets, respectively. The commonly DEGs in the three datasets are shown via Venn diagram software (Table 1 & Figure 1), of which 46 commonly DEGs were up-regulated genes and 65 commonly DEGs were down-regulated genes in BC.

GO and KEGG pathway analysis of DEGs in BC

The DAVID software was used to explore the biological process (BP), molecular function (MF) and cellular component (CC) (Table 2). Up-regulated DEGs in BP were significantly enriched in endodermal cell differentiation, regulation of cell cycle, mitotic spindle assembly, and negative regulation of cysteine-type endopeptidase activity involved in apoptosis process, forebrain neuroblast division and cell adhesion. Down-regulated DEGs were enriched in receptor internalization, multicellular organism development, positive regulation of glucose import, positive regulation of cell proliferation, muscle organ development and positive regulation of cell-matrix adhesion. For MF, up-regulated DEGs were enriched in in DNA binding, bending, chromatin binding, heparin binding. Down-regulated DEGs were enriched in heparin binding, nitric-oxide synthase binding, metalloendopeptidase activity. With respect to the CC, up-regulated DEGs were enriched in midbody, spindle microtubule, proteinaceous extracellular matrix, nucleus, while down-regulated DEGs were enriched primarily in cell surface, membrane raft, receptor complex, extracellular space, integral component of plasma membrane, proteinaceous extracellular matrix, and extracellular region.

Table 3. KEGG pathway analysis of DEGs in breast cancer

DEGs	*Pathway ID*	*Name*	*Count*	*%*	*p value*	*Genes*
Up-regulated	cfa05200	Pathways in cancer	7	0.09	3.67E-04	CCNE2, FGFR3, MMP9, CKS2, LEF1, BIRC5, FN1
	cfa04115	p53 signaling pathway	4	0.05	6.27E-04	CCNE2, CCNB1, CDK1, RRM2
	cfa04512	ECM-receptor interaction	4	0.05	1.00E-03	COMP, COL11A1, SPP1, iFN1
	cfa04151	PI3K-Akt signaling Pathway	6	0.07	1.00E-03	CCNE2, FGFR3, COMP, COL11A1, SPP1, FN1
Down-regulated	hsa03320	PPAR signaling pathway	4	0.04	1.00E-03	LPL, CD36, SORBS1, FABP4
	hsa05205	Proteoglycans in cancer	5	0.05	6.00E-03	CAV2, CAV1, GPC3, IGF1, TWIST2
	hsa04510	Focal adhesion	5	0.05	6.00E-03	CAV2, CAV1, COL6A6, IGF1, PDGFD

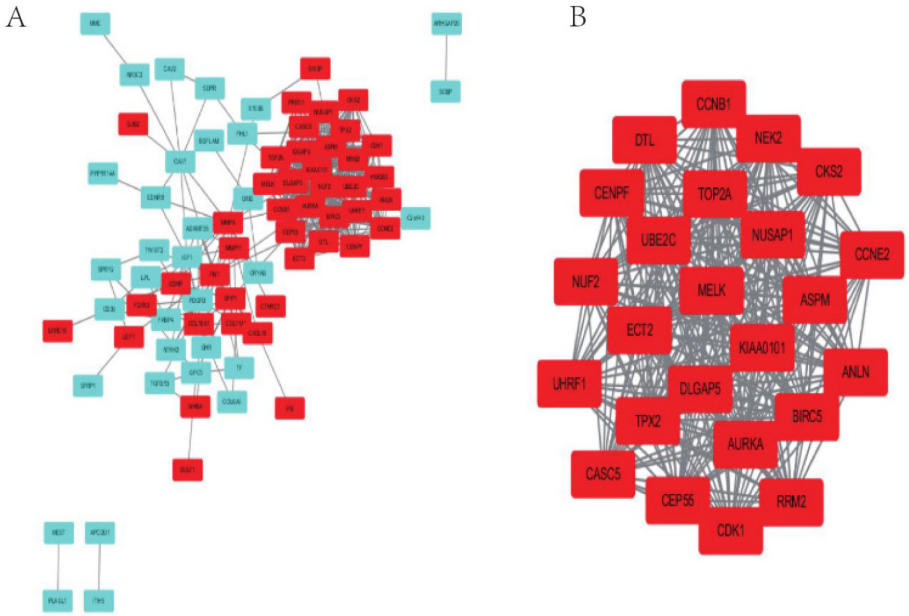

Figure 2. Shared DEGs PPI network established by STRING online database and Module analysis. The nodes indicated proteins: the edges indicated the interaction of proteins; green circles indicated down-regulated DEGs and red circles indicated up-egulated DEGs.

KEGG analysis revealed that up-regulated DEGs were particularly enriched in Pathways in cancer, p53 signaling pathway, ECM-receptor interaction, and PI3K-Akt signaling pathway. On the other hand, down-regulated DEGs were enriched in PPAR signaling pathway, proteoglycans in cancer, and focal adhesion (Table 3).

PPI and modular analysis

DEGs common across all three datasets were analyzed through the STRING online database (Figure 2A). The resultant PPI network consisted of 104 nodes and 399 edges, which was visualized with Cytoscape. Only 7 of the 111 DEGs were excluded from the PPI network. Cytotype MCODE was used to filter the core genes, revealing 24 central genes amongst the total of 104 nodes that were all from the group of up-regulated genes (Figure 2B).

Survival analysis

Kaplan-Meier analysis was performed on the selected 24 central genes. Of these, 20 genes were significantly indicative of worse prognosis and overall survival in BC (Table 4 & Figure 3). GEPIA was utilized to determine the relative expressions of these 20 genes between those with breast cancer and healthy individuals (Table 5). The results demonstrated that all 20 genes were highly expressed in BC samples in contrast to normal breast samples (Figure 4).

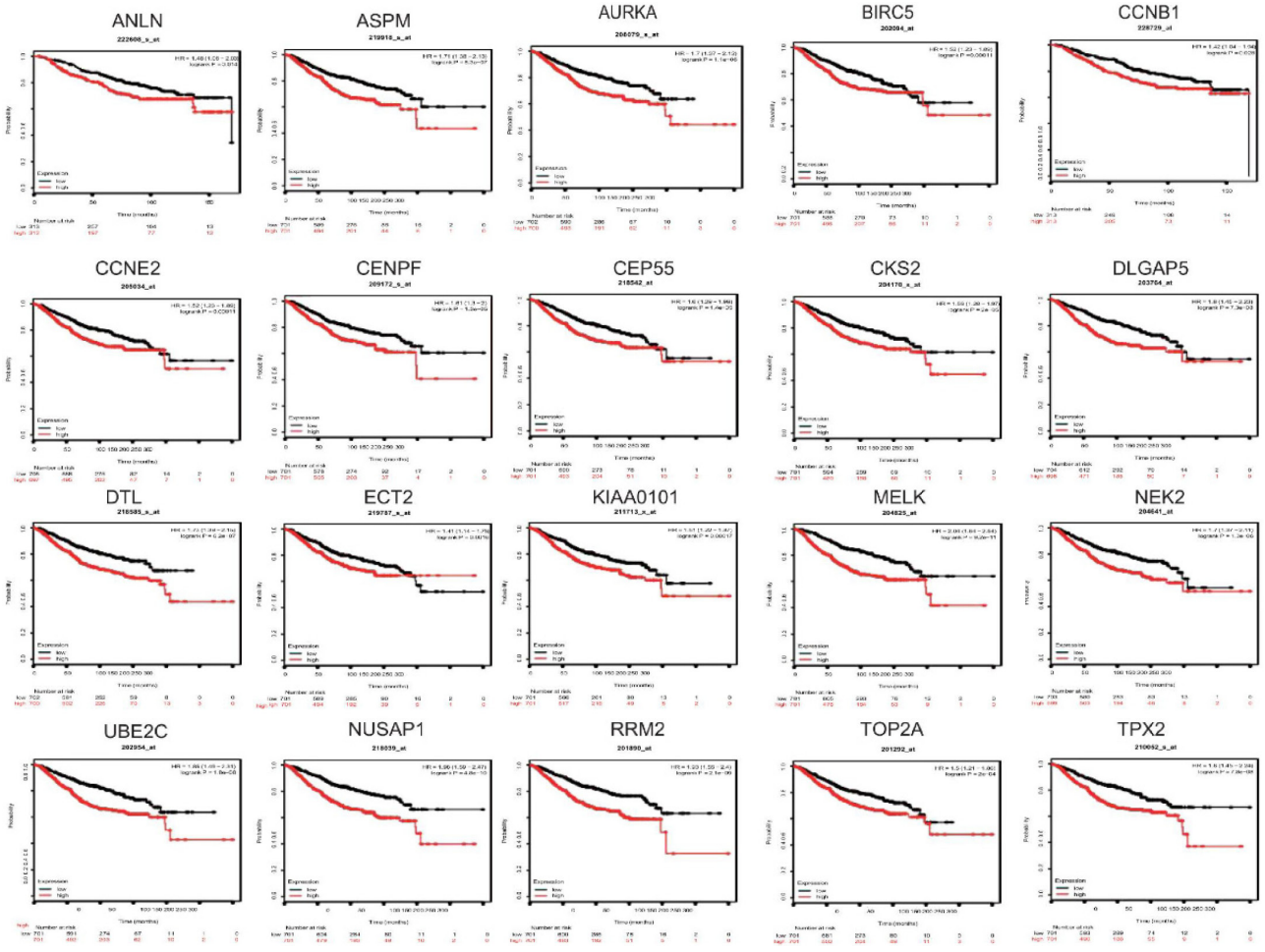

Figure 3. The Kaplan-Meier online tool hinted that 20 genes had a significantly worse survival in breast cancer.

Table 4. The prognostic analysis of the 24 key candidate genes

Category	*Genes*
Genes with significantly worse survival (p<0.05)	NUSAP1 TOP2A CEP55 KIAA0101 RRM2 BIRC5 UBE2C DTL CCNE2 DLGAP5 CCNB1 NEK2 TPX2 ECT2 CKS2 ASPM AURKA MELK ANLN CENPF
Genes without significantly worse survival (p>0.05)	CDK1 CASC5 UHRF1 NUF2

Table 5. The validation of 20 genes via GEPIA

Category	*Genes*
Genes with high expressed in BC (p<0.05)	NUSAP1 TOP2A CEP55 KIAA0101 RRM2 BIRC5 UBE2C DTL CCNE2 DLGAP5 CCNB1 NEK2 TPX2 ECT2 CKS2 ASPM AURKA MELK ANLN CENPF

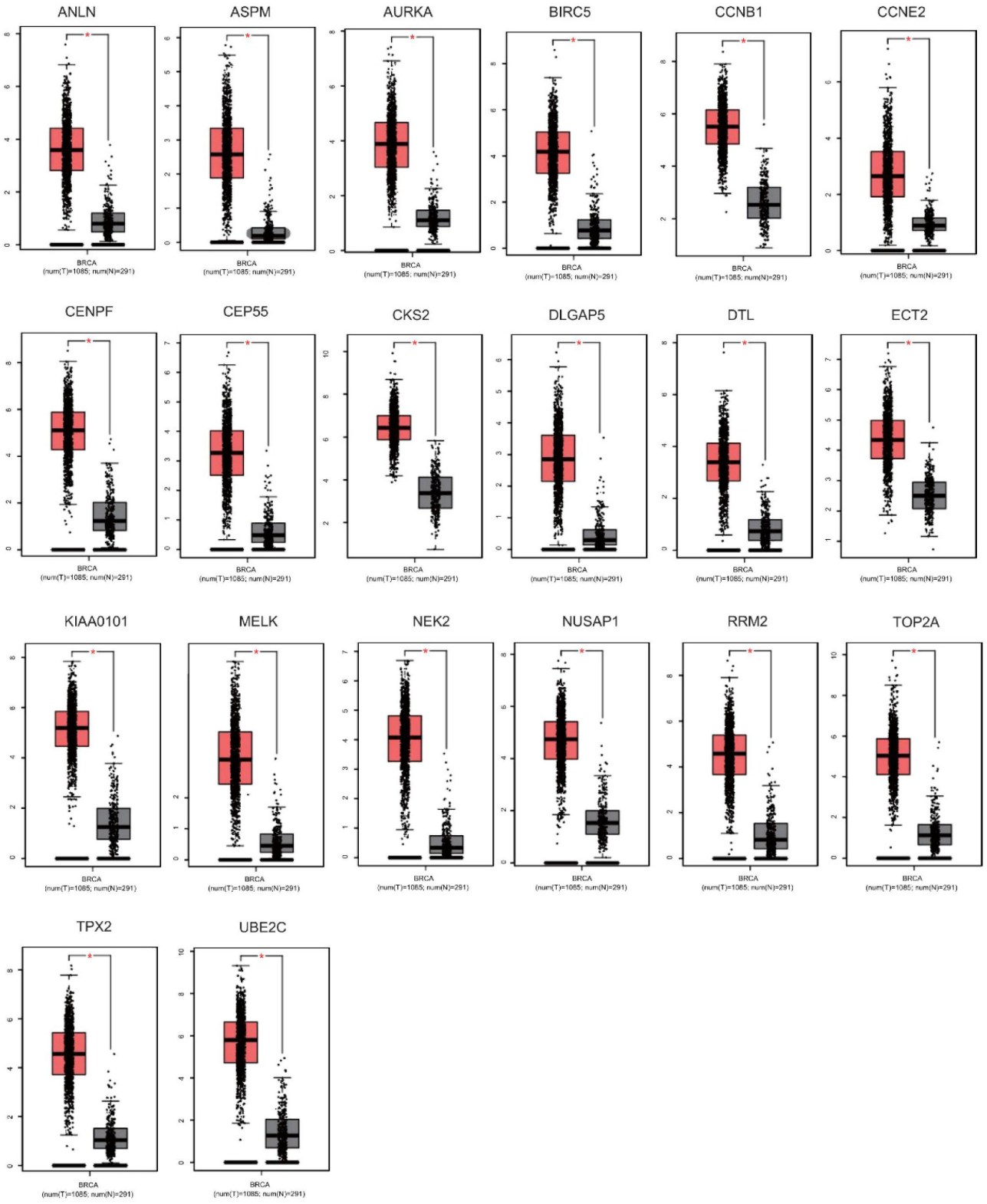

Figure 4. The GEPIA website suggested that 20 genes were highly expressed in breast cancer samples.

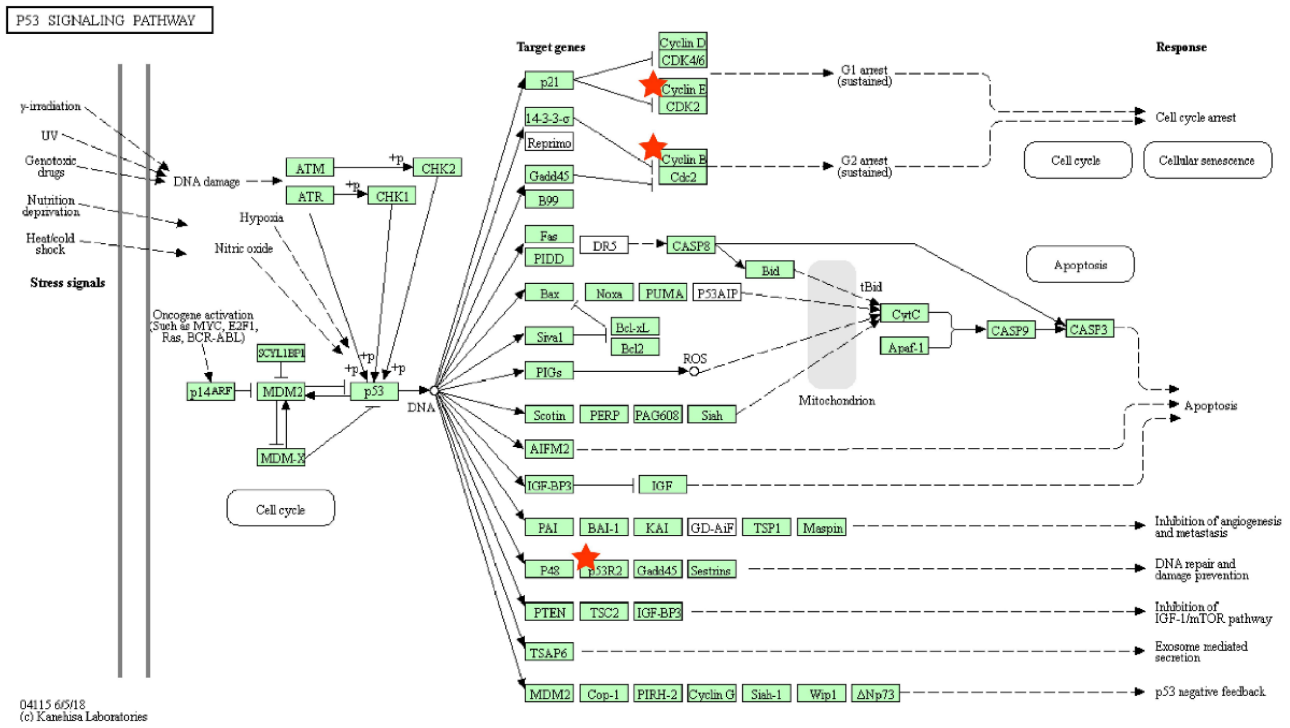

Figure 5. Re-analysis of 20 selected genes via KEGG pathway enrichment.

Table 6. Re-analysis of 20 selected genes via KEGG pathway enrichment

Pathway ID	*Name*	*Count*	*%*	*p value*	*Genes*
cfa04115	p53 signaling pathway	3	0.07	1.00E-03	CCNE2, CCNB1, RRM2
cfa05200	Pathways in cancer	3	0.07	4.20E-02	CCNE2, CKS2, BIRC5

Analysis of 20 genes related to survival on BC samples

KEGG pathway enrichment of these 20 genes was analyzed through DAVID. A final three genes (CCNE2, CCNB1 and RRM2) were found to be significantly enriched in the p53 signaling pathway (Table 6 & Figure 5).

Discussion

In the current study, we identified a total of 111 DEGs (46 and 65 up- and down-regulated, respectively) that were common amongst the three BC datasets. These DEGs were then subjected to several functional enrichment analyses. According to the BP in GO analysis, up-regulated DEGs were markedly enriched in endodermal cell differentiation, regulation of cell cycle, mitotic spindle assembly and negative regulation of cysteine-type endopeptidase activity involved in apoptosis process, forebrain neuroblast division and cell adhesion. On the other hand, down-regulated DEGs were enriched in receptor internalization, multicellular organism development, positive regulation of glucose import, positive regulation of cell proliferation, muscle organ development and positive regulation of cell-matrix adhesion. For MF, up-regulated DEGs were clustered in DNA binding, bending, chromatin binding, heparin binding. Down-regulated DEGs were enriched in heparin binding, nitric-oxide synthase binding, metalloendopeptidase activity. With respect to the CC, up-regulated DEGs were enriched in midbody, spindle microtubule, proteinaceous extracellular matrix, nucleus, while down-regulated DEGs were primarily enriched in cell surface, membrane raft, receptor complex, extracellular space, integral component of plasma membrane, proteinaceous extracellular matrix and extracellular region. A KEGG analysis uncovered that up-regulated DEGs were primarily linked to Pathways in cancer, p53 signaling pathway, ECM-receptor interaction, and PI3K-Akt signaling pathway. Down-regulated DEGs were primarily found to be in enriched in PPAR signaling pathway, Proteoglycans in cancer, and Focal adhesion. Furthermore, all jointly DEGs were used to generate a PPI network through the MCODE plug-in which revealed 24 key clustering modules.

Kaplan-Meier analysis of these 24 genes revealed 20 that were significant predictors of worse overall survival rates in BC. These results were consistent with GEPIA analysis. These 20 core genes were further subjected to DAVID analysis by KEGG pathway enrichment again, revealing a final three genes (CCNE2, CCNB1 and RRM2) involved in the p53 signal pathway that may be important prognostic markers of BC patients. Earlier studies have demonstrated an association between the dysregulation of the p53 signaling pathway and tumorigenesis [11-13].

Cyclin E2 is a member of the cyclin family encoded by the CCNE2 gene that is located on chromosome 8q22.1 [14]. CCNE2 was found to be overexpressed in both BC tissues and cells and is thought to mediate BC tumorigenesis and progression via the KCNQ1OT1/miR-145/CCNE2 axis regulated by lncRNA KCNQ1OT1 [15]. Moreover, evidence suggests synergy between CCNE2 overexpression and the c-myc gene in promoting the malignant transformation of mammary epithelial cells [16]. High CCNE2 expressions have been linked to trastuzumab resistance in HER2 positive BC [17]. CCNE2 has also been reported to be an effective prognostic marker for BC patients with negative lymph nodes [18]. Increasing evidence indicates that a higher CCNE2 expression correlates with shorter overall survival times in BC patients [19,20]. These results may be explained by the fact that CCNE2 may not only function as an oncogene, but also a promising prognostic biomarker and therapeutic target for BC, and one of the aims in our study was to confirm this hypothesis.

Another poor prognostic factor CCNB1 was found to be enriched in the p53 signaling pathway in our study. In accordance with the present results, previous studies have demonstrated that CCNB1 was associated to poorer survival in BC patients [21,22]. A 2014 study by Ding et al [23] describes a close association between CCNB1 and lymph node negative BC patients. The conclusion based on a series of experiments identifying the impacts of trastuzumab-emtansine on cyclin B1 levels, proliferation, and apoptosis, suggested that defective Cyclin B1 was shown to cause Trastuzumab-Emtansine resistance in HER2-positive BC [24]. Furthermore, Liu et al [25] suggested that CCNB1 regulated the cell cycle of BC cells through modulation of ubiquitin-specific peptidase 14. Given the scarce evidence linking CCNB1 to the p53 signaling pathway in BC, our study provides a new possibility of a biological relationship between the two.

In the present work, we also discovered that RRM2 was intimately related to the progression of BC. A notable research published in 2014 showed that RRM2 played a crucial role in AKT-induced tamoxifen resistance [26]. Both Putluri et al [27] and Shah et al [28] described a connection between RRM2 and resistance of BC to endocrine agents. Additionally, another important finding was that RRM2 was related to the doxorubicin resistance in BC, an effect that was enhanced with decreased RRM2 synthesis [29]. Chen et. al [30] suggested that the synergistic effects of RRM2 and KIF11 might affect BC progression and drug sensitivity.

There is an urgent indication for more effective prognostic markers with the increasingly high morbidity and mortality of BC. Previous studies have suggested the involvement of specific genes CCNE2, CCNB1 and RRM2 in the pathophysiology of BC; however, the underlying mechanism remains unknown.

Conclusions

Based on this study, it could conceivably be hypothesized that these three genes might be the promising biomarkers and therapeutic targets for BC. Further studies exploring the underlying mechanisms of these genes in BC are necessary in the future.

Conflict of interests

The authors declare no conflict of interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Sun W, Shang J, Zhang J, Chen S, Hao M. Correlations of DKK1 with incidence and prognosis of breast cancer. JBUON 2019;24:26-32.
3. Hao J, Lai M, Liu C. Expression of miR-335 in triple-negative breast cancer and its effect on chemosensitivity. JBUON 2019;24:1526-31.
4. Karim S, Malik IR, Nazeer Q et al. Molecular analysis of V617F mutation in Janus kinase 2 gene of breast cancer patients. Saudi J Biol Sci 2019;26:1123-8.
5. DeSantis CE, Ma J, Gaudet MM et al. Breast can-

cer statistics, 2019. CA Cancer J Clin 2019;69:438-51.
6. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LJ, Kinzler KW. Cancer genome landscapes. Science 2013;339:1546-58.
7. Chattopadhyay C, Oba J, Roszik J et al. Elevated Endogenous SDHA Drives Pathological Metabolism in Highly Metastatic Uveal Melanoma. Invest Ophthalmol Vis Sci 2019;60:4187-95.
8. Fang J, Ge X, Xu W et al. Bioinformatics analysis of the prognosis and biological significance of HMGB1, HMGB2, and HMGB3 in gastric cancer. J Cell Physiol 2020;235:3438-46.
9. Huang DW, Sherman BT, Lempicki RA. Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists. Nucleic Acids Res 2009;37:1-13.
10. Sun X, Wang S, Li Q. Comprehensive Analysis of Expression and Prognostic Value of Sirtuins in Ovarian Cancer. Front Genet 2019;10:879.
11. Joerger AC, Fersht AR. The p53 Pathway: Origins, Inactivation in Cancer, and Emerging Therapeutic Approaches. Annu Rev Biochem 2016;85:375-404.
12. Khan H, Reale M, Ullah H et al. Anti-cancer effects of polyphenols via targeting p53 signaling pathway: updates and future directions. Biotechnol Adv 2020;38:107385.
13. Sanchez-Vega F, Mina M, Armenia J et al. Oncogenic Signaling Pathways in The Cancer Genome Atlas. Cell 2018;173:321-37.
14. Gudas JM, Payton M, Thukral S et al. Cyclin E2, a novel G1 cyclin that binds Cdk2 and is aberrantly expressed in human cancers. Mol Cell Biol 1999;19:612-22.
15. Feng W, Wang C, Liang C et al. The Dysregulated Expression of KCNQ1OT1 and Its Interaction with Downstream Factors miR-145/CCNE2 in Breast Cancer Cells. Cell Physiol Biochem 2018;49:432-46.
16. Li Z, Meng Q, Yu Q, Zhou Z, Li L. Evaluation of c-myc and CCNE2 amplification in breast cancer with quantitative multi-gene fluorescence in-situ hybridization. Zhonghua Bing Li Xue Za Zhi 2014;43:455-8.
17. Tormo E, Adam-Artigues A, Ballester S et al. The role of miR-26a and miR-30b in HER2+ breast cancer trastuzumab resistance and regulation of the CCNE2 gene. Sci Rep 2017;7:41309.
18. Sieuwerts AM, Look MP, Meijer-van GM et al. Which cyclin E prevails as prognostic marker for breast cancer? Results from a retrospective study involving 635 lymph node-negative breast cancer patients. Clin Cancer Res 2006;12:3319-28.
19. Caldon CE, Sergio CM, Kang J et al. Cyclin E2 overexpression is associated with endocrine resistance but not insensitivity to CDK2 inhibition in human breast cancer cells. Mol Cancer Ther 2012;11:1488-99.
20. Rogers S, Gloss BS, Lee CS et al. Cyclin E2 is the predominant E-cyclin associated with NPAT in breast cancer cells. Cell Div 2015;10:1.
21. Aaltonen K, Amini RM, Heikkila P et al. High cyclin B1 expression is associated with poor survival in breast cancer. Br J Cancer 2009;100:1055-60.
22. Deng JL, Xu YH, Wang G. Identification of Potential Crucial Genes and Key Pathways in Breast Cancer Using Bioinformatic Analysis. Front Genet 2019;10:695.
23. Ding K, Li W, Zou Z, Zou X, Wang C. CCNB1 is a prognostic biomarker for ER+ breast cancer. Med Hypotheses 2014;83:359-64.
24. Sabbaghi M, Gil-Gomez G, Guardia C et al. Defective Cyclin B1 Induction in Trastuzumab-emtansine (T-DM1) Acquired Resistance in HER2-positive Breast Cancer. Clin Cancer Res 2017;23:7006-19.
25. Liu B, Liu Y, Wang Y et al. CyclinB1 deubiquitination by USP14 regulates cell cycle progression in breast cancer. Pathol Res Pract 2019;215:152592.
26. 26. Shah KN, Mehta KR, Peterson D, Evangelista M, Livesey JC, Faridi JS. AKT-induced tamoxifen resistance is overturned by RRM2 inhibition. Mol Cancer Res 2014;12:394-407.
27. Putluri N, Maity S, Kommagani R et al. Pathway-centric integrative analysis identifies RRM2 as a prognostic marker in breast cancer associated with poor survival and tamoxifen resistance. Neoplasia 2014;16:390-402.
28. Shah KN, Wilson EA, Malla R, Elford HL, Faridi JS. Targeting Ribonucleotide Reductase M2 and NF-kappaB Activation with Didox to Circumvent Tamoxifen Resistance in Breast Cancer. Mol Cancer Ther 2015;14:2411-21.
29. Zhang H, Liu X, Warden CD et al. Prognostic and therapeutic significance of ribonucleotide reductase small subunit M2 in estrogen-negative breast cancers. BMC Cancer 2014;14:664.
30. Chen WX, Yang LG, Xu LY et al. Bioinformatics analysis revealing prognostic significance of RRM2 gene in breast cancer. Biosci Rep 2019;39.