Original Article

Identification of adriamycin resistance genes in breast cancer based on microarray data analysis

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Background: Breast cancer is a common malignant tumor with increasing incidence worldwide. This study aimed to investigate the molecular mechanisms of the adriamycin (ADR) resistance in breast cancer.

Methods: The GSE76540 dataset downloaded from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database was adopted for analysis. Differentially expressed genes (DEGs) in chemo-sensitive cases and chemo-resistant cases were identified using the GEO2R online tool respectively. Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis of DEGs were carried out by using the DAVID online tool. The protein-protein interaction (PPI) network was constructed using the Search Tool for the Retrieval of Interacting Genes (STRING) and visualized with Cytoscape software. The impact of key tumor genes on the survival and prognosis were described.

Results: A total of 1,481 DEGs were excavated, including 549 up-regulated genes and 932 down-regulated genes. According to the GO analysis, the DEGs were significantly enriched in: extracellular matrix organization, positive regulation of transcription from RNA polymerase II promoter, lung development, positive regulation of gene expression, axon guidance and so on. The results of KEGG pathway enrichment analysis showed that the most enriched DEGs can be detected in: pathways in cancer, PI3K/AKT signaling pathway, focal adhesion, Ras signaling pathway and so on. In the PPI network analysis, hub genes of *CDH1*, *ESR1*, *SOX2*, *AR*, *GATA3*, *FOXA1*, *KRT19*, *CLDN7*, *AGR2*, *ESRP1*, *RAB25*, *CLDN4*, *IGF1R*, *CLDN3* and *IRS1* were detected. Finally, there is a correlation filter out these hub genes in resistance of ADR.

Conclusions: Hub genes associated with ADR resistance were identified using bioinformatic techniques. The results of this study may contribute to the development of targeted therapy for breast cancer.

Keywords: Breast cancer; microarray data analysis; adriamycin resistance

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Introduction

Breast cancer is a common malignant tumor in clinical practice, which occurs in the breast epithelium. Breast cancer is one of the leading life-threatening diseases in women, with the highest incidence rate of 1 million patients and a mortality rate of about 500,000 people (1). In China, breast cancer can cause 279,000 new cases and 66,000 deaths annually (2). Currently, surgery, chemotherapy, and radiotherapy are the therapeutic methods mostly adopted in clinical practice. Early neoadjuvant chemotherapy can

significantly improve the progression and prognosis (3). However, despite the advantages, chemotherapy has its limits due to the drug resistance emerged in certain patients (4), and adriamycin (ADR) resistance is the most common one. Therefore, it is of great significance to explore the mechanisms and molecular pathways of ADR resistance in breast cancer.

Nowadays, bioinformatic methods have been widely used in various fields of life sciences, especially in the field of oncology. By using functional genomics and proteomics, researchers can explore the pathogenesis of cancer, as well as the development of screening and targeted drugs, to provide new ideas and theoretical basis for cancer therapy (5). This study adopted bioinformatic techniques, aiming at analyzing gene expression profiles of ADR-resistant breast cancer with public data sources, and screening differentially expressed genes (DEGs) in ADR-resistant and ADR-sensitive cases, and also constructing DEGs-encoded protein-protein interaction (PPI) networks, to analyze and discover the potential genes associated with ADR resistance, and to provide new clues for further researches of the molecular mechanisms and the development of clinical treatment methods.

Methods

Data collection

The gene expression profile dataset was downloaded from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database (6) (http://www.ncbi.nlm.nih.gov/geo). The GSE76540 dataset (7) was based on the GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array, consisting of 3 chemo-sensitive samples and 3 chemo-resistant samples.

Screening for DEGs

The GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/, accessed January 25th, 2019) online tool was employed to detect the DEGs in chemo-sensitive cases and chemo-resistant cases (8), respectively. Adjusted $P<0.01$, $P<0.01$ and fold change (FC) ≥ 2 were considered as the cut-off criterion.

Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis of DEGs

GO analysis is a tool widely used for biological function annotation of specific genes and gene products, which can be divided into biological process (BP), molecular function (MF), and cellular component (CC) analysis (9). KEGG is a high-throughput database that uses molecular experimental techniques to explain the advanced biological functions of cells and other organisms at the genomic level (10). The GO analysis and KEGG enrichment analysis of DEGs were conducted with the Database for Annotation, Visualization and Integrated Discovery (DAVID) tool (https://david.ncifcrf.gov/), and $P<0.01$ and gene counts >10 were considered statistically significant (11,12).

PPI network construction

The relevant nodes and network diagrams of protein interaction were predicted and analyzed by using the Search Tool for the Retrieval of Interacting Genes (STRING) database (http://string-db.org/) (13). We predicted the protein information by uploading the selected differential genes to the STRING database. The protein interaction pairs with combine score greater than 0.4 were extracted and imported into the Cytoscape software (www.cytoscape.org/) (14) to achieve a clear visualization of protein interaction network. At the same time, the degree model of plug-in Cytohubba in Cytoscape software was adopted to evaluate the importance of each protein node and the overall contribution to the protein network. The 15 top-rated genes selected by degree method were regarded as hub genes.

Survival analysis of hub genes

GEPIA (http://gepia.cancer-pku.cn/detail.php) (15) is a public database based on tumor analysis, providing freely published tumor gene transcriptome data [including the Cancer Genome Atlas (TCGA) database], and also collecting and summarizing a large number of tumor-related gene expression levels and patient survival information. Herein, the impact of key tumor genes on the survival and prognosis were described based on the GEPIA database.

Results

Identification of DEGs

A total of 1,481 DEGs were achieved after analyzing the GSE76540 dataset by using the GEO2R online tool, including 549 up-regulated genes and 932 down-regulated

Table 1 The 5 up-regulated or down-regulated genes that were mostly enriched

Expression	Genes	Adjust P value	LogFC
Up-regulation	*MMP1*	1.02E–4	9.9795696
	TMEM200A	1.02E–4	9.2300751
	NEFH	1.02E–4	9.6770347
	KRTAP2-4	1.02E–4	11.1822447
	PPP1R14A	1.02E–4	8.9519095
Down-regulation	*SYTL5*	1.02E–4	–10.4814297
	MAL2	1.02E–4	–9.3188679
	WISP2	1.2E–4	–8.6980133
	GREB1	1.48E–4	–6.064777
	FXYD3	1.48E–4	–8.8321929

FC, fold change.

Table 2 The biological processes with enriched up-regulated or down-regulated genes

Expression	Term	Count	P value	Benjamin
Up-regulation	Extracellular matrix organization	24	6.9E–8	1.8E–4
	Positive regulation of transcription from RNA polymerase II promoter	57	1.4E–5	1.8E–2
	Lung development	12	2.6E–5	2.2E–2
	Positive regulation of gene expression	22	9.9E–5	6.2E–2
	Axon guidance	15	5.5E–4	2.1E–1
Down-regulation	Homophilic cell adhesion via plasma membrane adhesion molecules	15	2.9E–6	5.8E–3
	Positive regulation of transcription from RNA polymerase II promoter	36	4.8E–4	1.5E–1
	Signal transduction	38	2.5E–3	4.3E–1
	Cell-cell signaling	13	4.6E–3	4.8E–1
	Angiogenesis	12	4.7E–3	4.7E–1

genes. The five genes with the most significant up-regulation were *MMP1*, *TMEM200A*, *NEFH*, *KRTAP2-4*, and *PPP1R14A*, while the most significant down-regulated genes were *SYTL5*, *MAL2*, *WISP2*, *GREB1*, and *FXYD3* (*Table 1*).

Functional enrichment analysis of DEGs

The results of GO analysis indicated that the five BPs with the most up-regulated genes were: extracellular matrix organization, positive regulation of transcription from RNA polymerase II promoter, lung development, positive regulation of gene expression, axon guidance, while the BPs with the most down-regulated genes included: homophilic cell adhesion via plasma membrane adhesion molecules, positive regulation of transcription from RNA polymerase II promoter, signal transduction, cell-cell signaling, and angiogenesis (*Table 2*). The CC analysis showed that the up-regulated genes were mostly enriched in plasma membrane, extracellular space, extracellular region, basement membrane, and cell surface, in contrast of which, the down-regulated genes were mainly in extracellular exosome, bicellular tight junction, plasma membrane, integral component plasma membrane, and extracellular space (*Table 3*). According to the MF analysis, the most up-regulated genes could be detected in heparin binding,

Table 3 The cellular components with enriched up-regulated or down-regulated genes

Expression	Term	Count	P value	Benjamin
Up-regulation	Plasma membrane	179	3.2E–7	1.2E–4
	Extracellular space	75	8.1E–7	1.5E–4
	Extracellular region	84	2.1E–6	2.5E–4
	Basement membrane	13	5.1E–6	4.6E–4
	Cell surface	36	3.3E–5	2.4E–3
Down-regulation	Extracellular exosome	83	5.4E–5	1.4E–2
	Bicellular tight junction	11	6.6E–5	8.7E–3
	Plasma membrane	109	2.3E–4	1.5E–2
	Integral component plasma membrane	44	2.0E–4	9.8E–3
	Extracellular space	41	4.2E–3	1.5E–1

Table 4 The molecular functions with enriched up-regulated or down-regulated genes

Expression	Term	Count	P value	Benjamin
Up-regulation	Heparin binding	16	1.3E–4	8.6E–2
	Extracellular matrix structural constituent	11	2.1E–4	6.7E–2
	Signal transducer activity	18	2.1E–4	4.5E–2
	Transcription factor activity sequence-specific DNA binding	51	2.2E–4	3.6E–2
	RNA polymerase II core promoter proximal region sequence-specific binding	18	1.1E–3	1.2E–1
Down-regulation	Calcium ion binding	38	6.7E–8	3.4E–5
	RNA polymerase II core promoter proximal region sequence-specific binding	20	2.0E–7	4.9E–5
	RNA polymerase II core promoter proximal region sequence-specific binding	16	4.3E–3	4.1E–1
	Sequence-specific binding	20	6.5E–3	4.8E–1

extracellular matrix structural constituent, signal transducer activity, transcription factor activity, sequence-specific DNA binding, and RNA polymerase II core promoter proximal region sequence-specific binding, whereas the down-regulated genes were enriched significantly in calcium ion binding, transcriptional activator activity, RNA polymerase II core promoter proximal region sequence-specific binding, and sequence-specific binding (*Table 4*).

In addition, the KEGG pathway enrichment analysis suggested that the DEGs were enriched in: cancer pathways, PI3K AKT signaling pathway, focal adhesion, Ras signaling pathway, cytokine-cytokine receptor interaction, MAPA signaling pathway, hematopoietic cell lineage, amoebiasis, calcium signaling pathway, oxytocin signaling pathway, and proteoglycans in cancer (*Table 5*).

PPI network and hub genes identification

A total of 635 pairs of interacting proteins were achieved after screening and the network structure was constructed (*Figure 1*). Fifteen key genes were obtained by using the degree model of plug-in Cytohubba in Cytoscape software, which were considered as hub genes, including: *CDH1*, *ESR1*, *SOX2*, *AR*, *GATA3*, *FOXA1*, *KRT19*, *CLDN7*, *AGR2*, *ESRP1*, *RAB25*, *CLDN4*, *IGF1R*, *CLDN3*, and *IRS1* (*Table 6*, *Figure 2*).

Survival analysis of hub genes

After analyzing influences of the 15 hub genes on the overall survival (OS) and disease-free survival (DFS) prognosis, the results suggested that only the insulin like growth

Table 5 KEGG pathways with enriched differentially expressed genes (DEGs)

Term	Count	P value	Benjamin
Pathways in cancer	31	1.7E–6	3.8E–4
Focal adhesion	19	4.0E–5	4.6E–3
Hematopoietic cell lineage	11	2.5E–4	1.9E–2
Amoebiasis	11	1.2E–3	6.8E–2
Calcium signaling pathway	14	2.7E–3	1.2E–1
Ras signaling pathway	16	3.1E–3	1.1E–1
PI3K AKT signaling pathway	21	3.3E–3	1.0E–1
Oxytocin signaling pathway	12	5.2E–3	1.4E–1
Cytokine-cytokine receptor interaction	16	6.1E–3	1.3E–1
Proteoglycans in cancer	14	6.8E–3	1.3E–1
MAPA signaling pathway	16	8.7E–3	1.4E–1

KEGG, Kyoto Encyclopedia of Genes and Genomes.

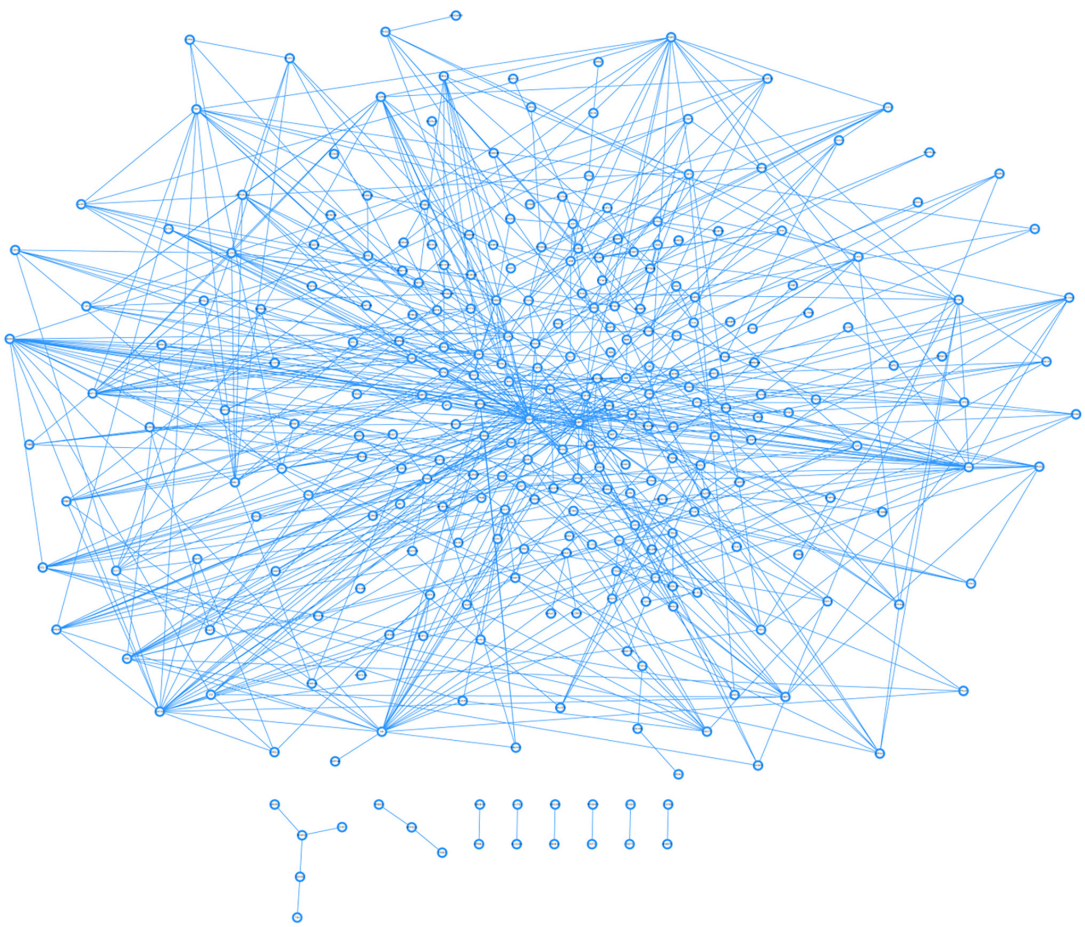

Figure 1 The visualization of differentially expressed genes in the protein-protein interaction (PPI) network predicted by the Cytoscape software.

Table 6 Degree assessment of hub genes

Gene	Degree	MCC	MNC
CDH1	50	1,817	43
ESR1	41	1,142	37
AR	24	430	20
SOX2	24	309	21
FOXA1	23	1,028	23
GATA3	23	762	23
AGR2	18	229	17
CLDN7	18	1,314	18
KRT19	18	372	15
ESRP1	16	922	14
IGF1R	15	114	13
CLDN4	15	1,256	13
RAB25	15	766	11
IRS1	14	98	12
CLDN3	14	1,284	14

factor 1 receptor (*IGF1R*) gene had significant impact on both OS and DFS (log-rank P=0.047, 0.038 respectively), and the epithelial splicing regulatory protein 1 (*ESRP1*) gene showed significant effect on the OS only (log-rank P=0.0019). The rest of hub genes did not have significant influence on the survival prognosis (*Figure 3*).

Discussion

ADR is a first-line neoadjuvant chemotherapy drug for breast cancer (16,17). Although it is effective, long-term use of ADR can always cause drug resistance. The mechanisms of drug resistance in tumor cells have not been completely clarified. However, theories have been established that tumor chemotherapy resistance is caused by a combination of multi-drug resistance pump and enzymes. In addition, genetic differences between individuals may also contribute to the drug resistance to some extent. In order to improve the efficacy of chemotherapy for breast cancer, it is necessary to explore the potential mechanisms of drug resistance.

It is widely believed that glycoprotein P-gp and multi-drug resistance protein MRP1 are involved in the resistance to several drugs in tumor cells. The catalytic ATP pumps can generate energy to expel the drugs out of cells, thus

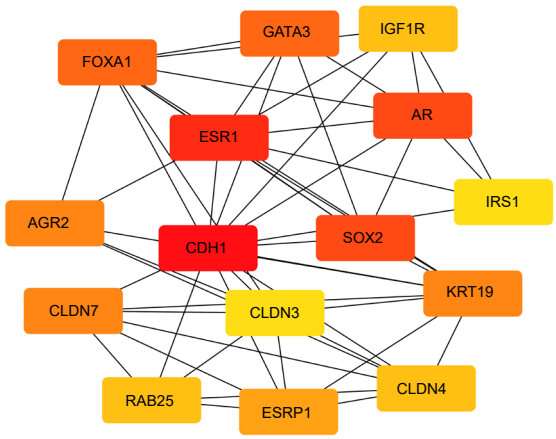

Figure 2 The predicted 15 hub genes (adriamycin resistance) in the PPI network with high degree of association in breast cancer.

reducing the effective intracellular concentration, and reducing the inhibition effect on tumor cells, which is manifested as drug resistance in clinical practice (18-23). In addition, a series of genes associated with ADR resistance were detected, such as *Nrf2*, *SOX2*, *SPIN1*, *COP1*, *Mdr1* and so on (24-29). In this study, we explored ADR resistance genes in breast cancer with the GSE76540 dataset. By analyzing 3 drug-resistant samples and 3 drug-sensitive samples, overall 1,481 DEGs were detected, including 932 down-regulated genes and 549 up-regulated genes. GO functional analysis and KEGG pathway analysis were conducted to obtain biological characteristics of the selected genes for further comprehensive analysis.

The GO analysis suggested that the BPs with the most enriched DEGs included: extracellular matrix organization, positive regulation of transcription from RNA polymerase II promoter, lung development, positive regulation of gene expression, axon guidance, homophilic cell adhesion via plasma membrane adhesion molecules, positive regulation of transcription from RNA polymerase II promoter, signal transduction, cell-cell signaling, and angiogenesis. The MF analysis showed that enriched DEGs can be detected in certain MFs, such as heparin binding, extracellular matrix structural constituent, signal transducer activity, transcription factor activity, sequence-specific DNA binding, RNA polymerase II core promoter proximal region sequence-specific binding, calcium ion binding, transcriptional activator activity, RNA polymerase II core promoter proximal region sequence-specific binding, RNA polymerase II core promoter proximal region sequence-

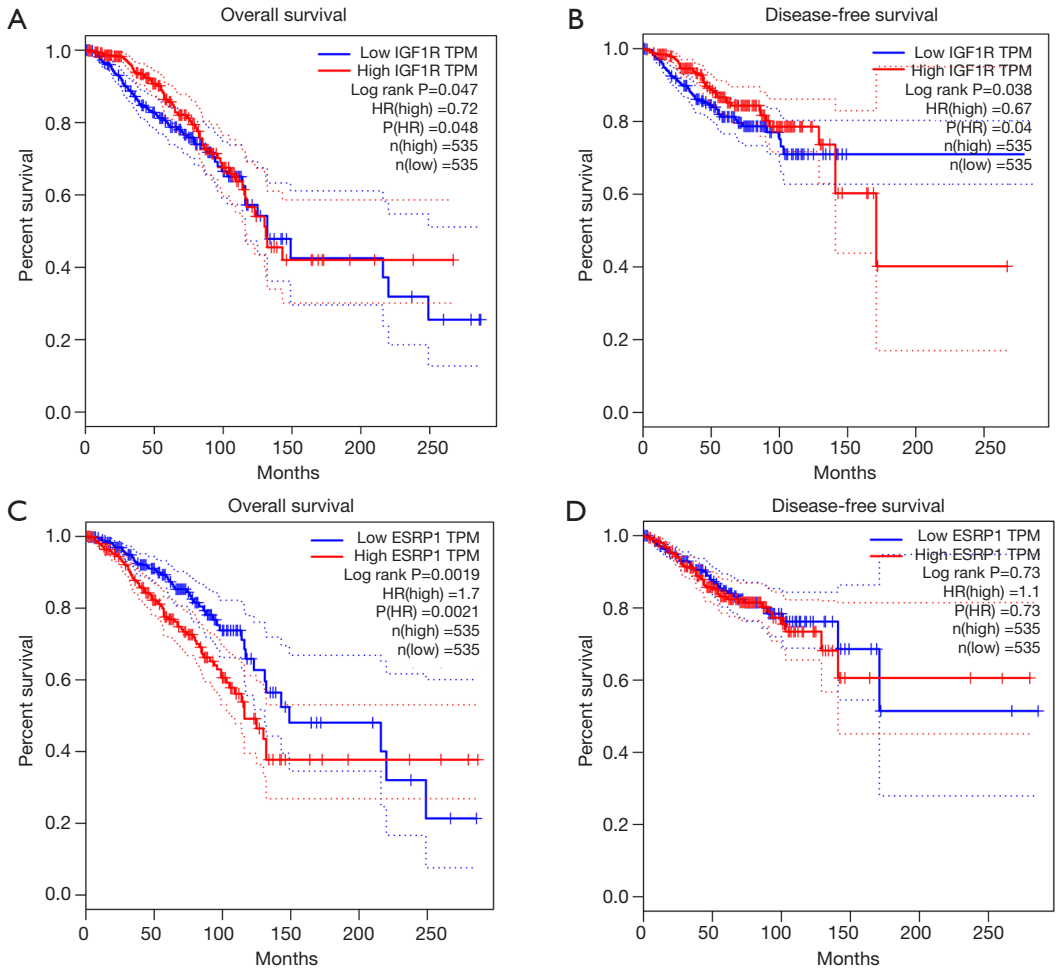

Figure 3 Survival analysis of the identified genes, insulin like growth factor 1 receptor (*IGF1R*) and epithelial splicing regulatory protein 1 (*ESRP1*), in breast cancer cases. High expression level of *IGF1R* was associated with prolonged overall survival (A) and disease-free survival (B) in patients with breast cancer; elevated *ESRP1* expression was associated with worse overall survival (C), but was not significant in disease free survival (D) in breast cancer cases.

specific binding, sequence-specific binding and so on. The CC analysis indicated that the DEGs were mostly enriched in plasma membrane, extracellular space, extracellular region, basement membrane, cell surface, extracellular exosome, bicellular tight junction, plasma membrane, integral component plasma membrane, and extracellular space.

The KEGG pathway analysis showed that DEGs were mainly enriched in cancer-associated pathways such as pathways in cancer, PI3K AKT signaling pathway, focal adhesion, Ras signaling pathway, cytokine-cytokine receptor interaction, MAPA signaling pathway, hematopoietic cell lineage, amoebiasis, calcium signaling pathway, oxytocin signaling pathway, and proteoglycans in cancer.

According to the PPI network and the analysis with the degree model, 15 genes with a high degree of association were selected as hub genes, among which *CDH1*, *ESR1*, *SOX2*, *AR*, and *GATA3* were the top five genes. The *CDH1* gene is a member of the cadherin superfamily, which has been demonstrated to be correlated with a series cancer occurring in different parts, such as gastric cancer, breast cancer, colorectal cancer, thyroid cancer, ovarian cancer and so on. Mutation of the *CDH1* gene can promote the progression and growth of tumor tissues, as a result of which, it may be related to drug resistance in tumor cells (30). The *ESR1* gene encodes an estrogen receptor involved in the pathological process of breast cancer. The *SOX2* gene plays an important role in the regulation of stem cell growth

and development. The *AR* gene encodes an androgen receptor that promotes androgen binding, and its mutation can lead to loss of control of tumor cells (31). The *GATA3* gene is a transcription factor-regulated protein whose mutation can lead to developmental disorders of immune cells thus damaging to the immune system (32).

In the prognostic survival analysis, only two genes were related with prognostic significance. The *IGF1R* gene had influence on both OS and DFS, while the *ESRP1* gene only affected the OS. Therefore, patients screened for these two genes may have worse prognosis and quality of life. It is necessary to modify the chemotherapeutic drugs in advance and redesign the chemotherapeutic regimen.

Conclusions

In summary, this study contributed to a better understanding of the molecular screening and potential mechanisms of drug resistance in breast cancer. By using bioinformatic techniques, 15 hub genes were selected among a total of 1,481 DEGs. The *IGF1R* and *ESRP1* genes might be options as prognostic biomarkers for breast cancer. Further studies are needed to verify the results.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-19-2145). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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