

Identification of high-risk genes in triple-negative breast cancer by bioinformatics

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Background: Current research has failed to find a target gene for Triple-negative Breast Cancer (TNBC), which has resulted in the treatment for TNBC being less effective than that for other types of breast cancer. Finding high-risk genes for TNBC by bioinformatics may help to identify target genes for TNBC.

Methods: The gene expression data of 4 chips (GSE7904, GSE31448, GSE45827, GSE65194) which contains of normal breast tissue and TNBC tissue were obtained from the Gene Expression Omnibus. The Differentially Expressed Genes (DEGs) between normal breast tissue and TNBC tissue were identified. Gene Ontology (GO) functional annotation analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of DEGs were performed by the DAVID website. Protein-protein interaction network analysis of DEGs was carried out by the STRING website, and the results were imported into Cytoscape. Then, module analysis was carried out by using the MCODE app. The online tool of the Kaplan-Meier Plotter website was used to analyse associations between Relapse-free Survival (RFS) and the expression of genes obtained by MCODE, and the Metastasis-free Survival (MFS) data from GSE58812 were used for survival verification. The difference in the expression of the identified genes was verified by the online tool of the UALCAN website.

Results: There were 127 up regulated and 293 down regulated genes in the DEGs. The GO and KEGG analysis showed that the DEGs were particularly enriched in mitotic nuclear division, extracellular space, heparin binding, and ECM-receptor interaction. MCODE obtained a total of 47 genes in 4 gene clusters, 29 of which were related to RFS. Survival verification indicated that 14 out of 29 genes were related to MFS, namely, CCNB1, AURKB, KIF20A, BUB1B, DLGAP5, CXCL11, CXCL9, CXCL10, CXCL12, IGF1, FN1, CFD, SGO2 and CDCA5.

Conclusion: We identified 14 genes as the high-risk genes for TNBC. Further research on these genes may identify the target genes of TNBC.

Key Words: Triple-negative breast cancer; High-risk gene; Target gene; Expressed genes; Prognostic; Survival

Abbreviations: TNBC: Triple-Negative Breast Cancer; ER: Estrogen Receptor; PR: Progesterone Receptor; HER-2: Human Epidermal Growth factor receptor-2; GEO: Gene Expression Omnibus; TCGA: The Cancer Genomes Atlas; DEGs: Differentially Expressed Genes; RFS: Relapse-free Survival; MFS: Metastasis-free Survival; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; DAVID: Database for Annotation; BP: Biological Process; CC: Cellular Component; MF: Molecular Function; PPI: Protein-protein Interaction; MCODE: Molecular Complex Detection

INTRODUCTION

Triple-negative Breast Cancer (TNBC) refers to breast cancer that is negative for Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor-2 (HER-2); TNBC accounts for 15%~20% of breast cancers [1,2]. TNBC favours young women and has the characteristics of strong invasiveness, easy metastasis and poor prognosis [3,4]. TNBC is a heterogeneous disease that can be classified into distinct molecular subtypes by gene expression profiling [5,6]. Until now, the target gene of TNBC has not been found. Chemotherapy is still the main method of systemic treatment, and the curative effect is not satisfactory, the side effect are unfavourable, and the patient survival time is short [7]. The study of target genes of TNBC may be important for improving the therapeutic effect and prolonging the survival period of TNBC patients.

Using bioinformatics to study the molecular mechanism of cancer has become a trend in cancer research. Public databases of biological information, such as the Gene Expression Omnibus (GEO) and The Cancer Genomes Atlas (TCGA), collect information on gene sequencing, methylation, mutation, miRNA, protein and other information; these databases have the advantages of including data from many kinds of organisms, many types of tumours, large sample sizes and so on. Through the screening of public databases, the Differentially Expressed Genes (DEGs) between tumour and normal tissues, as well as the relationship between genes and tumour prognosis, can

be recognized, and this process can facilitate the identification of high-risk genes in tumours. It is a strategy for finding tumour target genes.

This paper used the GEO and TCGA databases to find the DEGs between TNBC and normal breast tissues and identified the genes that were related to Relapse-free Survival (RFS) and Metastasis-free Survival (MFS) as high-risk genes of TNBC, to provide direction for target genes.

MATERIALS AND METHODS

Data source

Gene expression data from the GSE7904, GSE31448, GSE45827 and GSE65194 datasets were obtained from the GEO (<https://www.ncbi.nlm.nih.gov/geo/>). Gene expression data from GSE58812 was used as the source of survival verification. All these chips contains of gene information about normal breast tissue and TNBC tissue. The platform of these chips were GPL570 which complete coverage of the Human Genome U133 Set plus 6,500 additional genes for analysis of over 47,000 transcripts.

Identification of DEGs

Using the GEO2R online analysis tool provided by the GEO to screen the DEGs between normal breast tissue and TNBC, the screening conditions were $\log_{2}FC > 2$ (representing the upregulated of genes in TNBC) or $\log_{2}FC < -2$

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(representing the downregulated genes in TNBC) and adjusted $P < 0.05$.

Using the Venn diagram online tool on the Van de Peer Lab website (<http://bioinformatics.psb.ugent.be/beg/tools/venn-diagrams>), Venn diagrams of the DEGs of the above 4 chips were drawn to determine the intersecting DEGs as the final DEGs.

Functional and pathway enrichment analysis

Gene Ontology (GO) functional annotation analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of DEGs were performed by the Database for Annotation, Visualization and Integrated Discovery (DAVID) tools (<https://david.ncifcrf.gov/>, Version: 6.8). GO analysis includes information on the Biological Process (BP), Cellular Component (CC) and molecular function (MF) of genes. BP refers to an ordered biological process with multiple steps, such as cell growth, differentiation and maintenance, apoptosis, and signalling. CC is used to describe the location of gene products in cells, such as the endoplasmic reticulum, nucleus or proteasome. MF refers to the function of a single gene product, such as binding activity or catalytic activity. KEGG is a database that systematically analyses the metabolic pathways of gene products in cells and is one of the most commonly used metabolic pathway analyses. The results were arranged in ascending order of P-value, and the top 6 were displayed separately.

Protein-protein interaction network and module analysis

The Protein-protein Interaction (PPI) network of DEGs was analysed by the online tool of the STRING website (<http://string-db.org/>, Version: 11.0), with the minimum required interaction score as highest confidence (0.900) and the combined score > 0.4 . The results were imported into the Cytoscape software (Version: 3.7.1), and the sub-network was constructed by the Molecular Complex Detection (MCODE) app (node score cut-off=0.01, k-core=5, Version: 1.5.1).

Survival analysis and verification

Survival analysis of genes obtained from MCODE analysis was performed using an online tool from the Kaplan-Meier Plotter website (<https://kmplot.com/analysis/>). Set requirements were used as follows: split patients by=auto select best cutoff, survival: RFS, probe set options: only JetSet best probe set, restrict analysis to subtypes=ER negative and PR negative and HER2 negative, use following dataset for the analysis=all [8]. Genes with a log rank P -value < 0.05 were verified by external data.

The external data were from GSE58812. Verification was performed using SPSS software (Version: 22.0). The receiver operating characteristic curve

was used to evaluate the best cut-off value of the gene expression, and the patients were divided into a high expression group and a low expression group. The Kaplan-Meier method was used to compare the MFS of the two groups and $P < 0.05$ was considered to indicate a significant difference.

Verification of gene expression

To verify the expression of the genes obtained from the above survival analysis, the online tool of the UALCAN website (<http://ualcan.path.uab.edu>) was used, and the data source was the TCGA. Genes with $P < 0.05$ were considered high-risk genes of TNBC [9].

Data analysis process

The data analysis process is shown in Figure 1.

RESULTS

DEGs between normal breast tissue and TNBC tissue

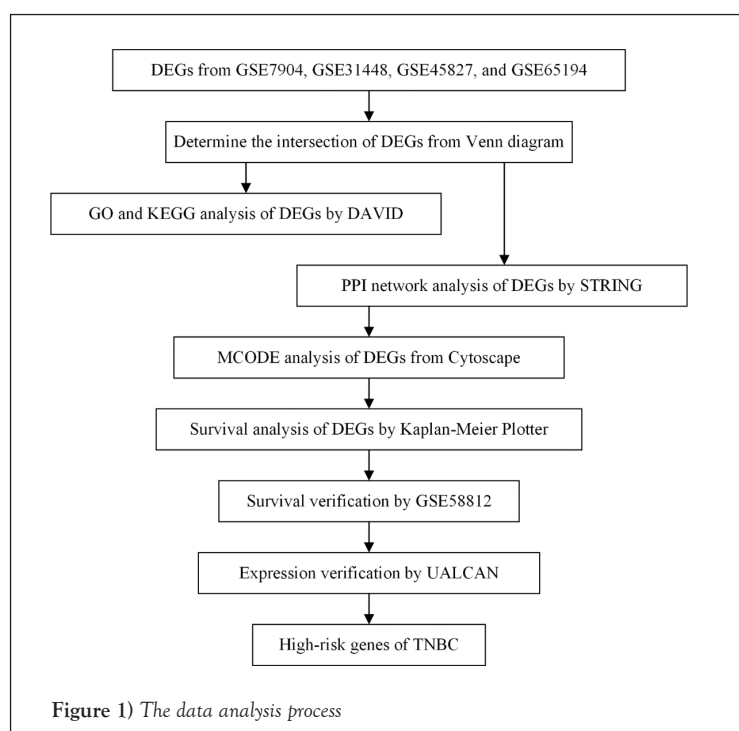
There were total of 33 normal breast tissue samples and 132 TNBC tissue samples from GSE7904, GSE31448, GSE45827, and GSE65194 (Table S1). The intersection of DEGs from the 4 chips was found by the Venn diagram; from which 127 genes were upregulated and 293 genes were downregulated (Figure 2) (Table S2).

GO and KEGG analysis of DEGs

The GO analysis results of DEGs were as follows: 1) for BP, DEGs were particularly enriched in mitotic nuclear division, cell division, sister chromatid cohesion, positive regulation of cell proliferation, cell chemotaxis and cell proliferation; 2) for CC, DEGs were particularly enriched in extracellular space, extracellular region, proteinaceous extracellular matrix, midbody, chromosome, centromeric region and extracellular exosome; and 3) for MF, DEGs were particularly enriched in heparin binding, chemokine activity, integrin binding, protein homodimerization activity, protein binding and metalloendopeptidase activity. The KEGG analysis results of DEGs revealed enrichment in ECM-receptor interaction, oocyte meiosis, cell cycle, and focal adhesion, pathways in cancer and cytokine-cytokine receptor interaction (Table 1).

PPI network and module analysis

A total of 227 nodes and 1207 edges were displayed in the PPI network of DEGs (Figure 3). There were 4 gene clusters obtained from the module analysis, including 20 genes in cluster 1, 12 genes in cluster 2, 9 genes in cluster 3 and 6 genes in cluster 4 (Figure 4) (Table 2).



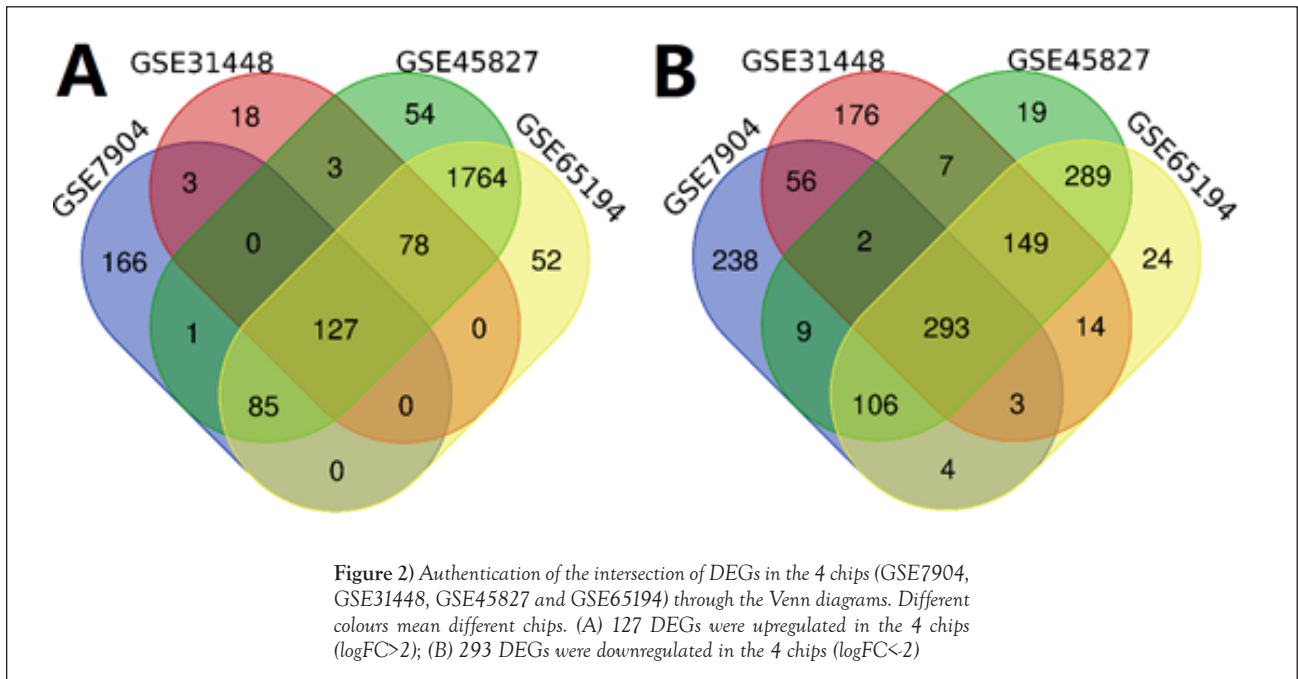


TABLE 1
The GO and KEGG analysis results

Category	Term	Description	Count	P-value
BP	GO:0007067	mitotic nuclear division	27	1.33E-10
BP	GO:0051301	cell division	32	1.60E-10
BP	GO:0007062	sister chromatid cohesion	17	1.75E-09
BP	GO:0008284	positive regulation of cell proliferation	34	1.21E-08
BP	GO:0060326	cell chemotaxis	12	2.54E-07
BP	GO:0008283	cell proliferation	25	4.81E-06
CC	GO:0005615	extracellular space	85	9.45E-18
CC	GO:0005576	extracellular region	93	5.12E-17
CC	GO:0005578	proteinaceous extracellular matrix	32	1.14E-13
CC	GO:0030496	midbody	16	2.59E-07
CC	GO:0000775	chromosome, centromeric region	11	5.71E-07
CC	GO:0070062	extracellular exosome	102	1.31E-06
MF	GO:0008201	heparin binding	20	4.24E-09
MF	GO:0008009	chemokine activity	10	1.36E-06
MF	GO:0005178	integrin binding	11	1.40E-04
MF	GO:0042803	protein homodimerization activity	34	1.43E-04
MF	GO:0005515	protein binding	236	1.60E-04
MF	GO:0004222	metalloendopeptidase activity	11	2.56E-04
KEGG	hsa04512	ECM-receptor interaction	11	8.58E-05
KEGG	hsa04114	oocyte meiosis	12	1.48E-04
KEGG	hsa04110	cell cycle	12	3.94E-04
KEGG	hsa04510	focal adhesion	14	2.95E-03
KEGG	hsa05200	pathways in cancer	21	3.32E-03
KEGG	hsa04060	cytokine-cytokinereceptor interaction	15	4.69E-03

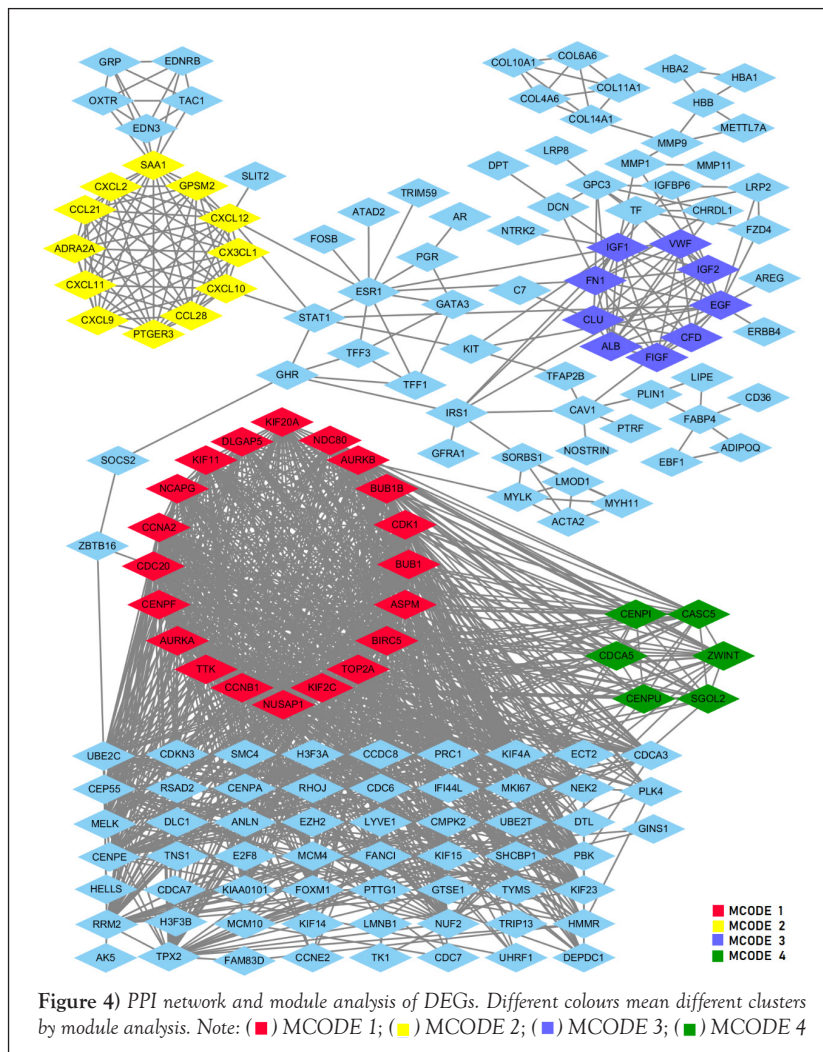
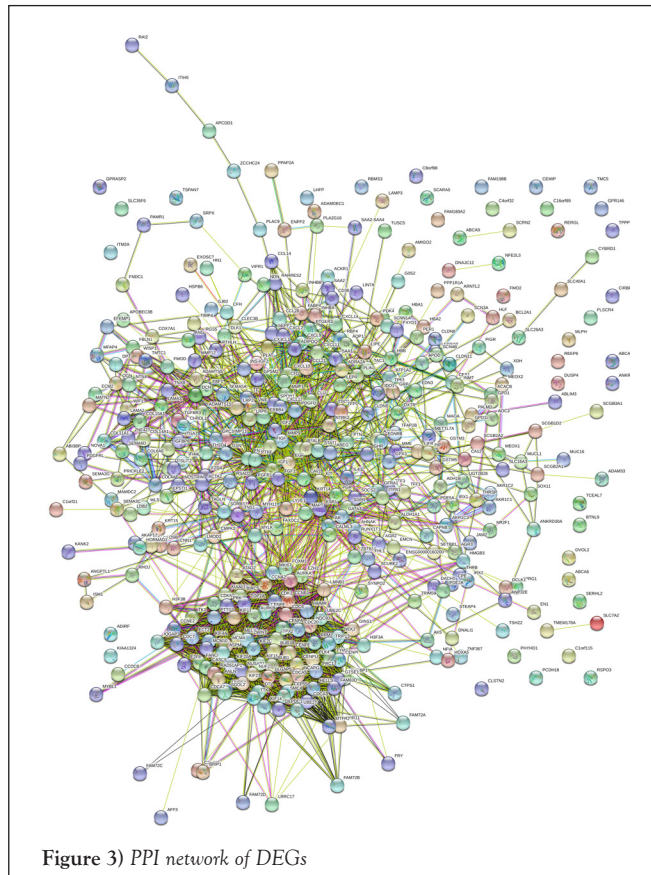


TABLE 2
Four gene clusters obtained from the module analysis

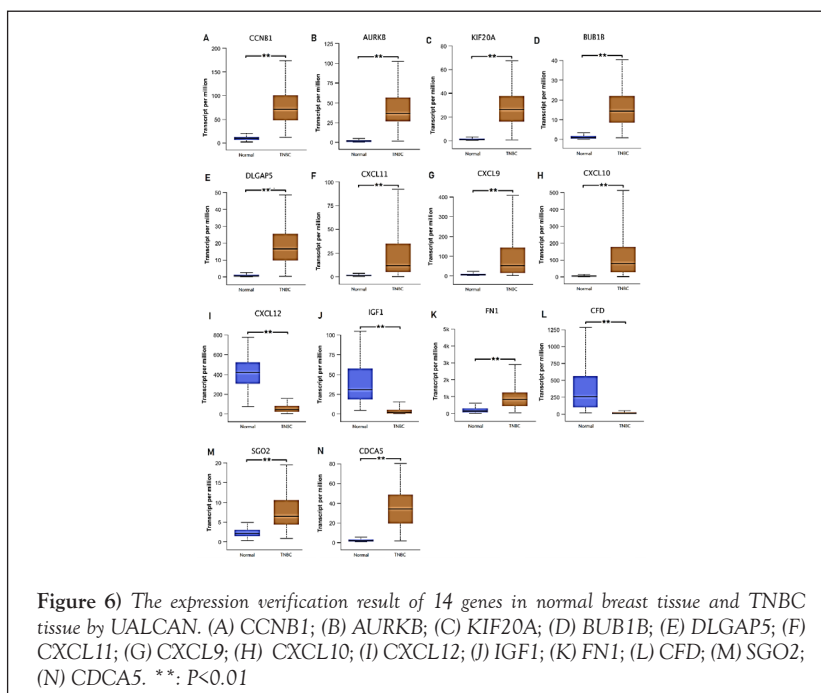
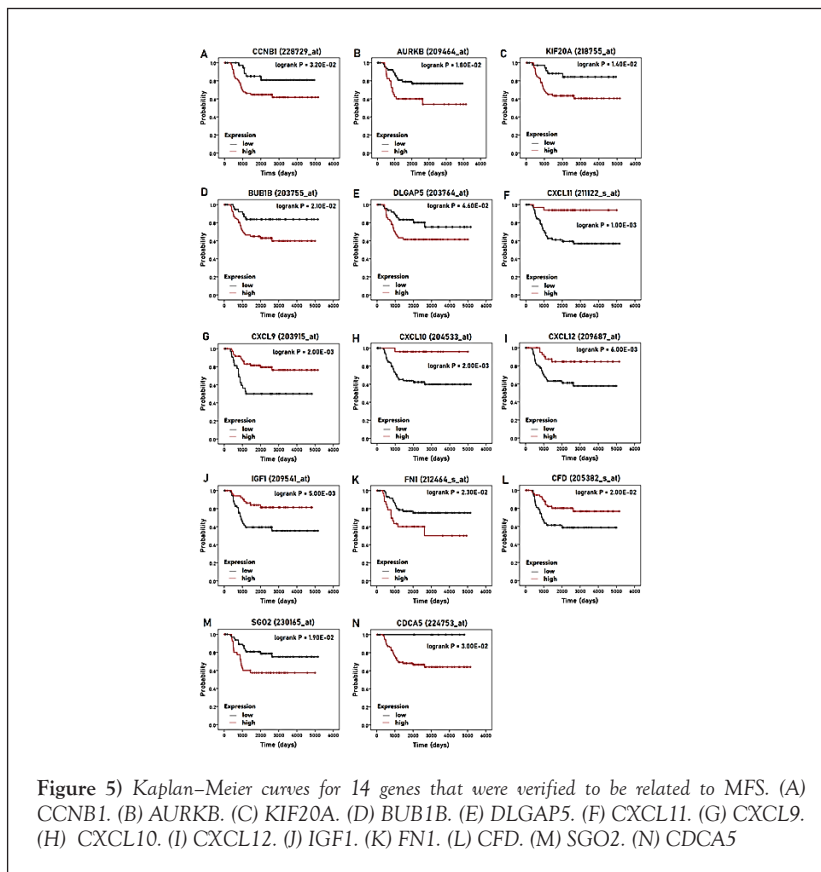
Cluster	Gene symbol	Gene title	Node Status	Up/Down
MCODE 1	NCAPG	non-SMC condensin I complex subunit G	Seed	Up
MCODE 1	CCNB1	cyclin B1	Clustered	Up
MCODE 1	KIF11	kinesin family member 11	Clustered	Up
MCODE 1	ASPM	abnormal spindle microtubule assembly	Clustered	Up
MCODE 1	AURKA	aurora kinase A	Clustered	Up
MCODE 1	AURKB	aurora kinase B	Clustered	Up
MCODE 1	KIF20A	kinesin family member 20A	Clustered	Up
MCODE 1	CENPF	centromere protein F	Clustered	Up
MCODE 1	KIF2C	kinesin family member 2C	Clustered	Up
MCODE 1	TOP2A	topoisomerase (DNA) II alpha	Clustered	Up
MCODE 1	BUB1B	BUB1 mitotic checkpoint serine/threonine kinase B	Clustered	Up
MCODE 1	CDK1	cyclin dependent kinase 1	Clustered	Up
MCODE 1	NUSAP1	nucleolar and spindle associated protein 1	Clustered	Up
MCODE 1	DLGAP5	DLG associated protein 5	Clustered	Up
MCODE 1	TTK	TTK protein kinase	Clustered	Up
MCODE 1	CCNA2	cyclin A2	Clustered	Up
MCODE 1	BIRC5	baculoviral IAP repeat containing 5	Clustered	Up
MCODE 1	BUB1	BUB1 mitotic checkpoint serine/threonine kinase	Clustered	Up
MCODE 1	CDC20	cell division cycle 20	Clustered	Up
MCODE 1	NDC80	NDC80, kinetochore complex component	Clustered	Up
MCODE 2	CXCL11	C-X-C motif chemokine ligand 11	Seed	Up
MCODE 2	CXCL9	C-X-C motif chemokine ligand 9	Clustered	Up
MCODE 2	CXCL10	C-X-C motif chemokine ligand 10	Clustered	Up
MCODE 2	CCL28	C-C motif chemokine ligand 28	Clustered	Down
MCODE 2	CXCL12	C-X-C motif chemokine ligand 12	Clustered	Down
MCODE 2	CXCL2	C-X-C motif chemokine ligand 2	Clustered	Down
MCODE 2	CX3CL1	C-X3-C motif chemokine ligand 1	Clustered	Down
MCODE 2	GPSM2	G-protein signaling modulator 2	Clustered	Up
MCODE 2	ADRA2A	adrenoceptor alpha 2A	Clustered	Down
MCODE 2	CCL21	C-C motif chemokine ligand 21	Clustered	Down
MCODE 2	PTGER3	prostaglandin E receptor 3	Clustered	Down
MCODE 2	SAA1	serum amyloid A1	Clustered	Down
MCODE 3	IGF2	insulin like growth factor 2	Seed	Down
MCODE 3	IGF1	insulin like growth factor 1	Clustered	Down
MCODE 3	FN1	fibronectin 1	Clustered	Up
MCODE 3	CLU	clusterin	Clustered	Down
MCODE 3	ALB	albumin	Clustered	Down
MCODE 3	EGF	epidermal growth factor	Clustered	Down
MCODE 3	CFD	complement factor D	Clustered	Down
MCODE 3	FIGF	c-fos induced growth factor	Clustered	Down
MCODE 3	VWF	von Willebrand factor	Clustered	Down
MCODE 4	ZWINT	ZW10 interacting kinetochore protein	Seed	Up
MCODE 4	SGO2	shugoshin 2	Clustered	Up
MCODE 4	CDCA5	cell division cycle associated 5	Clustered	Up
MCODE 4	CASC5	kinetochore scaffold 1	Clustered	Up
MCODE 4	CENPI	centromere protein I	Clustered	Up
MCODE 4	CENPU	centromere protein U	Clustered	Up

Survival analysis and verification

Survival analysis of 47 genes from 4 gene clusters obtained by module analysis revealed that 29 of them were related to RFS, namely, NCAPG, CCNB1, KIF11, ASPM, AURKA, AURKB, KIF20A, CENPF, KIF2C, TOP2A, BUB1B, CDK1, NUSAP1, DLGAP5, CXCL11, CXCL9, CXCL10, CCL28, CXCL12, CXCL2, IGF2, IGF1, FN1, CLU, ALB, EGF, CFD, SGO2 and CDCA5 (Figures S1 and S2). Gene expression data from GSE58812 was used to verify the survival of these 29 genes, and 14 of them were found to be related to MFs, namely, CCNB1, AURKB, KIF20A, BUB1B, DLGAP5, CXCL11, CXCL9, CXCL10, CXCL12, IGF1, FN1, CFD, SGO2 and CDCA5 (Figure 5).

Expression verification

The expression of the above 14 genes in normal breast tissue and TNBC tissue was verified by the online tool of UALCAN. The data was from TCGA, including 114 normal breast tissue samples and 116 TNBC tissue samples. The results showed that the difference in the expression of all these genes between normal breast tissue and TNBC tissue was statistically significant. The upregulated genes were CCNB1, AURKB, KIF20A, BUB1B, DLGAP5, CXCL11, CXCL9, CXCL10, FN1, SGO2 and CDCA5. The downregulated genes were CXCL12, IGF1 and CFD. This result was consistent with the results in GSE7904, GSE31448, GSE45827, and GSE65194 (Figure 6).



DISCUSSION

In this paper, the DEGs between normal breast tissue and TNBC tissue were obtained from 4 chips. The GO analysis indicated that the identified DEGs were related to mitotic nuclear division, cell division, sister chromatid cohesion, positive regulation of cell proliferation, cell chemotaxis, cell proliferation, heparin binding, chemokine activity, integrin binding, protein homodimerization activity, protein binding and metalloendopeptidase activity. The KEGG analysis indicated that the DEGs were related to ECM-receptor interaction, oocyte meiosis, cell cycle, focal adhesion, pathways in cancer and cytokine-cytokine receptor interaction. This is consistent with the active proliferation of TNBC cells.

The PPI network shows the relationship between the proteins expressed by these genes. Due to the large number of proteins in the PPI network and the complex network relationship, it was necessary to further explore the more important gene modules through module analysis. PPI network analysis and module analysis of DEGs finally obtained 47 genes in 4 clusters. Survival analysis is an important method of studying tumour-associated genes. Due to the limitation of clinical follow-up data sources, RFS was used as the observation index of survival analysis, and MFS was used for verification in this paper. Through the survival analysis, 14 genes closely related to the prognosis of TNBC were obtained, namely, CCNB1, AURKB, KIF20A, BUB1B, DLGAP5, CXCL11, CXCL9, CXCL10, CXCL12, IGF1, FN1, CFD, SGO2 and CDCA5.

The cell cycle consists of five phases: G0 (gap 0), G1, S (synthesis), G2, and M (mitosis). Mitosis proceeds in five phases: prophase, prometaphase, metaphase, anaphase, and telophase [10]. To ensure that only healthy cells proliferate, checkpoints have evolved that induce cell-cycle arrest in response to the detection of defects that may have arisen during DNA replication or other steps leading to mitosis [11]. The abnormal distribution of cells throughout the cell cycle is a hallmark of human cancer due to accumulating alterations of genes in the cell cycle pathway, possibly resulting in impaired abilities of cell division, cell proliferation and DNA damage response [12].

Among the high-risk genes found in this paper, the genes related to cell cycle and mitosis included AURKB, BUB1B, SGO2, CDCA5, CCNB1, DLGAP5 and KIF20A. These genes were overexpressed in TNBC and were associated with poor prognosis. AURKB is a member of the serine/threonine kinase family and is a major member of the chromosome passenger complex, which plays a key role in chromatin condensation and segregation and cytokinesis. Genetic instability caused by overexpression of AURKB is a direct cause of tumor formation [13,14]. Previous studies have found that AURKB expression is up regulated in leukemia, lymphoma, liver cancer and breast cancer and is associated with poor prognosis, which is consistent with the results of this study [15-18]. BUB1B encodes a kinase involved in the spindle assembly checkpoint and chromosome separation [19]. During the G2 phase, BUB1B inhibits anaphase-promoting complex/cyclosome activity, allowing cyclin B to accumulate before mitosis begins and slows the cell cycle [20]. Previous studies have found that BUB1B expression is upregulated in prostate cancer, breast cancer and lung cancer and is associated with poor prognosis [21-23]. SGO2 is a centromere-localized protein whose main function is to protect the cohesin of the sister chromatid from degradation. SGO2 regulates the localization of chromosomal passenger proteins and mediates spindle assembly and chromosome congression to prevent the generation of chromosomal instability associated with malignant cell transformation [24,25]. SGO2 is also a key substrate of AURKB, which plays a central role in ensuring faithful chromosome segregation [26]. CDCA5 is a substrate of the anaphase-promoting complex and participates in the regulation of sister chromatid cohesion [27]. Previous studies have found that CDCA5 expression is upregulated in lung cancer and hepatocellular carcinoma and is associated with poor prognosis [28,29]. CCNB1 belongs to a highly conserved family of cyclins that regulates the cell cycle and promotes cell proliferation. It is essential to control the cell cycle during G2/M transformation. Previous studies have found that CCNB1 overexpressed in ER-positive breast cancer and is associated with poor prognosis [30]. DLGAP5 belongs to the discs large-associated protein family, encodes the disc large homolog 7 (DLG7) protein, and controls on spindle stability [31,32]. The overexpression of DLGAP5 in colorectal cancer and prostate cancer is associated with poor prognosis [33,34]. KIF20A is a member of the kinesin super family - 6 that participates in spindle assembly and interacts with mitotic regulators [35]. The overexpression of KIF20A in hepatocellular carcinoma and lung adenocarcinoma is associated with poor prognosis [36,37].

CXCL9, CXCL10, CXCL11, and CXCL12 belong to the chemokine family. They are small molecular cytokines that are produced by many kinds of cells. After binding with the receptor, they mediate cell migration, activate antigen-presenting cells and immune active cells, and regulate the immune process of the body. In this study, we found that CXCL9-11 was overexpressed in TNBC, CXCL12 was not overexpressed, and patients with overexpressed CXCL9-12 had a better prognosis. Possible reasons were that the large amount of CXCL9-12 can promote the infiltration of cytotoxic T lymphocytes into the tumour cell area to kill tumour cells and induce T or NK cells to inhibit tumour angiogenesis [38-43].

IGF1 is a key growth factor of the mammary terminal end bud and for ductal formation during development, and it also plays an important role in breast cancer development, progression and metastasis [44,45]. Upregulating IGF1 may promote TNBC progression [46]. However, in this study, IGF1 overexpression represented a better prognosis, which is difficult to explain and is worthy of further study.

FN1 encodes two forms of fibronectin, soluble plasma fibronectin-1 and insoluble cellular fibronectin-1 [47]. It regulates cell adhesion and migration processes [48]. Previous studies have found that overexpressed FN1 in oesophageal squamous cell carcinoma was associated with poor prognosis, which is consistent with this study [49].

CFD is a member of the serine protease family, which stimulates the transport of triglycerides to fat cells and inhibits lipolysis. CFD is a key component in the regulation of alternative pathways [50,51]. This study found that CFD gene expression was downregulated in TNBC and correlated with poor prognosis, which was consistent with the changes seen in gastric cancer and oral tongue squamous cell carcinoma [52,53].

CONCLUSION

In this paper, 14 genes related to TNBC survival were obtained by using bioinformatics and public databases. Some of the genes were related to cell proliferation and division, and some were related to chemokines. There was no NCBI article found to study the function of SGO2, DLGAP5, KIF20A and CFD in TNBC before, which means some novel research directions. It is necessary to study these genes and their biological pathways, as these studies may be a way to find the target genes of TNBC. There are also some shortcomings in this paper, such as the lack of experimental intervention data in the public database. In the future, it is necessary to design relevant experiments to verify the research results.

DECLARATIONS

Not applicable

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

AUTHORS' CONTRIBUTIONS

XL and MT conceived and designed the study. XL and CPC collected and analyzed data. CPC and GHN prepared tables and figures. XL and GHN drafted the manuscript. CPC and MT revised the manuscript. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analysed during the current study are available in the Gene Expression Omnibus (<https://www.ncbi.nlm.nih.gov/geo/>), The Cancer Genome Atlas database (<https://cancergenome.nih.gov/publications/publicationguidelines>) and additional files.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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CONSENT TO PUBLICATION

Not applicable.

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