Research Square

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Analysis of differential gene expression of heart failure based on Gene Expression Omnibus database

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Research article

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Abstract

Background

To screen and identify key genes involved in heart failure and explore underlying molecular mechanisms.

Methods

The expression profile of GSE26887 was downloaded from Gene Expression Omnibus (GEO), which contained 24 samples, including 19 left ventricle cardiac tissue of heart failure and 5 controls. The differentially expressed genes (DEGs) were obtained and got further analysis by bioinformatics methods. The DEGs and volcano plot were acquired with the use of 'lima' package in 'R' software and heat map was drawn through the 'heatmap' package. Gene ontology (GO) and pathway analysis of DEGs were performed by means of Database for Annotation, Visualization and Integrated Discovery (DAVID) and Kyoto Encyclopedia of Genes and Genomes (KEGG) online analyses, respectively. The DEGs interaction and network map were constructed through Search Tool for the Retrieval of Interacting Genes (STRING) database and Cystoscope(v3.6.0)software.

Results

The transcriptome analysis of left ventricle cardiac tissue showed that 236 genes were differentially expressed between heart failure and control, of which 124 were significantly upregulated ($P < 0.01$) and 101 genes downregulated ($P < 0.01$). GO analysis uncovered that DEGs were enriched in extracellular space, extracellular matrix, extracellular matrix organization, cell adhesion, proteinaceous extracellular matrix and heparin binding. Thus, the function of extracellular matrix is mainly affected. The KEGG pathway enrichment indicated that the DEGs were involved in eight pathways, of these pathways, ECM-receptor interaction, Drug metabolism-cytochrome P450 and Pathogenic Escherichia coli infection are dominant. Protein-protein interaction (PPI) revealed the interactions of 30 protein products encoded of DEGs. Of the 30 protein products, the critical gene, called Interleukin-6 (IL6), was identified with the use of Cystoscope software.

Conclusion

Extracellular matrix and IL6 play an important role in the development of heart failure. Functional annotation and pathway analysis of these main genes were identified, which provide the basis for insight into the underlying pathogenetic mechanisms and predicting therapeutic targets of heart failure.

Background

Heart failure is a complex clinical syndrome caused by coronary artery disease, valvular heart diseases, hypertension, diabetes[1], characterized by impaired myocardial systolic performance resulting in the heart fails to provide sufficient blood to meet the needs of peripheral blood tissue. According to the report from 2017 American Heart Association (AHA), heart failure patients have reached 6.5 million in Americans over the age of 20[2]. Worldwide, the mortality of chronic heart failure in patients within 5 years is over 50%[3, 4]. Previous study has showed that almost two third patients experienced a readmission, 35.8% died of the hospitalization[5] and numerous patients will be readmitted once more within a year[6]. This brings about an enormous financial burden on patients, families and society. Despite considerable progress of optimal medical therapy,clinical outcomes are still poor. Thus, it is an imperative issue to offer reasonable guidelines and drug treatment for patients with heart failure.

Currently, a number of studies have revealed the therapeutic targets and signal pathways associated with heart failure, such as mitochondrial function[7], microRNAs[8], Granulocyte colony-stimulating factor[9], Ras homolog gene family, member A Rho kinase (RHOA/ROCK) pathway[10], AMP-activated protein kinase (AMPK) activation[11], Janus kinase/signal transducer and activator of transcription 3 (JAK-STAT3) pathway[12]. The occurrence and development of heart failure are affected by multiple factors (vascular endothelial injury, oxidative stress, inflammatory stimulation, cardiac autophagy, hypertrophy, apoptosis, cardiac remodeling), among them, cardiac remodeling is closely related to the development of heart failure, and inflammatory stimulation and the activation of fibrosis signaling pathways play a vital role in cardiac remodeling[13, 14]. A variety of cellular and molecular changes involved in the occurrence and development of heart failure, such as cardiomyocytes, fibroblasts, vascular smooth muscle cells, endothelial cells[15], which then cause the changes of intracellular Ca2 + concentration, apoptosis, extracellular matrix and metabolic[16], and activate corresponding signaling pathways to promote the progression of heart failure. Changes of extracellular matrix exert substantial influence on cardiac remodeling, cell migration, and proliferation. Inflammation, oxidative stimulation and apoptosis can facilitate the pathological reconstruction of extracellular matrix. Therefore, the activation of anti-inflammatory, antioxidant and anti-apoptotic signaling pathways[17–21] can protect the heart and improve heart failure. Although progress has been made for some drugs in improving or treating heart failure, the mortality and readmission rate of heart failure are still on the rise, indicating the potential mechanisms have not been adequately addressed by current therapies[2, 22, 23]. In recent years, the expression profiles of heart failure genes have been extensively studied and screened thousands of differential genes by high-throughput sequencing technology. However, sample heterogeneity and different sequencing platforms can lead to differences of expressed mRNA and gene profiles[24]. Although the etiology and mechanisms of heart failure have been extensive studied, the cause remains unclear. Therefore, the differentially genes of heart failure gene chips can be excavated by bioinformatics methods, which provides the basis for further research on the interaction between genes involved in heart failure.

The aim of this study is to elucidate the underlying genes by the bioinformatics method to identify DEGs in left ventricle cardiac tissue of patients with heart failure. With the development of bioinformatics, differential gene expression profile analysis and data mining based on bioinformatics have been

increasingly used to analyze the potential mechanism of disease[25–27]. Our study provides the basis for further research on the interaction and underlying functions between genes involved in heart failure.

Methods

Acquisition of DEGs

The series number GSE26887 was downloaded from the GEO database. GSE26887 was provided by Affymetrix Gene Chips Human Gene 1.0 ST array, using total RNA extracted from 24 samples, including 19 left ventricle cardiac tissue of heart failure and 5 controls. The DEGs were extracted based on the R/bioconductor lima package. DEGs with fold change (|log FC| > 1, $P < 0.05$) were obtained for the next step.

Analysis of DEGs

PPI network was constructed by STRING (http://string-db.org/), a database resource provides the protein interaction information of direct and indirect functional connections in the system biology[28]. In this paper, by setting a confidence score to 0.77, the web-based STRING database was used to construct PPI network association predictions of upregulation and downregulate on DEGs. It can be clearly seen that the direct and indirect nodes from the protein interaction network and the key genes were identified on DEGs. Bioinformation of the identified DEGs was uncovered by GO and KGEE pathway analysis applying the DAVID platform (version6.8, http://david.ncifcrf.gov/). $P < 0.05$ was set as significance cut-off to determine enrichment terms. DEGs were analyzed by network analysis using STRING online software, which can be accessed free of charge via https://string-db.org/. The relationship between protein and protein was constructed by Cystoscope (v3.6.0)software.

Results

Screening of DEGs

A total of 236 DEGs were obtained from the GSE26887 as shown in the volcano plot (Fig. 1). and 124 genes were significantly upregulated and 101 genes downregulated (*P*-value < 0.01, | log FC| > 1). The first 10 major differential genes are presented according to the *P*-value < 0.01 in Table 1. Fifty DEGs with the lowest *P*-values were displayed on the heat map (Fig. 2).

Table 1
First 10 major differential genes

Gene	lock	*P*-value	Adjusted *P*-value
FAXDC2	1.616355629	4.74E-10	7.18E-06
DSC1	2.48063432	8.04E-10	7.18E-06
FPR1	-1.162986842	1.51E-09	7.18E-06
NPPA	3.320438596	1.68E-09	7.18E-06
CD163	-1.788722196	1.88E-09	7.18E-06
DUSP5	-1.164211806	2.12E-09	7.18E-06
GFPT2	-1.712208299	7.43E-09	1.89E-05
CFAP61	1.30847076	1.43E-08	3.01E-05
TMEM140	1.221705905	1.48E-08	3.01E-05
HTR4	1.13711038	6.47E-08	9.40E-05

GO enrichment analysis

The DEGs have uploaded the database of DAVID bioinformatics resources network (https://david.ncifcrf.gov/), which has the function of annotation, visualization and integrated discovery and extracts biological information associated with large gene lists[29, 30]. The identifier was selected as OFFICIAL_GENE_SYMBOL and the list type as Gene List. Other parameters were all fixed. The results showed that DEGs enriched these categories via GO analysis, containing biological process, cellular component and molecular function and mainly concentrated in the following fields: extracellular space, extracellular matrix, extracellular matrix organization, cell adhesion, extracellular region, proteinaceous extracellular matrix, heparin binding, were demonstrated in Figs. 3 and 4.

KEGG pathway analysis

DEGs were analyzed using DAVID online website (version6.8, http://david.ncifcrf.gov/) for KEGG pathway analysis and functional annotation, and three key KEGG pathways were identified, including ECM-receptor interaction, Drug metabolism - cytochrome P450, and Pathogenic Escherichia coli infection, HIF-1 signaling pathway and so on, among which ECM-receptor interaction pathway was considered to be the most important one (Fig. 5).

Analysis Of Protein Network Interaction

With PPI analysis making use of STRING software, 30 outstanding proteins were identified, among which IL6, CD44, SOCS3, ITGA5, ITGA8, MYC, RPS4Y1 and THBS1 are relatively important. IL6 was deemed to be the significantly important protein and connected 13 nodes (Figs. 6 and 7).

Discussion

In this article, the main pathogenesis and biomarkers of heart failure were obtained by screening the DEGs of clinical heart failure expression profile GSE26887 and analyzing the GO function, KEGG pathway enrichment and PPI. The occurrence of heart failure is the result of multi-factors and genes. Therefore, the exploration of the molecular mechanism of heart failure is very important for the occurrence and development of heart failure. The target genes of heart failure have been widely predicted by microarray and the high-throughput sequencing technology, most research has focused on animal experiments for heart failure, and the present study was based on isolated left ventricular myocardial tissue from patients with clinical heart failure, through bioinformatics method to analyze the raw data and identify 236 DEGs. Further information of 236 DEGs was mined based on functions enrichment and signaling pathways, respectively.

This study is to explore the underlying mechanism of action on patients with heart failure. We analyzed the DEGs between patients with heart failure and control by multiple bioinformatics methods including enrichment, KEGG analysis and PPI analysis. According to GEO database, we analyzed the chip GSE26887 making use of R software package, and the DEGs 236 were screened out. PPI analysis showed that IL6, CD44 and SOCS3 genes were key factors for patients with heart failure. A pleiotropic cytokine, IL6, could activate immune cells to protect the host from damage in the short term, however, it became pathogenic to the host in a condition of remaining long-term activation. Chronically elevated IL6 levels result in chronic inflammation and fibrotic disorders for the heart tissue[31]. Studies had shown that elevated serum IL6 levels may be a potential prognostic predictor associated with heart disease, such as heart failure, myocardial infarction, and angina[32–35]. CD44 is a multifunctional transmembrane glycoprotein, which interacts with hyaluronic acid to mediate the migration and proliferation of endothelial cells, macrophages, fibroblasts and other cell types. Meanwhile, it was involved in the stimulation of

Tumor necrosis factorα/Nuclear-factor-kappa-B (TNFα/NFkB) signaling pathway to promote the production of inflammation and development of cardiac fibrosis[36–38], causing the remodeling of extracellular matrix. Excessive remodeling of the extracellular matrix was likely to result in heart failure. Therefore, CD44 may be considered as a novel potential therapeutic target for the treatment of heart failure. Another gene, SOCS3, is one of the negative regulators of gp130/JAK/STAT3 signaling pathway, indicating that SOCS3 is closely related to STAT3. Activation of STAT3 signaling pathway is one of the important mechanisms of myocardial hypertrophy, and myocardial remodeling is a compensation method adopted by the body under the condition of overload anterior and posterior of cardiomyocytes,

which is one of the important mechanisms of heart failure. However, negative feedback regulation of SOCS3 slows down the development of heart failure by inhibiting the overexpression of STAT3. In addition, IL6 can also reduce the expression of SOCS3 by activating STAT3[39, 40], therefore, SOCS3 may be a new potential target for the treatment of heart failure. According to the above discussion,IL6□CD44 and SOCS3 have a bearing on the remodeling of the extracellular matrix, which act as markers of heart failure to provide a reference basis for the early prevention and treatment of heart failure.

Further analysis of the DEGs revealed that the function was mainly involved in extracellular space, extracellular matrix, extracellular matrix organization by GO enrichment analysis. Extracellular matrix alterations are closely related to cardiac remodeling, which play a pivotal role in the development and evolution of heart failure[41]. IL6, CD44 and SOCS3 can impact the alterations of the extracellular matrix, so they are crucial factors leading to heart failure. KEGG pathway analysis showed the major role of ECM-receptor interaction, drug metabolism - cytochrome P450 and pathogenic Escherichia coli infection pathways in heart failure. Studies have indicated that extracellular matrix is considered as an important role in cardiac remodeling. CD44 is a cell-surface receptor of extracellular matrix proteins, which may serve as an underlying target for inhibiting extracellular matrix remodeling and slowing down the development of heart failure[36]. Other pathways are cytochrome P450 and pathogenic Escherichia coli infection associated with heart failure, among which cytochrome P450 is a multigene superfamily of enzymes that plays an important role for progression and prognosis of heart failure[42], such as cardiac CYP2A, CYP1B, CYP2B and CYP2E mRNA levels, which are related to cytochrome P450, usually increase in heart failure[43]. Moreover, pathogenic Escherichia coli infection is also associated with the progression of heart failure in patients, which can impair tight junctions and perturbs intestinal barrier function[44], possibly leading to intestinal flora disorders. Growing evidence shows that dysbiosis of gut microbiota has an underlying connection with heart failure [45–47], which can contribute to the body inflammation that accelerates the deterioration of heart failure. Therefore, gut microbiota can be considered as potential therapeutic targets for further research on the treatment of heart failure. Through the above analysis of the major genes and pathways of heart failure, it can be seen that inflammation and the alterations extracellular matrix play a major role in the progression of heart failure. Further research is needed to bring insight into the specific mechanisms of heart failure.

Conclusion

In this study, the mining of clinical specimens is more conducive to the analysis of the mechanism of heart failure. Potential molecules and mechanisms were observed linked to heart failure. Extracellular matrix, ECM-receptor interaction, IL6, CD44 and SOCS3 play a major role by analyzing expression profile of GSE26887 involved in left ventricle cardiac tissue of heart failure.

Declarations

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Authors' contributions

Jingyuan Mao contributed to study concept and design. Haifeng Yan drafted the manuscript. Xianliang Wang acquired data and contributed to the analysis and interpretation of data. Yazhu hou and Zhihua Yang critically revised the manuscript and contributed to statistical analysis. Haifeng Yan is the guarantor of this work, and takes responsibility for the accuracy of the data analysis. All authors have approved the final version of the manuscript.

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Availability of data and materials

The chip data analyzed in this study be obtained from corresponding author.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

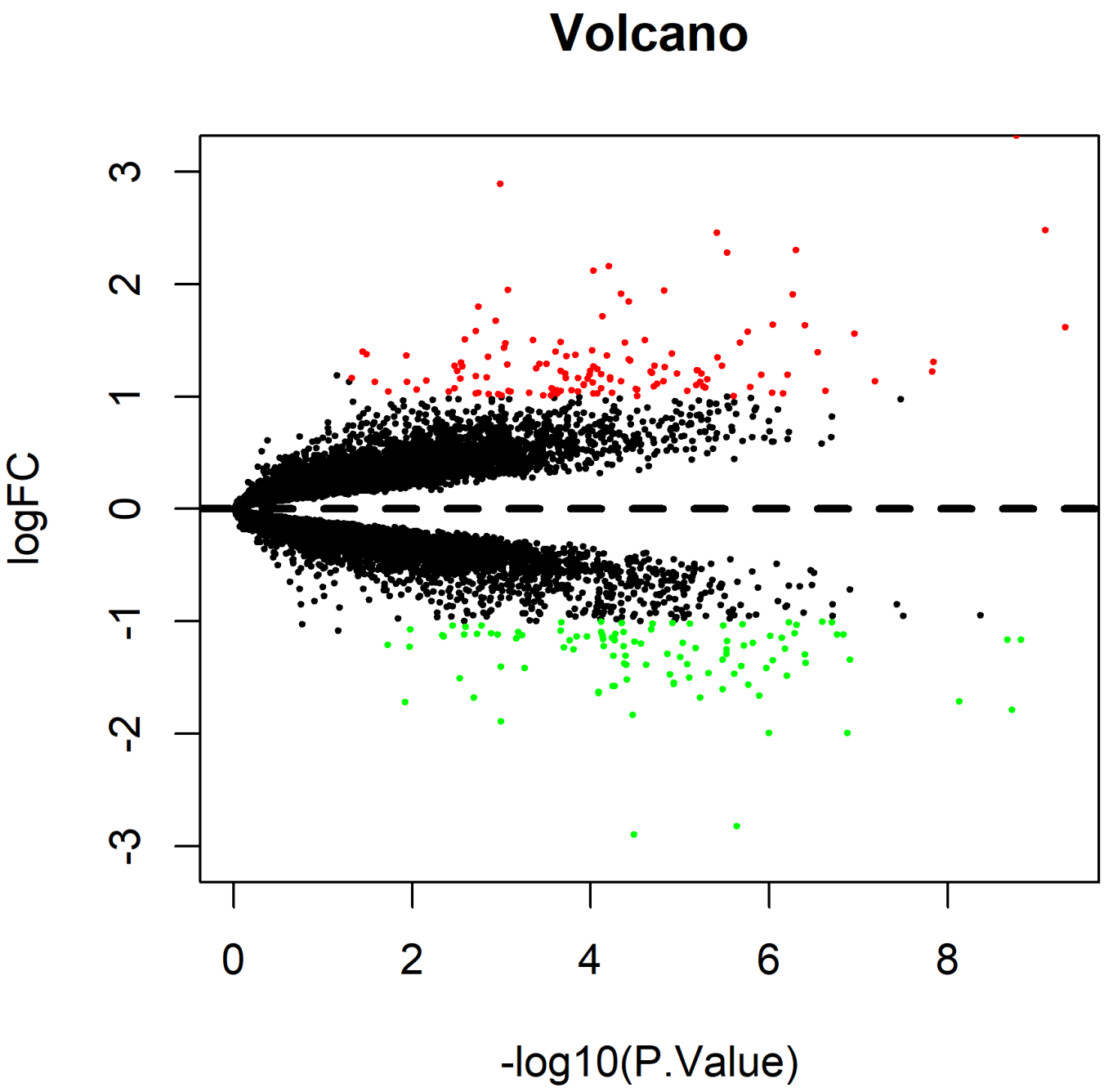

Figure 1

Volcano Plot of DEGs. Red spots indicate upregulated genes; green means downregulated genes. X axis revealed the P-value; and Y axis expressed as fold change of DEGs.

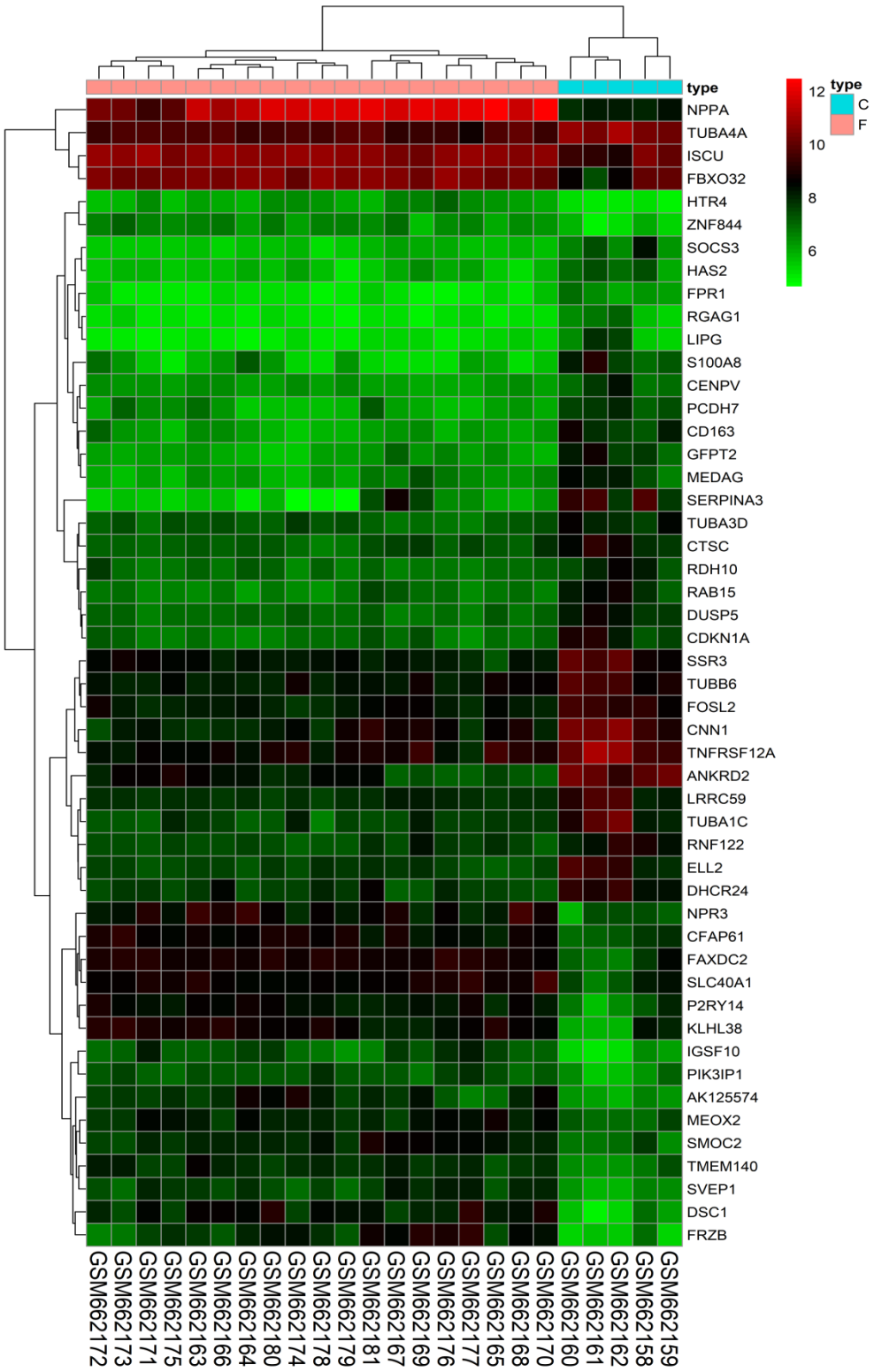

Figure 2

The first 50 DEGs were analyzed in the heat map. The rows represent samples and the columns represent genes. The red represents upregulated genes, the green represents downregulated genes (C represents control groups, F represents heart failure groups). 8, 6, 10 and 12 illustrate the gene expression level.

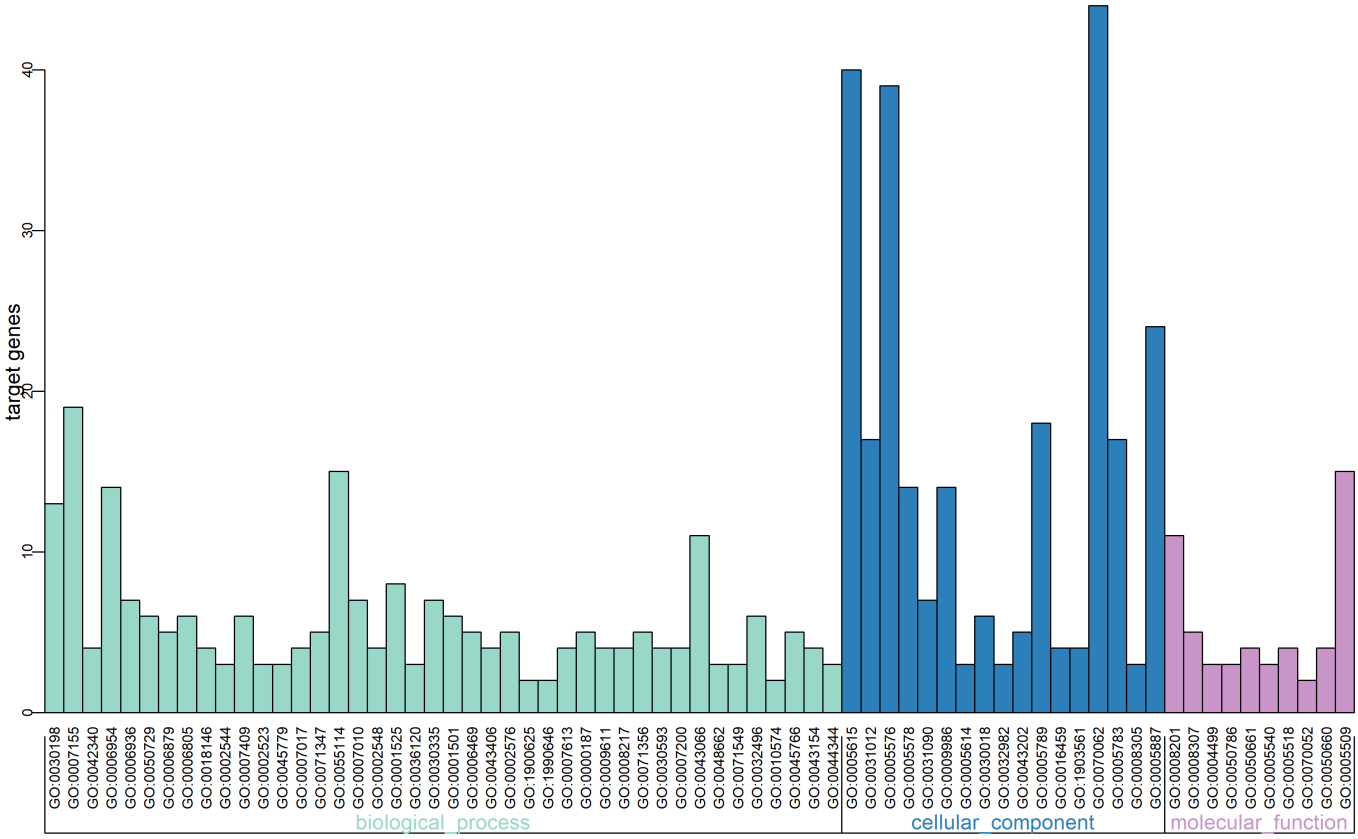

Figure 3

GO analysis of DEGs involved in three groups. Different colors correspond to distinct GO categories.

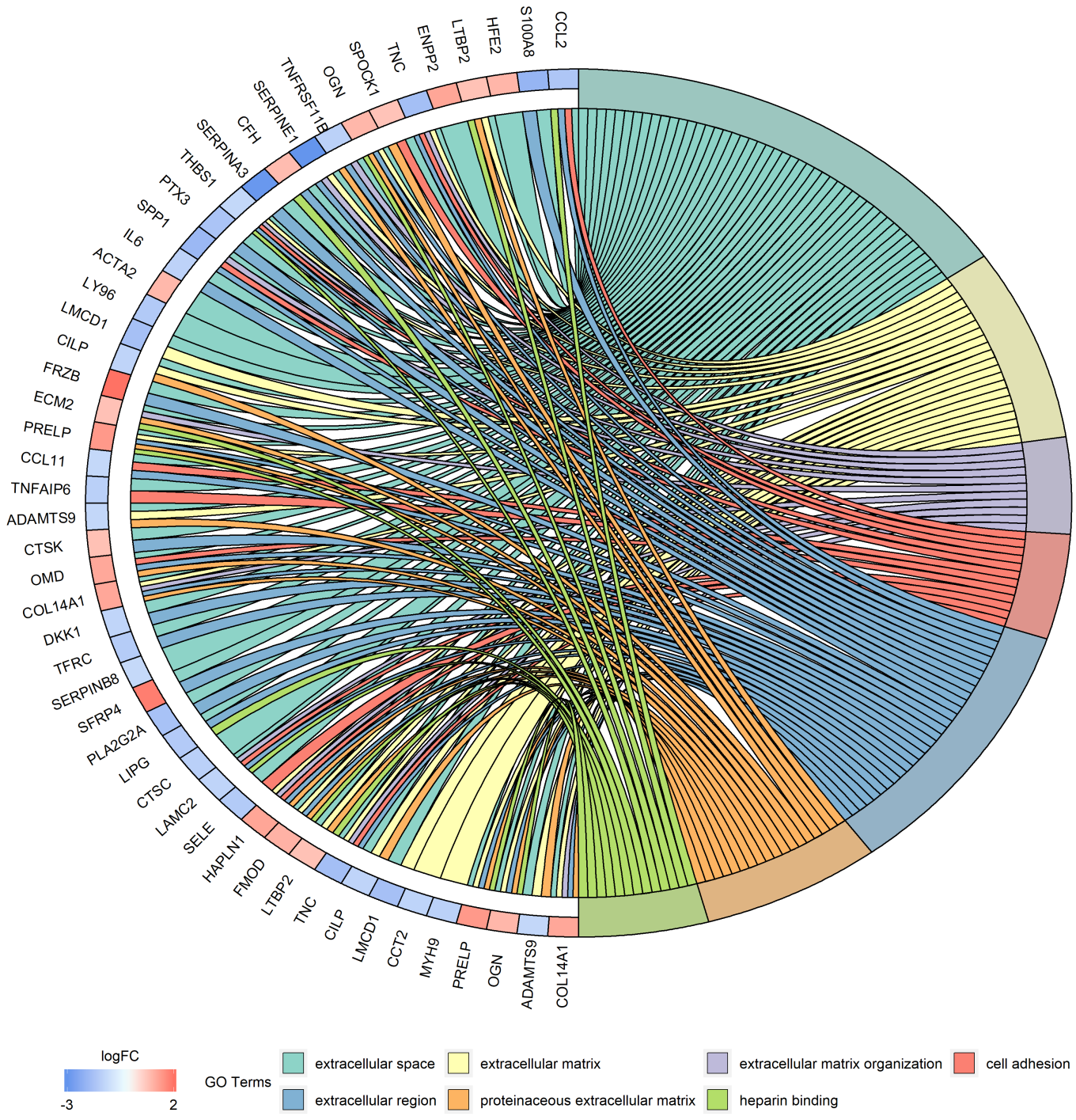

Figure 4

The first 50 DEGs enriched seven GO terms. The red represents upregulated genes, the blue represents downregulated genes.

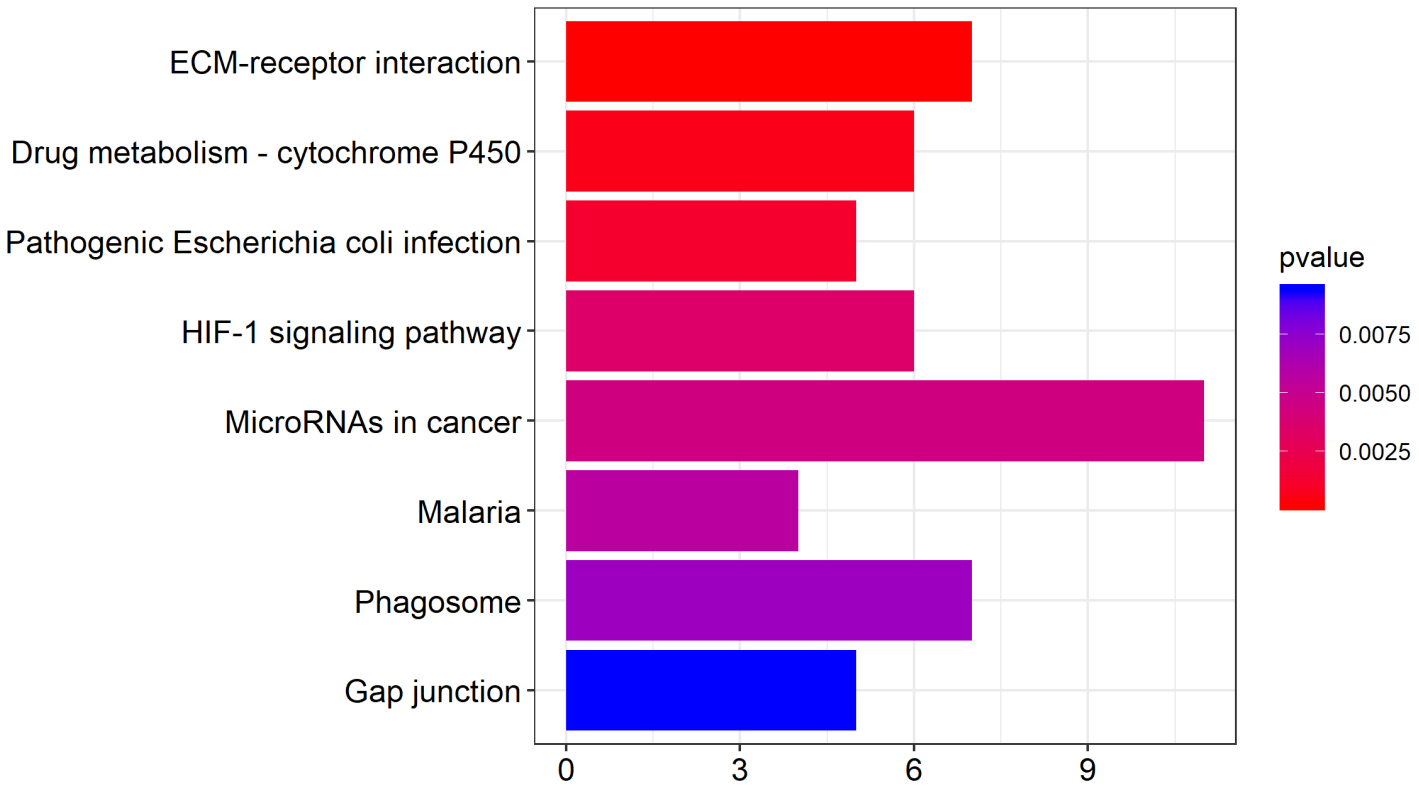

Figure 5

The color represents different P-value degree. The smaller the-value the more meaningful the pathway.

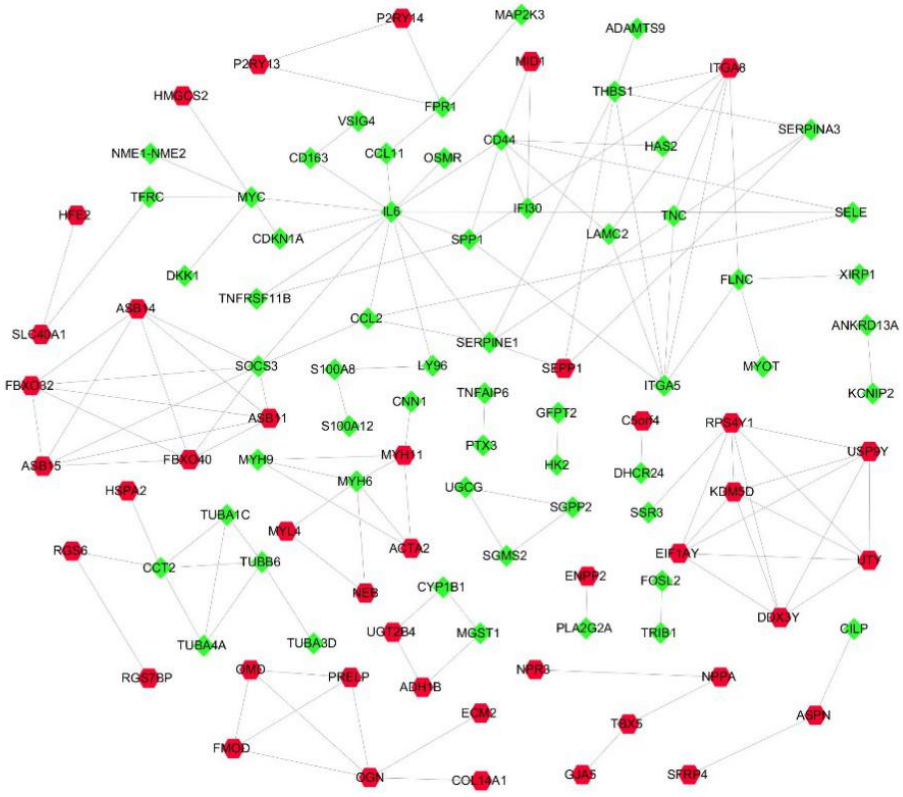

Figure 6

PPI diagram. Rhombus and hexagon represent the gene, and lines represent the interaction between the genes. The red indicates upregulated genes; the green represents downregulated genes.

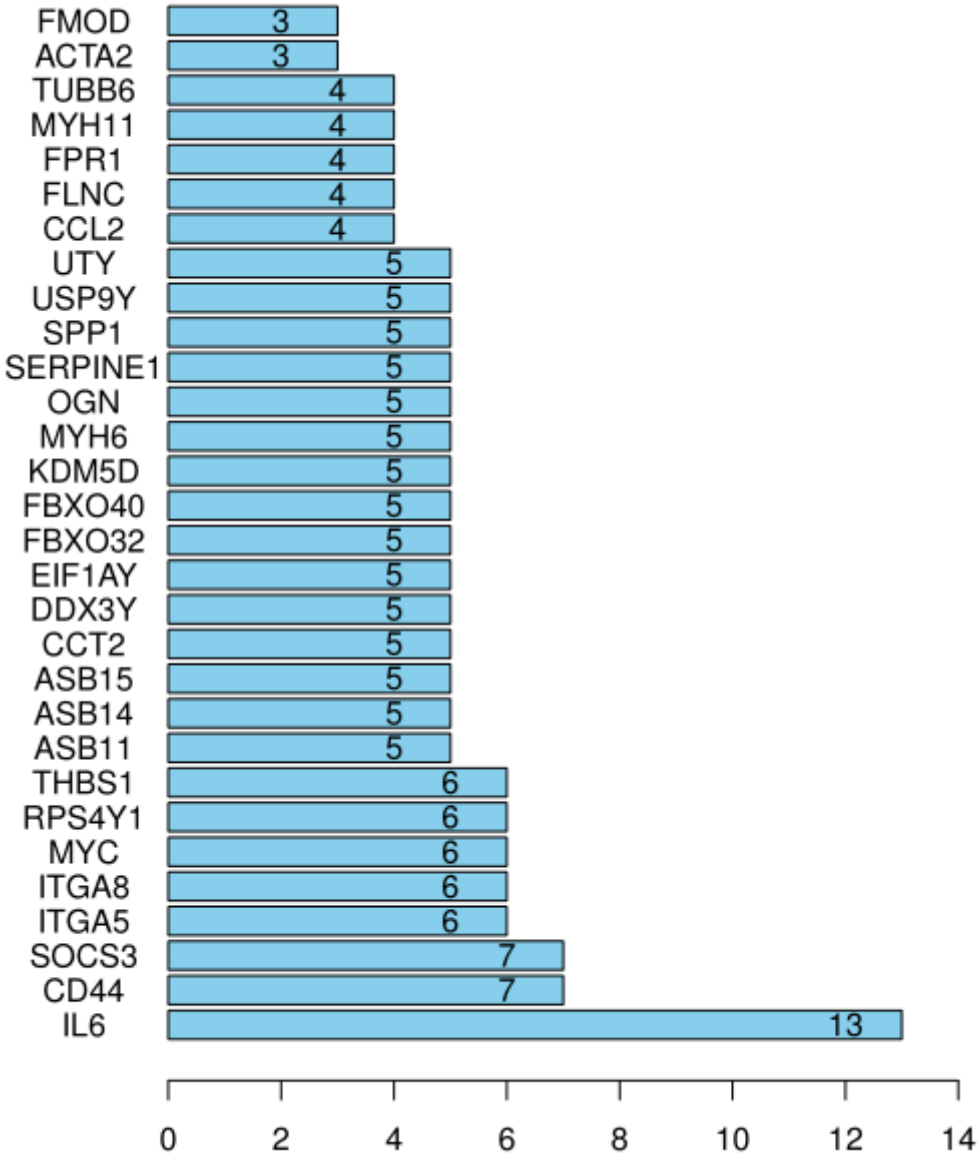

Figure 7

The key proteins histogram. The y-axis represents the name of the first 30 genes, the x-axis represents the number of key genes.