Identification of biomarkers correlated with IgA nephropathy with co-expression analysis

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Research Article

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Abstract

Background. IgA nephropathy (IgAN) is the most common type of chronic glomerular disease with rapid disease progression. However, the pathogenesis of IgAN remains undefined, and it is necessary to improve treatments. Recently, many potential genes closely associated with the molecular mechanism of various diseases have been identified by weighted gene co-expression network analysis.

Results. We identified the 9 gene co-expression modules by performing WGCNA and the tan module was closely related to IgAN biological process. The most of the genes in this module largely involved in immunoreaction, and inflammatory response such as T cell activation, positive regulation of leukocyte-cell adhesion, positive regulation of cell activation. After performing PPI network, we found Protein Tyrosine Phosphatase Receptor Type C(PTPRC) was located at the center. It was identified as a key gene related to IgAN potentially associated to the progression in IgAN. Additionally, validation with other three datasets from GEO also indicated that PTPRC was upregulated in IgAN compared with normal control. Finally, Pearson's correlation analysis between the expression of PTPRC and IgAN kidney function indicated that the aberrant overexpression of PTPRC was related to IgAN renal lesions.

Conclusions. Our study has demonstrated that PTPRC is a potential gene linked with the pathogenesis of IgAN for new interventions.

Methods. We obtained microarray data from the GSE11662 dataset from the gene expression omnibus (GEO) database containing 52 patients with IgAN and 7 healthy controls. Weighted gene co-expression network analysis (WGCNA) was conducted to find the trait-related module. Then, we conducted Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses for further biological information. Finally, we identified the hub gene by protein-protein interaction (PPI) network and other three datasets validation, followed by exploring the associations between the key gene and kidney function with IgAN using the Nephroseq v5 online database.

Introduction

IgAN is the most common type of chronic glomerular disease with rapid disease progression. About 20–40% of patients progress to end-stage renal disease (ESRD) within 10–20 years of diagnosis. Due to the deficiency of a satisfactory treatment for IgAN, it is imperative to further explore the underlying pathogenesis and instruct the treatment of it. Many potential genes closely associated with the molecular mechanism of various diseases have been identified by weighted gene co-expression network analysis(WGCNA). WGCNA can divide genes into modules based on the gene co-expression similarities, resulting in a cluster of genes with common biological regulatory functions, whereas the most central genes in a crucial module are regarded as hub genes, and thus the correlation networks can be applied to screen out key genes and pathophysiological-related pathways. In this research, our efforts concentrated on obtaining gene-network signature and hub genes to elucidate the pathophysiology of IgAN development at the molecular level, which may be utilized as therapeutic targets.

IgA nephropathy (IgAN) is the most leading chronic glomerular disease globally, and the patients were very young1. About 20–40% of patients progress to end-stage renal disease (ESRD) within 10–20 years of diagnosis2-5. Major clinical risk factors for progression to ESRD are persistent proteinuria, arterial hypertension, decreased estimated glomerular filtration rate (eGFR), and renal histology1, 4, 6, 7. Due to the deficiency of a satisfactory treatment for IgAN, it is imperative to further explore the underlying pathogenesis and instruct the treatment of it. Currently, a lot of attention has been given to the field of molecular mechanisms underlying IgAN, involving gd-IgA18, oxidative stress9, growth factor10, as well as gasotransmitters11. Additionally, there must be ethnic and genetic components contributing to IgAN. Recent genome-wide association studies (GWAS) and many studies on common variants increase our understanding of it12-14. For example, the genetic background has an important value in evaluating the progress in patients with this disease15. Furthermore, there is extensive evidence supporting that the expression of genes or proteins, distinguished from the relatively static DNA sequences, represents the dynamics of IgAN16, 17. However, the underlying genetic basis remains largely unknown.

To date, the microarray technique has developed rapidly and bioinformatic data-mining of the gene has widely been used for differential expression analysis to detect novel biomarkers of diseases related to the pathogenesis of diseases. Weighted gene co-expression network analysis (WGCNA) is one of the data mining methods, widely used to identify key genes in various diseases, such as heart disease18, 19, endocrine disease 20-22, mental diseases23, 24, tumors25-28, and kidney diseases29-31. WGCNA32 can divide genes into modules based on the gene co-expression similarities, resulting in a cluster of genes with common biological regulatory functions, whereas the most central genes in a crucial module are regarded as hub genes, and thus the correlation networks can be applied to screen out key genes and pathophysiological-related pathways.

In this research, our efforts concentrated on obtaining gene-network signature and hub genes to elucidate the pathophysiology of IgAN development at the molecular level, which may be utilized as therapeutic targets.

Results

Evaluation and preparation of data

A total of 88 renal tissue biopsies sample raw data were downloaded from the GEO Database. We extracted expression profiles of 20784 genes from 52 renal samples in IgAN and 7 normal renal samples for further WGCNA analysis. Then we performed cluster analysis for the 59 renal samples above and the final results are shown in Fig. 1.

Construction of the weighted gene co-expression network

Based on the Scale-Free Networks principles of WGCNA, we screened the soft-threshold and the result was shown in Fig. 2. When selecting $\beta = 4$, we can obtain better Connectivity (Fig. 2). The co-expression modules were identified by Dynamic Tree Cutting and with diverse colors (Fig. 3). 10 mRNA modules were

generated, in which the size of genes ranged from 79 to 2,829. Genes in each module had similar co-expression traits.

Selection of trait-related modules

The correlations between modules and Traits were presented in Fig. 4A. The tan module (231 genes) was the most positively related to IgAN (r = 0.28, P = 0.03). We plotted a scatterplot of the GS and MM in the tan module. There was a highly significant correlation between the GS and MM in that (cor = 0.33, p = 2.9e − 07) (Fig. 4B). Hence, tan modules were confirmed as the most valuable modules for further analysis.

Functional enrichment analysis

We performed GO and KEGG enrichment analysis in the tan module. GO analyses revealed 506 BPs, 33 CCs, and 33 MFs. The top 10 GO items in the tan module were present in Fig. 5. In the case of their biological process (BP), the most of genes largely involved in immunoreaction, and inflammatory response, such as T cell activation (40 genes, P = 2.16E-25), leukocyte cell − cell adhesion (31 genes, P = 4.20E-20), positive regulation of leukocyte cell − cell adhesion (24 genes, P = 1.48E-17), positive regulation of cell activation (30 genes, P = 2.62E-17). Regarding cellular component (CC), the enriched genes were associated with the external side of the plasma membrane (34 genes, P = 3.36E-21), plasma membrane signaling receptor complex (16 genes, P = 1.01E-07), and immunological synapse (7 genes, P = 1.15E-07) secretory granule lumen (15 genes, P = 1.06E-06). For their molecular function (MF), the enriched genes were closely related to immune receptor activity (13 genes, P = 2.08E-09), cytokine receptor activity (9 genes, P = 9.16E-07), and antigen-binding (11 genes, P = 1.86E-06).

The top 10 terms of the KEGG enrichment analysis in the tan module were shown in Fig. 6, in which most of the genes were linked to immunity and inflammation. The top fourth genes were the following: Hematopoietic cell lineage (16 genes, P = 8.77E-13) and Viral protein interaction with cytokine and cytokine receptor (12 genes, P = 2.43E-08), Primary immunodeficiency (8 genes, P = 6.53E-08), and Staphylococcus aureus infection (11 genes, P = 1.56E-07).

Construction of PPI network

We imported the genes of the tan module in the STRING database for constructing the PPI network to determine the protein interactions (Fig. 7). A total of 146 interaction pairs were identified among those genes. CentiScape plugin was applied for visualization. We calculated the MCC values of each gene and identify the key gene. Ultimately, PTPRC, with the largest MCC value, was confirmed as the hub gene potentially associated with IgAN.

GEO validation

The expression of the hub gene in three other datasets (GSE93798, GSE37460, GSE104948) was calculated. Data analysis revealed compared with the expression level in normal kidney tissues, the

PTPRC was overexpressed in IgAN. This conformed to our finding(Fig. 8).

Clinical validation

We explored the expression of PTPRC correlated to the clinical attributes of IgAN using the Nephroseq v5 online database. The expression of PTPRC correlates negatively with glomerular filtration rate (GFR) with IgAN ($r = -0.588$, $P = 0.003$), suggesting high PTPRC expression may be the risk of IgAN exacerbations (Fig. 9).

Discussion

IgAN is the most common type of chronic glomerular disease with rapid disease progression1. Prompt diagnosis and early therapeutic intervention are the success of delaying the progression of IgAN. Thus, reliable biological markers for diagnosis and treatment related to IgAN are important in clinical practice. We used the WGCNA widely utilized system biology method to screen out the tan module most closely related to IgAN. Subsequently, we performed GO enrichment analysis and KEGG pathway enrichment analysis to investigate the underlying pathogenesis. GO enrichment analyses enriched 231 genes chiefly in T cell activation and cell-cell adhesion. And the result of KEGG enrichment analysis revealed genes were mostly involved in immune and inflammatory responses. Moreover, PPI network analysis showed PTPRC was one of the hub genes with 18 interaction pairs. PTPRC was upregulated in IgAN kidney tissue compared to normal tissues. External validation from the other three GEO databases also revealed the same result. Furthermore, we conducted the Pearson's correlation analysis between the level of PTPRC and renal function in IgAN, showing it may associate with the progress of IgAN.

PTPRC(CD45) is a type I transmembrane protein tyrosine phosphatase (PTPase) located on chromosome 1q31.3-q32.1, widely expressed on the surface of lymphocytes and nuclear hematopoietic lineage cells33. Activation of the Janus kinase/signal transducer and activator of transcriptions (JAK/STAT) signaling pathway promotes the development of various diseases,such as leukemia and lymphoma, diabetes, cancer,and immunological disorders. PTPRC is the negative regulator of the JAK/STAT signaling pathway34. PTPases have become important targets for treatment35-37.

PTPRC also is a modulator of antigen receptor signaling in T and B lymphocytes38, playing a key role in lymphoid-mediated signaling: development, proliferation, activation, and secretion39, 40, which is closely related to the body's immune response function, autoimmunity, and viral infectivity37, 41, 42.

While the knowledge regarding the function of PTPRC and its relationship with kidney disease is very limited.

The specific cause of systemic lupus erythematosus (SLE) is still unknown. It has been reported that abnormal JAK / STAT signaling pathway may be associated with the onset of SLE43, 44.A 2016 interracial GWAS Meta-analysis study identified PTPRC as strongly associated with SLE 45. The decreased PTPRC mRNA expression may play suggestive roles in the pathogenesis of SLE46.

Various diabetic milieus, like high glucose, Ang II, and advanced glycation end products (AGE) can activate the JAK/STAT pathway. The activated JAK/STAT pathway further stimulates excessive proliferation and growth of glomerular mesangial cells, contributing to diabetic kidney injury47, 48. PTPRC with an upregulated expression level may be an indicator for early diagnosis of DN.

The relationship between PTPRC and IgAN has not been previously elucidated. However, an unbalanced expression of the JAK/STAT signaling pathway may be involved in the pathogenesis of IgAN patients and associated with the Dysregulation of subsets of CD4 + T lymphocytes49.

It is shown that CD4 + T lymphocytes play an important role in regulating IgA1 generation, dysregulation of CD4 + T lymphocytes may lead to excessive abnormal IgA1 in B lymphocytes, deposition in the glomerulus, disorder of the promoting immune system, ultimately leading to the development of IgAN50. The JAK/STAT signaling pathway plays a key role in CD4 + T lymphocyte differentiation51. Besides, the expression level in IgAN of CD45 in tubulointerstitial areas has a direct correlation with albuminuria, renal function level in patients of IgAN52.

Conclusions

Therefore, we propose that PTPRC overexpression regulates immune and inflammatory pathways that are involved in the pathogenesis of IgAN.

We identified PTPRC as a key gene related to IgAN by constructing a WGCNA network. Our study provides new insight into the molecular mechanisms underlying IgAN and may offer a novel candidate target for the precise treatment of this disease.

Materials & Methods

Microarray Data information and Data pre-processing

We obtained GSE116626 matrix format files from the Gene Expression Omnibus (GEO) database of the National Center of Biotechnology Information (NCBI)(GPL14951 platform, Illumina HumanHT-12 WG-DASL V4.0 R2 expression bead chip). GSE116626 contains 81 samples, including 52 renal tissue samples from the patients with IgAN and 7 renal tissue samples from healthy controls. All of the high-throughput gene expression data were available online. We converted the probes into the corresponding gene symbol based on the annotation information in a Perl environment. If a gene matched several probes, the average value of the different probes would be calculated. We deleted the microarray probes that matched multiple genes.

WGCNA network construction and identification of modules

We performed the co-expression network using the WGCNA R package based on the GSE116626 microarray dataset32. Initially, gene expression correlation was calculated with Pearson’s correlation

coefficient. A correlation matrix was generated by the pair-wise correlations of all genes in each group. Next, an appropriate soft power threshold was selected to calculate the adjacency matrix and form a scale-free network translation. Subsequently, it was converted into a Topological Overlap Matrix (TOM). Based on TOM, modules of correlated genes were generated with hierarchical clustering and cut tree Dynamic function visualized in a dendrogram. Module eigengenes (MEs) were the major components of module genes, which were representatives of gene expression profiles of a given module32. We calculated the correlations of the MEs in different modules and merged modules with highly correlated MS into one. Further, the modules correlated to the clinical traits were selected based on module membership (MM) and gene significance (GS). Finally, the eigengene network was visualized.

Bio-function enrichment analysis

We performed the Gene Ontology(GO)and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis using the cluster profile package in Bioconductor. P□0.05 indicated that there was a significant difference.

Protein-protein interaction (PPI) network construction

STRING2 database (https://string-db.org/) is a major bioinformatics tool for proteins, analyzing their interactions and functions. We searched STRING online and built the PPI network to detect the biological relationships among genes in the trait-related module. After that, we imported the exported data into Cytoscape for network visualization. The genes with the highest degree of connectivity were identified as the key genes.

GEO validation

To confirm the findings through the co-expression network, we compared the expression level of the key genes associated with IgA and healthy controls in three other datasets downloaded from GEO.

Clinical validation

Nephroseq v5 online database (http://v5.nephroseq.org) is a database resource for gene expression data sets of kidney diseases. We analyzed the correlation between the hub gene and the clinical traits of IgAN for clinical validation using the Nephroseq v5 online database. P value of < 0.05 was considered statistically significant.

Declarations

Acknowledgements

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Data Availability

The raw data of GSE116626, GSE104948, GSE37460, GSE93798 were available from the GEO website (https://www.ncbi.nlm.nih.gov/geo)

Ethic

All authors did not perform any experiments on humans or animals.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript

Author Contributions

Wang Lijuan and Wang Dan participated in the design, performed the WGCNA, and drafted the manuscript,these authors share first authorship.Baokun and Zhaodaixin designed this research, and created the final revision of the manuscript. Hongxiaofan and Liping contributed in formal analysis. All authors read and approved the final manuscript.

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Conflict of interests

The authors declare that there are no conflicts of interests.

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Figures

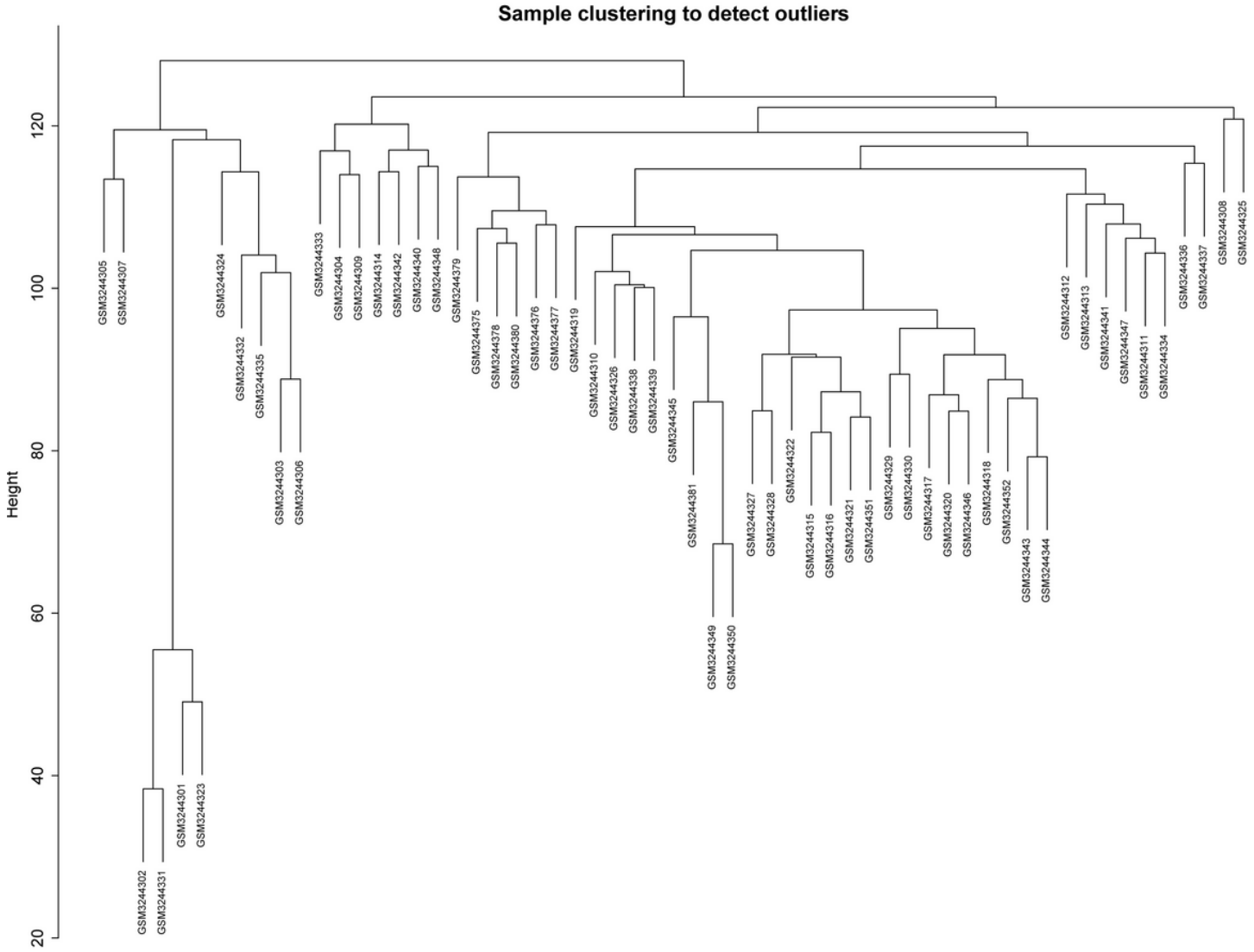

Figure 1

Gene cluster analysis. The branches of the dendrogram correspond to clustered samples.

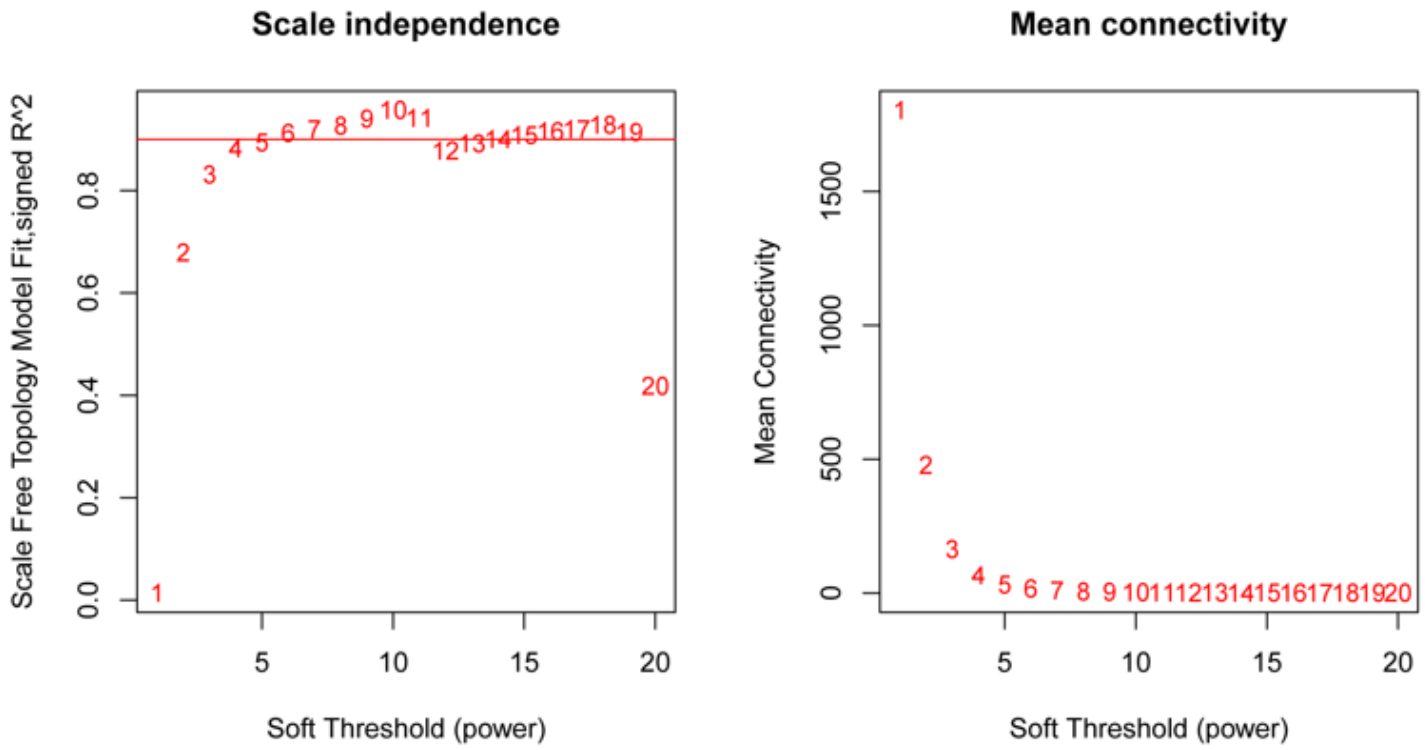

Figure 2

Construction of the scale-free network with a suitable soft-thresholding power (β). The red line symbolizes the value of the scale-free fit index (0.85).

Figure 3

Construction of the weighted gene co-expression network. Each branch represents a module.

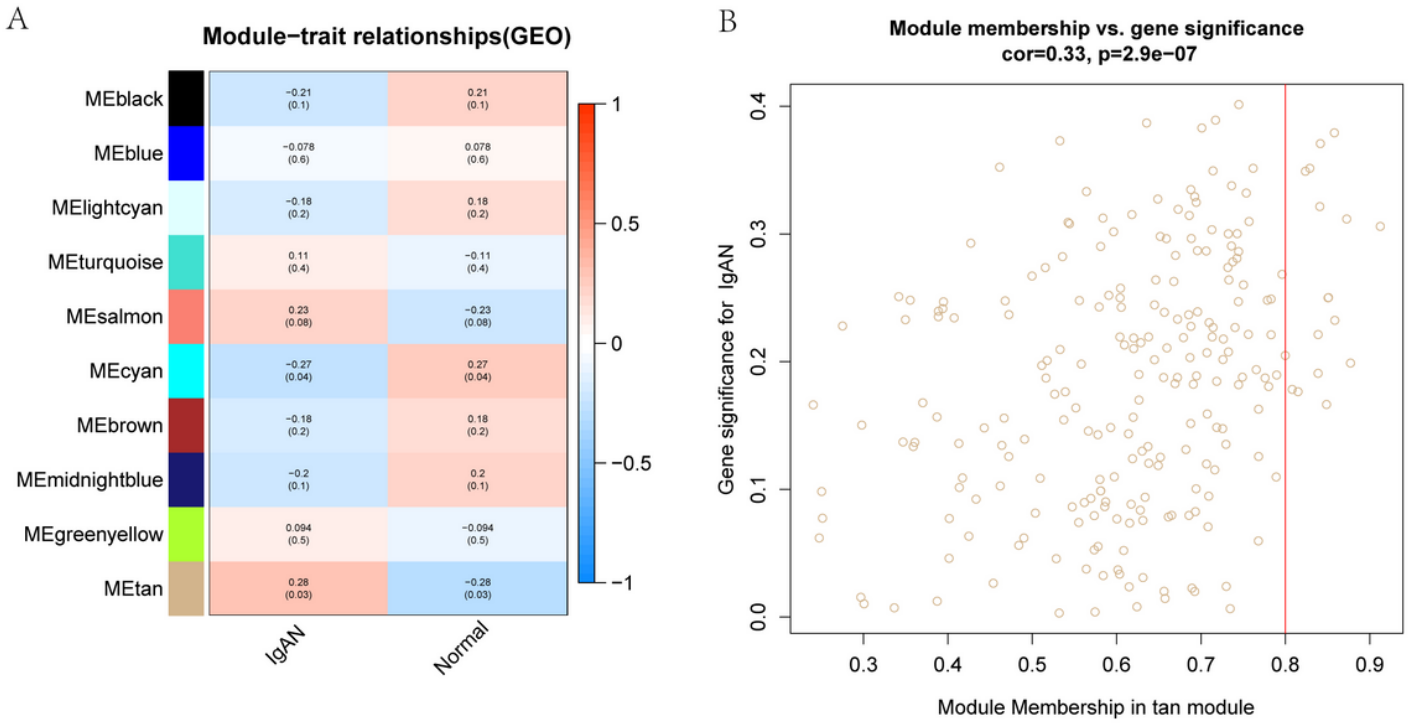

Figure 4

Selection of trait-related modules. (A) Module-trait relationships heatmap. Rows correspond to modules, while columns correspond to traits. The correlation and P values are shown in the cells. Colors from blue to red correspond to the correlation between the module and the trait from low to high. (B) The relationship between the module membership and gene significance in the tan module.

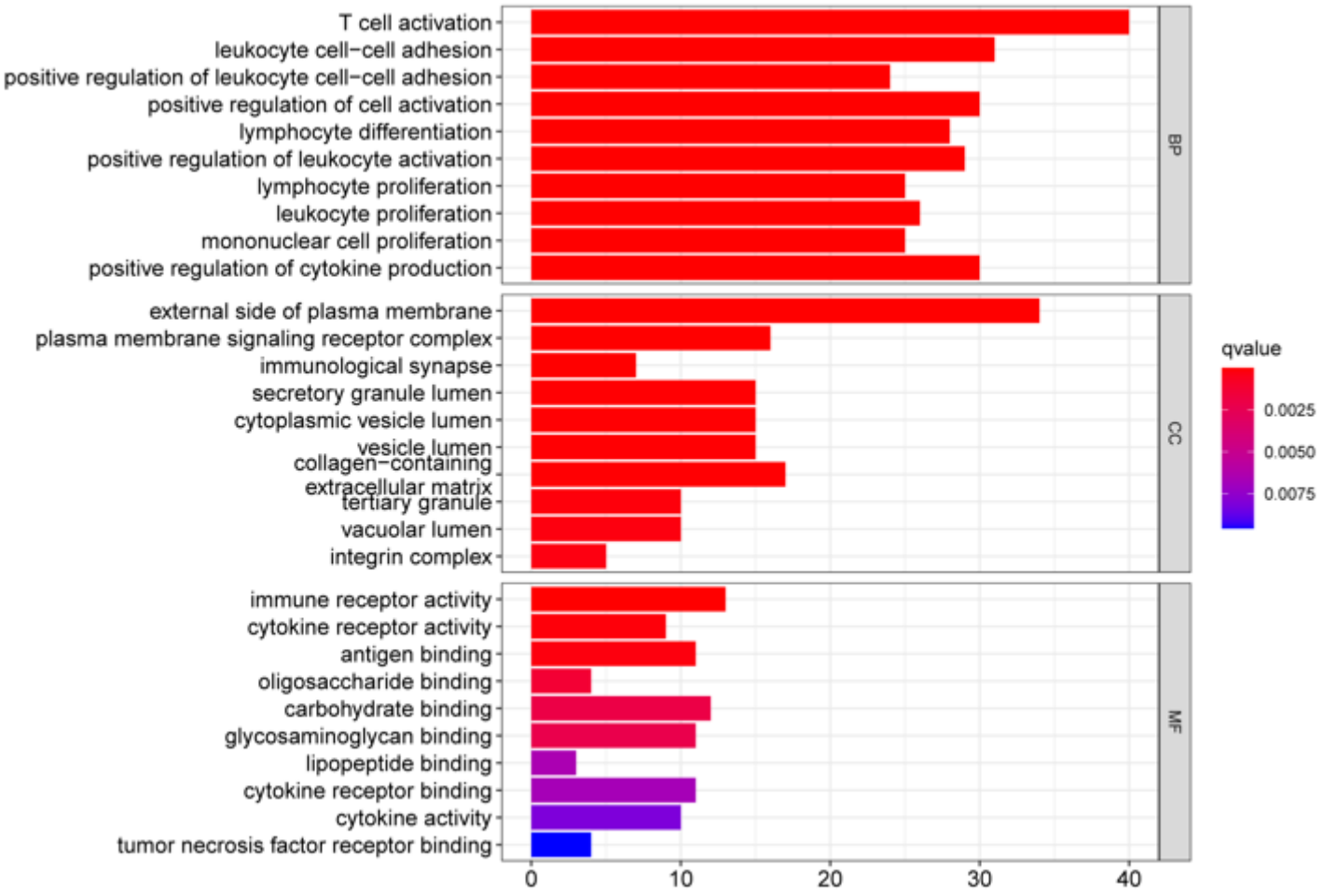

Figure 5

The top 10 most statistically significant terms of the enrichment analyses of the tan module: biological process (BP) terms; cellular component (CC) terms; molecular function (MF) terms. The length of the strip denotes the gene count and the color scale corresponds to the significance of the enrichment.

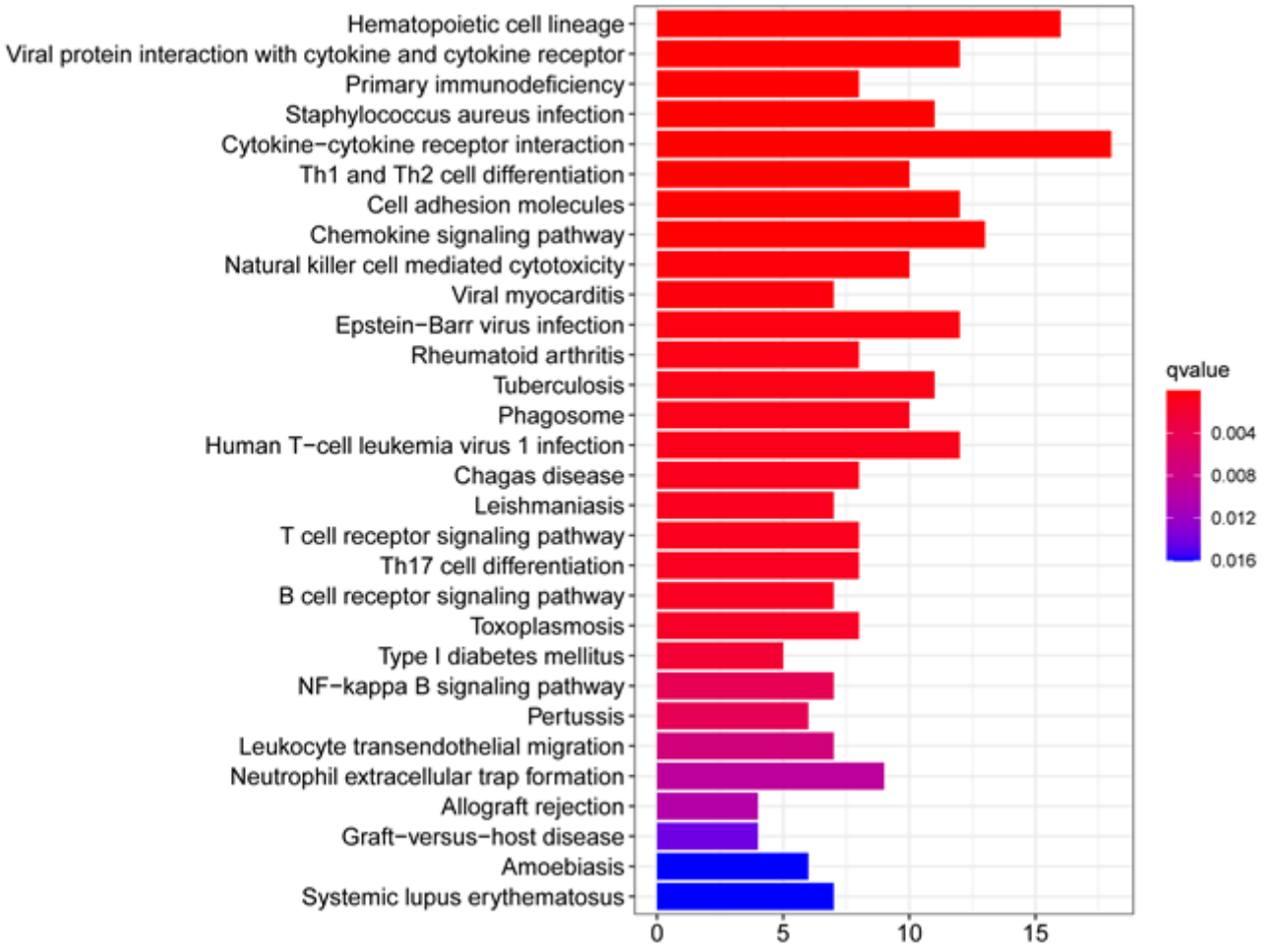

Figure 6

The top 10 most statistically significant terms of the enrichment analyses of the tan module: Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

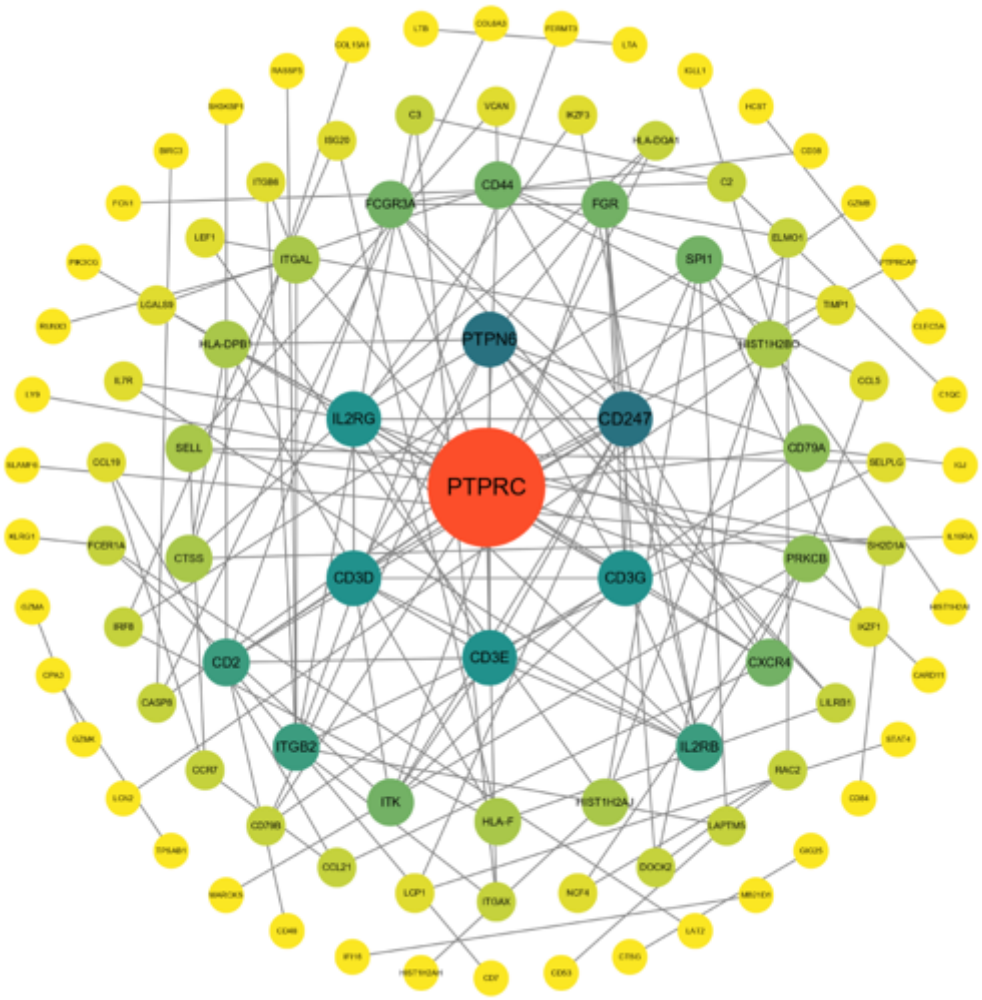

Figure 7

Protein-protein interaction (PPI) network creation in the tan module.

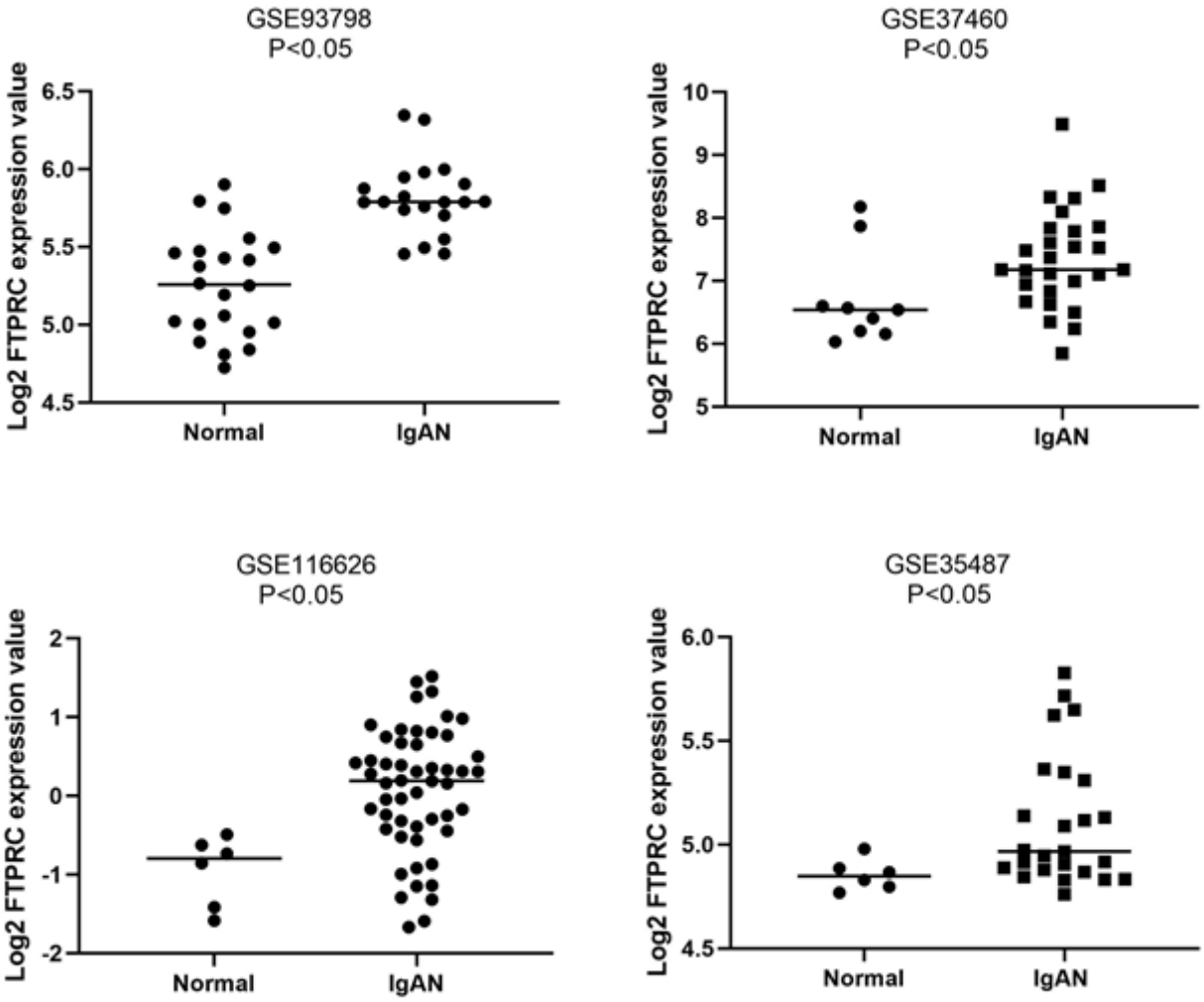

Figure 8

GEO validation: the expression of PTPRC in IgAN compared with normal tissues in the GSE93798, GSE37460, GSE35487 datasets.

Figure 9

Correlation between the GFR and the expression of PTPRC in IgAN kidney tissue, a P value of <0.05 was statistically significant.