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Exploring Potential Novel Causal Genes for Chronic Kidney Disease

Fangyi Hao[1], Tian Tian[1], Zhen Yang[1] and Jiaxin Zheng[2]*

[1]Department of Nephrology, Heilongjiang Academy of Traditional Chinese Medicine, Harbin, 150001, Heilongjiang Province, China
[2]Department of Nephrology, Second Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine, Harbin, 150001, Heilongjiang Province, China

ABSTRACT

Functional genes underlying chronic kidney disease (CKD) remain unclear. This work explored susceptibility genes related to serum creatinine (Scr) and CKD through Mendelian randomization (MR) analysis.Data from genome-wide association study (GWAS) were selected, with Scr, single nucleotide polymorphisms (SNPs), and CKD as exposure factor, instrumental variables, and outcome variable, respectively. SNPs related to Scr and CKD were screened with $P<5.0\times10^{-8}$ and $r^2=0.001$. Correlation between Scr and CKD was analyzed using inverse variance-weighted (IVW), MR-Egger regression, and weighted median estimator (WME). Intercept term of the MR-Egger method was adopted to assess the SNP sensitivity. Genes regulated by SNPs were identified in the eQTL database, and the intersecting target genes were subjected to GO analysis. Furthermore, interactions among proteins were predicted using the Search Tool for the Retrieval of Interacting Genes (STRING) database.47 SNPs related to Scr and CKD were identified in the retrieved GWAS database. Results from the MR-Egger, WME, IVW, and Weighted mode methods all indicated a negative correlation (NC) between Scr and CKD ($P<0.05$). 22 SNPs regulated 19 genes, which were associated with various biological processes (BPs). Key genes associated with CKD were DAB2, UBE2Q2, KCNQ1, SHROOM3, and PRKAG2.A NC between Scr and CKD was observed. DAB2, UBE2Q2, KCNQ1, SHROOM3, and PRKAG2 were linked with CKD, providing new insights for understanding the pathogenesis of CKD and the design of drug targets.

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FH and TT collected the samples. ZY and JZ analysed the data. FH conducted the experiments and analysed the results. All authors discussed the results and wrote the manuscript, and approved the final version for publication.

Key words
Serum creatinine, Chronic kidney disease, Mendelian randomization, Single nucleotide polymorphisms, Susceptibility genes

INTRODUCTION

Chronic kidney disease (CKD) is defined as the sustained reduction or damage of kidney function over a period of three months or more, characterized by features such as decreased glomerular filtration rate (GFR), urinary protein excretion, or renal pathology (Ruiz-Ortega *et al*., 2020). Clinical manifestations of CKD often include symptoms like proteinuria, hematuria, edema, hypertension, and anemia. The global prevalence of CKD ranges from 7% to 12% (Naber and Purohit, 2021), with particularly high incidence rates observed in some developing countries, likely attributed to the rising prevalence of diabetes and hypertension (Evans *et al*., 2022). CKD incidence significantly increases with advancing age (Yanai *et al*., 2021). CKD ranks among the major causes of premature death worldwide, accounting for around 7% of global mortality (Zhu *et al*., 2022). Current research findings indicate that various risk factors, including hypertension, diabetes, glomerular and tubular diseases, genetic factors, lipid metabolism disorders, age, gender, smoking, obesity, and unhealthy dietary habits, contribute to the development of CKD (Wang *et al*., 2019; Hu *et al*., 2018). Current clinical interventions for CKD involve strategies such as dietary control and nutritional support, hypertension management, blood sugar control, medication, hemodialysis, and kidney transplantation.

Despite some progress made in research and clinical practice, the specific causes and pathogenesis of CKD remain incompletely understood. In recent years, with the rapid advancement of genetics, researchers have discovered that specific genetic mutations are associated with certain hereditary forms of CKD, indicating the significant role of genetic factors in influencing patient risk and disease progression. Genome-wide association studies (GWAS) for CKD are methods employed to investigate the genetic factors contributing to the risk of CKD development. Through GWAS, researchers have identified multiple

* Corresponding author: zjxemail@163.com
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genetic variants associated with CKD (Yamada *et al*., 2013; Kim *et al*., 2021), which may be located within gene regions relevant to kidney function and structure. GWAS has also identified novel genetic risk markers (Sugawara *et al*., 2023) that could be relevant to the pathogenesis of CKD. In addition to identifying genetic variations associated with CKD, GWAS can pinpoint specific gene regions with high precision (Khan *et al*., 2022). Mendelian randomization (MR) analysis is a causal inference method that utilizes genetic variations as naturally randomized instruments to explore causal relationships. Based on Mendelian genetics principles, MR leverages genetic variations to estimate the relationship between the exposure variable and the potential influencing factor in the outcome variable. As a powerful genetic epidemiology approach, MR can mitigate biases introduced by confounding factors and offer a novel approach to address causal relationships. MR assesses whether a risk factor leads to a specific disease by examining the impact of genetic variations on that risk factor (Birney, 2022). By combining large-scale genomic data with clinical information on CKD, MR analysis can help uncover potential novel causal genes related to CKD and further reveal their mechanistic roles in the occurrence and development of the disease.

Serum creatinine (Scr) is a crucial clinical marker for assessing kidney function; however, the causal relationship between Scr and CKD remains contentious, and the functional genes contributing to CKD onset remain unclear. Hence, this work employed MR analysis based on aggregated data to explore potential novel causal genes for CKD to enhance our understanding of the genetic links with CKD, providing new targets and strategies for prevention, treatment, and personalized medicine for CKD. Simultaneously, it contributed new scientific evidence to the prevention and management of CKD.

METHODS AND METHODS

Research design

The MR analysis method was employed, with Scr as the exposure factor and single nucleotide polymorphisms (SNPs) significantly associated with CKD serving as instrumental variables, while the outcome variable was CKD itself. SNPs closely related to Scr were selected from the GWAS database to obtain SNPs associated with both Scr and CKD. The reliability of the causal association was assessed and validated through Cochran's Q test and the MR-Egger method.

Screening the CKD-related SNPS

The GWAS (https://gwas.mrcieu.ac.uk/) was searched for SNPs associated with Scr and CKD. In this work, two GWAS ID datasets from the GWAS database were utilized: The genomic association ID for Scr was ieu-a-1105, with a Pubmed ID of 26831199, encompassing a sample size of 133,814 individuals, a total of 2,198,208 SNPs, conducted on a mixed population, and established in the year 2015. For CKD, the genomic association ID was ieu-a-1102, with a Pubmed ID of 26831199, involving a sample size of 117,165 individuals, a total of 2,191,877 SNPs, conducted on a mixed population, and established in the year 2015.

Based on the relevant data in the GWAS database, SNPs that were significantly associated with both Scr and CKD were selected using the following criteria: P<5.0×10-8, an r^2=0.001, and an interval of 10,000 base pairs (kb). When conducting heterogeneity tests, SNPs exhibiting obvious heterogeneity were excluded to obtain the effective SNPs tightly correlated with Scr.

Screening genes regulated by SNPS in EQTL

SNPs related to Scr and CKD were retrieved from online databases. The eQTL Browser (https://www.hsph.harvard.edu/liming-liang/software/eqtl/) and Ensembl (https://www.ensembl.org/Homo_sapiens/Location/View?db=core) were adopted for this purpose. The eQTL Browser offers a Genome Browser (GBrowse) interface that allowed users to explore eQTL associations in different tissues across the genome. Through this tool, users can select specific tissues or datasets of interest and view eQTL analysis results associated with the chosen gene. Ensembl served as a comprehensive genome annotation database, providing detailed gene and variant annotation information. Ensembl was utilized to retrieve information such as gene names, functions, and potential impacts associated with the identified SNPs.

MR analysis

In this work, Scr and CKD were utilized as outcome variables, while gene expression served as the exposure factor. The most significant eQTL effect sites were selected as instrumental variables to establish the MR model. The objective was to analyze whether eQTLs might lead to the occurrence of CKD through changes in gene expression levels. The effect of gene expression levels on Scr and CKD was computed using the least squares method. The calculation of the effect value followed the equation:

$$B= b_1/b_2$$

In the equation above, B represented the effect value, where b_1 signified the impact of the eQTL effect site on gene expression levels, and b_2 indicated the influence of the eQTL effect site on Scr and CKD.

The analysis of the correlation between gene expression levels and Scr/CKD was conducted using the IVW, MR-Egger regression, and WME methods. Statistical

significance was considered for P values greater than 0.05.

Heterogeneity test

To eliminate the linkage model, further analysis was undertaken using a heterogeneity test. The greater the differences between different SNPs, the higher the level of heterogeneity. Genes with a heterogeneity test P value greater than 0.05 were selected, leading to the exclusion of genes involved in the linkage model. Additionally, SNPs that were in linkage with each other (with a pairwise correlation coefficient r2>0.8) were removed. The screening criteria included eQTLs with P<5×10-8 for inclusion in the calculations.

GO analysis

The SNPs-associated genes were filtered, and the intersecting target genes obtained from the filtering process were subjected to a Gene Ontology (GO) pathway analysis using the DAVID 6.8 database. All screening criteria were set with P<0.05. In the results analysis, the key genes within the signaling pathways (SPWs) were listed to highlight their role.

Protein-protein interaction (PPI) network analysis

The PPIs were predicted using the STRING database (https://string-db.org/) and assessed based on the PPI scores, which indicated the likelihood of interactions among proteins. Differential genes encoding proteins were input into the STRING database, with a filtering threshold set at a binding score > 0.4. A PPI network diagram was constructed, and key genes were selected. The degree algorithm predicted the scores, which were represented by varying shades of color, indicating the strength of the interactions.

RESULTS

Screened SNPS related to Scr and CKD

In the retrieved GWAS database, 47 SNPs associated with Scr and CKD were identified. The detailed statistical information for these SNPs was presented in Table I.

Analysis on SNPS related to Scr and CKD

Four different methods, namely MR Egger, WME, IVW, and Weighted mode, were employed to analyze the correlations between Scr and CKD, and the results of the analysis were presented in Table II. All four methods yielded statistically great associations between Scr and CKD (P<0.05).

The funnel plot for the MR analysis of the correlation between Scr and CKD was illustrated in Figure 1. It was evident that the results obtained from various analysis methods were consistent with the aforementioned findings, indicating an obvious association between Scr and CKD (OR= -7.28, 95% CI: -8.19 to -7.03) (P<0.05).

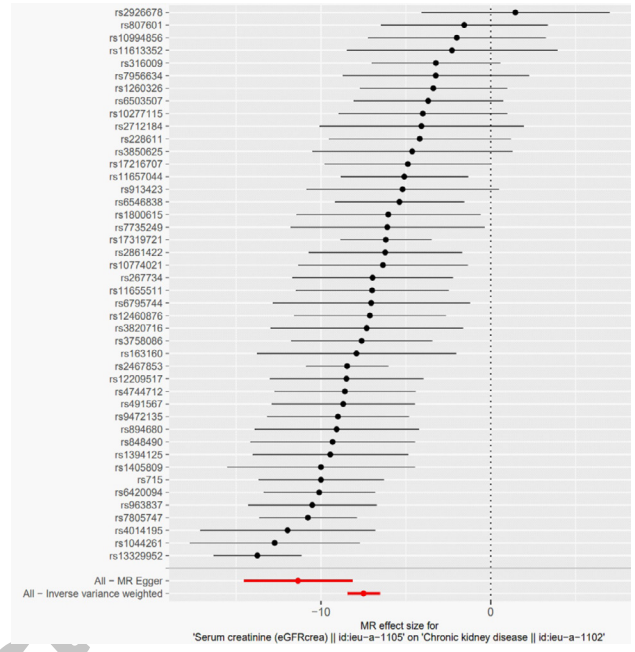

Fig. 1. The funnel plot for the MR analysis of the correlation between Scr and CKD.

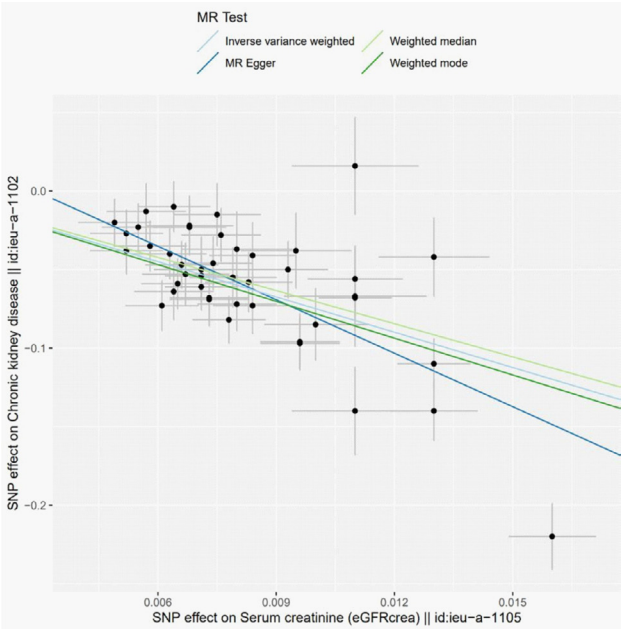

Fig. 2. The scatter plot for the MR analysis of the correlation between Scr and CKD.

The scatter plot for the MR analysis of the correlation between Scr and CKD was depicted in Figure 2.

Table I. Screened SNPs related to Scr and CKD.

SNPs	Effect allele	Other allele	Location	Chr	Scr-related SNPs				CKD-related SNPs			
					β	Eaf	SE	P value	β	Eaf	SE	P value
rs10277115	T	A	1285195	7	-0.0095	0.785	0.0014	1.10E-10	0.038	0.785	0.024	0.12
rs1044261	T	C	1065710	10	-0.011	0.084	0.0016	1.20E-11	0.14	0.084	0.028	3.60E-07
rs10774021	T	C	349298	12	-0.0063	0.695	0.00092	4.80E-12	0.04	0.695	0.016	0.012
rs10994856	A	G	52645248	10	0.0075	0.186	0.0011	1.20E-10	-0.015	0.186	0.02	0.46
rs11613352	T	C	57792580	12	0.0057	0.25	0.001	4.70E-08	-0.013	0.25	0.018	0.47
rs11655511	T	C	59287269	17	-0.0083	0.779	0.0011	1.00E-13	0.058	0.779	0.019	0.00269998
rs11657044	C	T	59450105	17	0.011	0.82	0.0012	7.90E-22	-0.056	0.82	0.021	0.00659994
rs11959928	A	T	39397132	5	-0.0083	0.431	0.00092	1.70E-20	0.054	0.431	0.015	0.000420001
rs12209517	G	C	1.61E+08	6	-0.01	0.096	0.0013	1.10E-14	0.085	0.096	0.023	0.00016
rs12460876	C	T	33356891	19	0.0066	0.423	0.00092	1.90E-13	-0.047	0.423	0.015	0.00219999
rs1260326	C	T	27730940	2	-0.0068	0.58	0.00092	3.40E-14	0.023	0.58	0.015	0.14
rs12975033	T	A	49249443	19	0.0052	0.433	0.00092	4.70E-09	-0.047	0.433	0.015	0.00189998
rs13329952	C	T	20366507	16	0.016	0.217	0.0011	9.50E-43	-0.22	0.217	0.021	2.00E-25
rs1394125	A	G	76158983	15	-0.0073	0.35	0.001	5.50E-14	0.069	0.35	0.017	3.00E-05
rs1405809	A	G	1.56E+08	7	0.0064	0.235	0.001	8.30E-10	-0.064	0.235	0.018	0.000389996
rs163160	G	A	2789955	11	-0.0067	0.143	0.0011	9.70E-09	0.053	0.143	0.02	0.00680002
rs17216707	C	T	52732362	20	0.0084	0.212	0.0011	6.00E-13	-0.041	0.212	0.021	0.0470002
rs17319721	A	G	77368847	4	-0.011	0.42	0.00092	1.30E-37	0.068	0.42	0.015	7.70E-06
rs1800615	T	C	15832281	1	-0.0058	0.231	0.00092	1.90E-09	0.035	0.231	0.016	0.0340001
rs228611	A	G	1.04E+08	4	-0.0055	0.447	0.00092	4.70E-10	0.023	0.447	0.015	0.12
rs2467853	G	T	45698793	15	-0.013	0.328	0.00092	1.00E-42	0.11	0.328	0.016	1.90E-11
rs267734	C	T	1.51E+08	1	0.0079	0.208	0.0011	4.00E-13	-0.055	0.208	0.019	0.00350002
rs2712184	A	C	2.18E+08	2	-0.0049	0.541	0.00092	2.70E-08	0.02	0.541	0.015	0.2
rs2861422	T	C	1.42E+08	3	0.0074	0.248	0.001	9.10E-14	-0.046	0.248	0.017	0.00759994
rs2926678	T	C	87305818	2	0.011	0.621	0.0016	2.20E-11	0.016	0.621	0.031	0.61
rs316009	C	T	1.61E+08	6	-0.013	0.903	0.0014	4.40E-19	0.042	0.903	0.025	0.0969996
rs3758086	A	G	23714992	8	-0.0071	0.446	0.00092	1.70E-15	0.054	0.446	0.015	0.000409996
rs3820716	A	G	1.49E+08	2	-0.0052	0.5	0.00092	2.70E-09	0.038	0.5	0.015	0.0129999
rs3850625	A	G	2.01E+08	1	0.008	0.097	0.0014	6.40E-09	-0.037	0.097	0.024	0.13
rs4014195	G	C	65506822	11	-0.0061	0.327	0.00092	2.20E-11	0.073	0.327	0.016	2.90E-06
rs4744712	C	A	71434707	9	0.0071	0.617	0.00092	4.30E-15	-0.061	0.617	0.015	7.60E-05
rs491567	C	A	53946593	15	0.0084	0.208	0.001	2.90E-15	-0.073	0.208	0.018	7.50E-05
rs6088580	C	G	33285053	20	-0.0055	0.51	0.00092	7.20E-10	0.056	0.51	0.015	0.000219999
rs6420094	G	A	1.77E+08	5	-0.0096	0.367	0.001	4.90E-22	0.097	0.367	0.016	3.70E-09
rs6503507	T	C	37525274	17	0.0076	0.27	0.001	1.50E-14	-0.028	0.27	0.017	0.11
rs6546838	G	A	73679280	2	0.0093	0.252	0.001	7.70E-20	-0.05	0.252	0.018	0.00460002
rs6795744	A	G	13906850	3	0.0071	0.133	0.0012	9.60E-09	-0.05	0.133	0.021	0.0179999
rs715	C	T	2.12E+08	2	-0.0096	0.292	0.001	2.30E-21	0.096	0.292	0.018	5.40E-08
rs7735249	G	C	53310139	5	0.011	0.093	0.0018	2.10E-09	-0.067	0.093	0.032	0.0340001
rs7805747	A	G	1.51E+08	7	-0.013	0.296	0.0011	8.00E-29	0.14	0.296	0.019	2.10E-14
rs7956634	C	T	15321194	12	0.0068	0.174	0.0011	2.50E-09	-0.022	0.174	0.019	0.26
rs807601	T	G	15793014	2	0.0064	0.319	0.00092	6.60E-12	-0.01	0.319	0.016	0.53
rs848490	C	G	77555005	7	0.0073	0.727	0.001	7.80E-13	-0.068	0.727	0.018	0.000140001
rs894680	A	G	19440538	17	-0.0065	0.42	0.00092	1.00E-11	0.059	0.42	0.016	0.000340001
rs913423	A	G	94845036	10	-0.0052	0.535	0.00092	5.10E-09	0.027	0.535	0.015	0.0790005
rs9472135	C	T	43809802	6	0.008	0.266	0.001	3.30E-15	-0.072	0.266	0.017	3.40E-05
rs963837	C	T	30749090	11	0.0078	0.456	0.00092	5.70E-18	-0.082	0.456	0.015	9.00E-08

Chr, chromosome; β, allelic effect value; Eaf, effector allele frequency; SE, standard error of beta.

It was evident from the plot that the correlation results between Scr and CKD were consistent across all four methods. The findings indicated an observable association between Scr and CKD (P<0.05).

Heterogeneity and bias analysis on association between scr and CKD

Heterogeneity testing was conducted on SNPs associated with both Scr and CKD using the IVW and MR-Egger regression analysis methods. The results were presented in Table III. The Cochran's Q test results for both IVW and MR-Egger methods indicated visible heterogeneity among SNPs related to Scr and CKD (P<0.05).

Table □. Data for correlation of Scr and CKD obtained by MR analysis.

Method	SNPs	β	SE	P value
MR Egger	44	-11.35	1.628	1.585e-8
WME	44	-0.741	0.5504	1.827e-37
IVW	44	-7.492	0.4849	7.507e-54
Weighted mode	44	-7.809	1.404	0.000001578

Table □. Heterogeneity test results of SNPs.

Methods	SNPs	Q	Q-df	P value
MR Egger	44	82.42	42	0.0001946
IVW	44	94.41	43	0.00001018

A funnel plot was utilized to assess potential bias in the association between Scr and CKD, as illustrated in Figure 3. The symmetric distribution of the Scr and CKD association effects within the funnel plot suggested a relatively low likelihood of substantial underlying bias affecting the association between Scr and CKD.

GO analysis

In the eQTLBrowser database, 30 SNP-mRNA pairs were identified, consisting of 25 cis-eQTL pairs and 5 trans-eQTL pairs. Among these, 22 SNPs were involved in regulation of 19 genes, which were GTP binding protein 4 (GTPBP4), solute carrier family (SCF) 6 member 13 (SLC6A13), breast carcinoma amplified sequence 3 (BCAS3), disabled homolog 2 (DAB2), solute carrier family 7 member 9 (SLC7A9), ubiquitin-conjugating enzyme E2 Q2 (UBE2Q2), ring finger protein 32-distal transcript (RNF32-DT), potassium voltage-gated channel subfamily Q member 1 (KCNQ1), shroom family member 3 (SHROOM3), spermatogenesis-associated protein

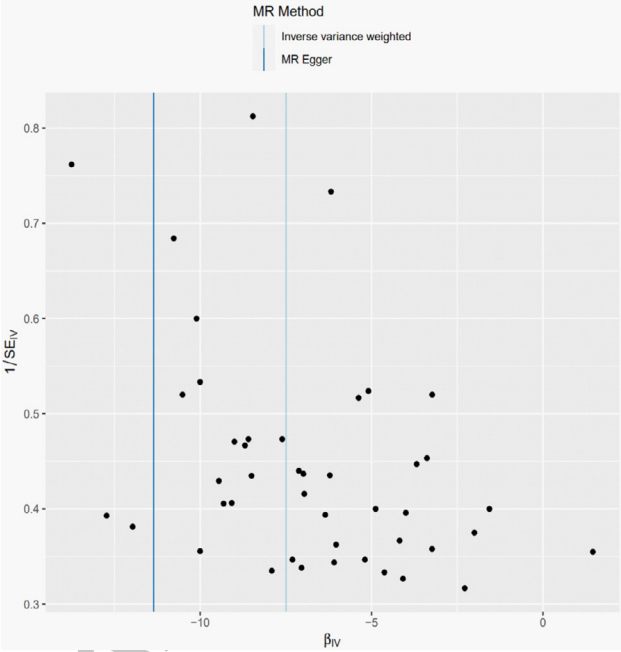

Fig. 3. Funnel plot for potential bias in association between Scr and CKD.

5-like 1 (SPATA5L1), transcription factor Dp-2 (TFDP2), phosphatidylinositol-4-phosphate 5-kinase type 1 beta (PIP5K1B), WD repeat domain 72 (WDR72), GTP binding protein 4 (GTPBP4), SCF 34 member 1 (SLC34A1), alström syndrome protein 1 (ALMS1), protein kinase AMP-activated non-catalytic subunit gamma 2 (PRKAG2), RNA polymerase I subunit C (POLR1C), and long intergenic non-protein coding RNA 2859 (LINC02859). The GO results for these genes were depicted in Figure 4. The biological processes (BPs) associated with these proteins included localization, negative regulation of molecular function (MF), importing across plasma membrane (PM), transportation of sodium ion transmembrane (SIT), importing into cells, response to starvation (ROS), and transportation of sodium ion. In terms of cellular components (CC), these genes were linked to apical plasma membrane (APM), brush border membrane (BBM), cytosol, cytoplasm, and perinuclear region of cytoplasm (PRoC). For MF, they were related to anion binding, activity of secondary active transmembrane transporter (SATT), activity of modified amino acid transmembrane transporter (AATT), activity of anion transmembrane transporter (ATT), activity of ion transmembrane transporter (ITT), activity of monovalent inorganic cation transmembrane transporter (MICTT), and activity of substrate-specific transmembrane transporter (SSTT).

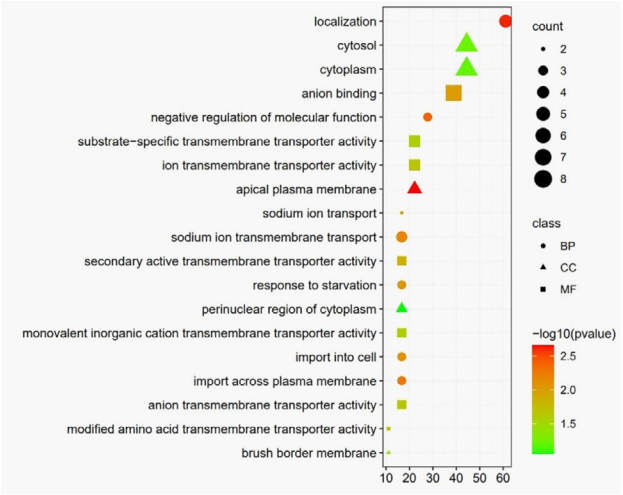

Fig. 4. Diagram for GO pathway for CKD-related genes.

Results of PPI network analysis

The diagram for PPI network of these genes was illustrated in Figure 5. As it demonstrated, the PPI network comprised 16 nodes and 13 edges, with an average node degree of 1.62 and an average local clustering coefficient of 0.594. The expected number of edges was 2. The key genes associated with CKD occurrence were DAB2, UBE2Q2, KCNQ1, SHROOM3, and PRKAG2.

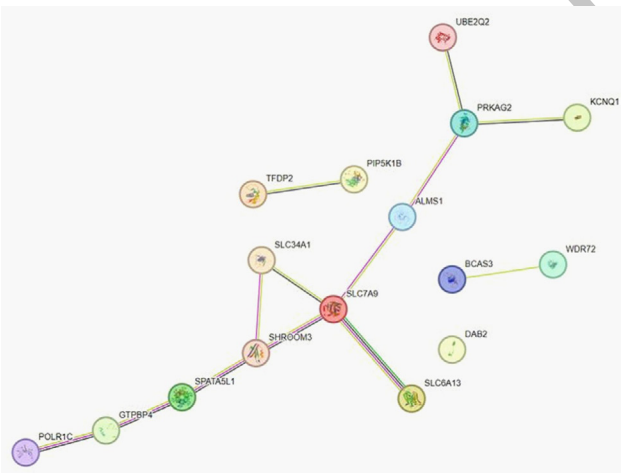

Fig. 5. The diagram for PPI network.

DISCUSSION

In this work, the MR analysis method was adopted to explore potential novel causal genes influencing CKD. The research findings revealed that 19 genes were associated with CKD occurrence: GTPBP4, SLC6A13, BCAS3, DAB2, SLC7A9, UBE2Q2, RNF32-DT, KCNQ1, SHROOM3, SPATA5L1, TFDP2, PIP5K1B, WDR72, GTPBP4, SLC34A1, ALMS1, PRKAG2, POLR1C, and LINC02859. These proteins were involved in various BPs such as localization, negative regulation of MF, importing across PM, transportation of SIT, importing into cells, ROS, and transportation of sodium ion. In terms of CC, these genes were linked to APM, BBM, cytosol, cytoplasm, and PRoC. For MF, they were related to anion binding, activity of SATT, activity of modified AATT, activity of ATT, activity of ITT, activity of MICTT, and activity of SSTT. These findings suggest that these proteins exert crucial roles in multiple essential functions and processes within cells, exerting critical influences in different cellular locations. They may also be involved in various CFs and pathways, participating in numerous molecular-level transport and metabolic processes. This provides vital clues for further studying and understanding the functions and roles of these proteins, potentially contributing to the elucidation of CKD disease mechanisms and physiological processes (Enenkel *et al.*, 2022). The importance of intracellular localization in maintaining cellular homeostasis and function is well-documented (Naito *et al.*, 2015). Disruption of intracellular localization can lead to cellular dysfunction and damage. In the pathological process of CKD, perturbations in intracellular localization could result in abnormal cellular functions and injuries (Voelkl *et al.*, 2019). Anomalies in intracellular SPWs regulation may lead to pathological processes like inflammation, fibrosis, and glomerular injury in CKD. Sodium ion transport is crucial for maintaining water and electrolyte balance, and dysregulation in sodium ion transmembrane transport can lead to imbalances in electrolytes and kidney function (Peng *et al.*, 2018). These disruptions can contribute to pathologic changes like elevated blood pressure and decreased glomerular filtration rate in CKD (Rastogi *et al.*, 2021). In CKD, abnormalities in intracellular transport can lead to the accumulation of metabolic waste products and disturbances in cellular function (Ito *et al.*, 2023). Dysregulation of sodium ion transport may result in fluid retention, edema, and hypertension (Pathak *et al.*, 2018). Nutritional deficiencies and metabolic disturbances are common in CKD patients (Hu *et al.*, 2021), and thus, the response to starvation might be linked to the development and progression of kidney disease. It's apparent that the biological processes involving the aforementioned proteins are closely associated with the progression of CKD.

Results of this work revealed that key genes associated with CKD occurrence included DAB2, UBE2Q2, KCNQ1, SHROOM3, and PRKAG2. DAB2 functions as a negative regulator involved in cell signaling transduction and endocytosis. Some studies have indicated (Long *et al.*, 2022; Qiu *et al.*, 2018) that the DAB2

undergoes significant changes in its expression for patients with CKD, particularly in glomerulonephritis and renal interstitial fibrosis pathological processes where DAB2 expression varies notably. This suggests that DAB2 may be involved in the regulation of signaling transduction and endocytosis in renal pathological processes. Diabetic kidney disease is a common cause of CKD, and DAB2 may exert an impoatant role in this context (Corbi *et al*., 2020). Increased expression of DAB2 in renal tubular epithelial cells has been associated with tubular injury and pathological changes (Schütte-Nütgen *et al*., 2019). Additionally, DAB2 may be involved in the development of diabetic kidney disease by regulating the TGF-β SPW (Böger *et al*., 2011). DAB2 exerts an important role in renal epithelial cells by regulating cellular homeostasis, cell polarity, endocytosis, and membrane transport processes. Abnormal DAB2 function might lead to impaired metabolism and dysfunction of renal epithelial cells, thereby promoting the development of CKD (Rbaibi *et al*., 2023). UBE2Q2 is a ubiquitin-conjugating enzyme involved in protein degradation regulation. In CKD, abnormal protein aggregation and metabolic disturbances could lead to renal damage (Böger *et al*., 2011). Therefore, proteins associated with cytoplasmic protein degradation, like UBE2Q2, might play a role in the development of CKD. Inflammation plays a significant role in the progression of CKD. UBE2Q2 may interact with pathways and proteins related to inflammation, such as the NF-κB SPW and the NLRP3 inflammasome (Zhang *et al*., 2023). This implies that UBE2Q2 may regulate inflammation response and play a role in CKD through its involvement in inflammatory pathways.

KCNQ1 is an ion channel protein that plays a role in regulating cell membrane potential and ion transport. KCNQ1 protein is widely expressed in renal tubules, particularly in the proximal and distal convoluted tubules (Ahmad *et al*., 2020). Renal tubules are vital components of the kidney, involved in processes such as urine formation, ion transport, and acid-base balance. The expression of KCNQ1 protein in renal tubules may be related to its function in these processes (Tavira *et al*., 2011). As a voltage-gated potassium ion channel, KCNQ1 protein participates in potassium ion transport in renal tubules. Maintaining potassium ion balance is crucial for kidney function, and abnormal potassium ion transport can lead to electrolyte disturbances, such as hypokalemia (Park *et al*., 2021). Therefore, abnormal functioning of the KCNQ1 protein may be related to electrolyte imbalances and the development of CKD. Mutations in the KCNQ1 gene have been associated with certain genetic kidney disorders, such as Bartter syndrome and congenital chloride diarrhea. These disorders often involve tubular dysfunction, including electrolyte imbalances and acid-base imbalances (Liu *et al*., 2011). While a direct association between KCNQ1 mutations and these diseases has been established, further research is needed to elucidate the relationship with CKD. SHROOM3 is a protein involved in the regulation of cell polarity and morphogenesis. Mutations in the SHROOM3 gene have been identified in some genetic CKD conditions. These mutations may lead to abnormal SHROOM3 protein function, affecting normal kidney development and function. Research has shown that SHROOM3 is related to the development of glomeruli and the morphology of renal tubules (Matsuura *et al*., 2020). The expression pattern of SHROOM3 protein changes in CKD patients, particularly in relation to glomerular lesions and renal interstitial fibrosis. SHROOM3 may play a role in the development and progression of CKD by regulating fundamental biological processes such as renal vascular morphology, epithelial cell shape, and cell polarity (Khalili *et al*., 2016). PRKAG2 is a protein kinase involved in regulating energy metabolism and cellular physiology. In CKD, the gene expression level of PRKAG2 undergoes changes. These expression changes may be related to the role of PRKAG2 protein in regulating energy metabolism and cellular survival processes within kidney cells. PRKAG2 is involved in regulating renal inflammation and cell injury. CKD is often accompanied by inflammation and cellular damage (Wang *et al*., 2018), and PRKAG2 may contribute to the development and progression of CKD by regulating inflammatory SPWs and cell survival mechanisms.

CONCLUSION

In this work, the MR two-sample analysis method was utilized to investigate potential genes associated with CKD. The results indicated a significant relationship between SCr levels and CKD, with key genes related to both SCr and CKD identified as DAB2, UBE2Q2, KCNQ1, SHROOM3, and PRKAG2. However, this work was subjected to several limitations. It focused solely on the exploration of potential genes associated with CKD using the MR analysis method, without delving into the underlying biological mechanisms. In future work, further validation of these study findings will be conducted at the molecular level. In conclusion, this research provides novel targets and strategies for the prevention, treatment, and personalized care of CKD.

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IRB approval

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Statement of conflict of interest

The authors have declared no conflict of interest.

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