



Research on key pathogenesis and potential intervention targets of idiopathic renal calculi composed of calcium oxalate (CaOx) based on bioinformatics

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Background: Calcium oxalate (CaOx) kidney stones are the most common type of stones in the urinary system, and their formation involves a complex mechanism with multiple contributing factors. In recent years, with the development of bioinformatics, there has been a deeper understanding of the pathogenesis of this type of disease. This study aimed to analyze the gene expression profiles of idiopathic kidney stones composed of CaOx using bioinformatics methods. By investigating the pathogenesis at the molecular level and identifying potential therapeutic targets, the study also integrated clinical data to validate the clinical relevance of the target genes.

Methods: Gene expression profiles from the GSE73680 dataset were analyzed via the Gene Expression Omnibus (GEO) database to identify differentially expressed genes (DEGs) between Randall's plaques (RPs) from kidney papillae associated with CaOx stones and normal kidney papillae tissues. The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database was employed to construct transcription factor (TF)-DEG-microRNA (miRNA) networks, and key genes were screened using the Molecular Complex Detection (MCODE) plugin. A gene set enrichment analysis (GSEA) was performed to investigate the possible underlying mechanisms of the key genes. The clinical data of idiopathic CaOx kidney stone patients who received treatment at the General Hospital of Northern Theater Command from January 2020 to December 2022 were retrospectively analyzed. Enzyme-linked immunosorbent assay (ELISA) kits were used to measure the transcriptional activity of the key genes in calcified kidney papillae tissues. Univariate and multivariate logistic regression analyses were employed to analyze the transcriptional activity of the key genes and their association with idiopathic kidney stones composed of CaOx.

Results: In the GSE73680 dataset, 276 upregulated and 538 downregulated DEGs were identified. Protein-protein interaction network construction revealed one significant module and three candidate genes [interleukin 11 (*IL-11*), interleukin 16 (*IL-16*), and interleukin 32 (*IL-32*)]. The TF-DEG-miRNA network indicated that *IL-11* might be regulated by 25 TFs and interact with six miRNAs. The GSEA suggested that *IL-11* could influence the development of idiopathic CaOx stones through chemokine expression and via the signaling pathways of the nucleotide-binding oligomerization domain-like receptors [NOD-like receptors (NLRs)] and toll-like receptors (TLRs). The clinical data analysis revealed that the *IL-11* serum levels were significantly elevated in the patients with idiopathic kidney stones composed of CaOx compared to the control subjects ($P < 0.001$). Additionally, *IL-11* was identified as an independent risk factor for the development of idiopathic CaOx kidney stones ($P < 0.001$).

Conclusions: The bioinformatically identified key genes and signaling pathways provide a deeper understanding of the potential mechanisms underlying idiopathic CaOx kidney stones. Preliminary clinical trials suggest that elevated serum *IL-11* levels in idiopathic CaOx kidney stone patients could serve as a possible diagnostic biomarker and treatment target.

Keywords: Idiopathic CaOx kidney stones (idiopathic calcium oxalate kidney stones); interleukin 11 (*IL-11*); bioinformatics; renal pelvis infection; pathogenesis

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Introduction

It is estimated that more than 1–5% of the global population has a history of urolithiasis (1). In China, the incidence of kidney stones in adults is approximately 7.54% (2). The incidence rate is significantly higher in men than women (3). Calcium oxalate (CaOx) stones are the most common type of kidney stones, accounting for over 80% of kidney stones. The formation of kidney stones is a multifactorial and complex process involving the interaction of multiple aspects such as genetics, metabolism, environment, and lifestyle habits. The formation of CaOx stones in urine may be related to various factors such as pH value, urine volume, concentration of inhibitors and promoters in urine, and can usually be clearly displayed on X-rays (4). Apart from the rare cases in which single-gene genetic changes result

in hereditary calcium renal calculi, and some CaOx stones secondary to gastrointestinal diseases, the majority of CaOx stones in clinical settings are idiopathic, lacking a clear genetic background and obvious etiological factors. The exact pathogenesis and molecular mechanisms of idiopathic CaOx stones remain largely unclear (5). Currently, the prevention and treatment of CaOx stones primarily rely on lifestyle modifications, medication, and surgical intervention (6). However, these treatments have limited efficacy and a high recurrence rate, significantly compromising the overall well-being of individuals. Therefore, exploring the key pathogenesis and potential intervention targets of CaOx kidney stones is of great clinical significance to improving treatment outcomes.

Research has shown that calcium phosphate crystals, also called Randall's plaque (RP), deposited at the tips of the renal papillae in the renal medulla, serve as the initial site for kidney stone formation (7). Thus, the investigation of the key genes and signaling pathways involved in the formation of RP is essential to understand the pathogenesis of idiopathic renal calculi composed of CaOx. With the advent of high-throughput genomic research technologies, bioinformatics analysis software based on gene chip data has become an efficient tool for identifying and screening important genes related to the occurrence and progression of diseases (8). Our study used bioinformatics methods to analyze gene chip datasets from the public Gene Expression Omnibus (GEO) database to detect differentially expressed genes (DEGs) between kidney papilla tissues of idiopathic renal calculi composed of CaOx and normal kidney papilla tissues. This allowed us to screen the key genes and potential biochemical processes involved in the development of idiopathic renal calculi composed of CaOx, and thus identify novel targets and perspectives for its prevention and treatment. This study also retrospectively analyzed the clinical data of patients with idiopathic renal calculi composed of CaOx who underwent percutaneous nephrolithotomy (PCNL) to examine the expression of the key genes in their serum. By correlating the expression levels of these key genes with the incidence of idiopathic

Highlight box

Key findings

- This study utilized bioinformatics technology to analyze the gene expression profile chip data of idiopathic calcium oxalate (CaOx) kidney stones in depth, aiming to reveal their key pathogenesis and identify potential therapeutic targets.

What is known and what is new?

- CaOx kidney stones are the most common type in the urinary system with complex formation mechanisms.
- This study is the first to use bioinformatics methods to reveal the pathogenesis of idiopathic CaOx kidney stones at the molecular level and to identify the key gene interleukin 11 (*IL-11*) and its related signaling pathways. It further confirmed that the abnormal expression of *IL-11* is closely associated with postoperative pyelonephritis, providing new insights for the prevention and treatment of postoperative infections.

What is the implication, and what should change now?

- Implications include the potential for *IL-11* to be used in diagnostic and therapeutic strategies for idiopathic CaOx kidney stones.
- Further clinical trials are needed to validate *IL-11* as a treatment target, potentially leading to new interventions and management approaches for patients with idiopathic CaOx kidney stones.

renal calculi composed of CaOx, we aimed to further clarify the clinical significance of these key genes. We present this article in accordance with the STREGA reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-24-302/rc>).

Methods

Microarray data information

We retrieved the dataset GSE73680 using the keywords “idiopathic calcium oxalate stones” and “Randall’s plaques”, which compared the gene expression of renal papillary Randall plaques and normal tissues in 13 pairs of idiopathic CaOx stone forming individuals, annotations from the GEO database (<https://www.ncbi.nlm.nih.gov/geo/>) was used to label all identity documents (IDs) with corresponding gene symbols, and duplicate gene names were removed using the mean method.

Identification of DEGs

The limma package [3.52.2] (<https://bioconductor.org/packages/release/bioc/html/limma.html>) was used to screen the DEGs across all the datasets. Preprocess the raw data, including removing low-quality samples, correcting batch effects, standardizing gene expression levels, etc., to ensure data consistency and comparability. Provide necessary inputs for the linear model in the limma package based on the grouping information of the samples (i.e., RP renal papillary tissue formed by calcium stones and normal renal papillary tissue). Use the empirical Bayesian method in the limma package to statistically test the differences in gene expression levels. Use $P < 0.05$ and \log_2 fold change (FC) > 1 as screening criteria. DEGs with \log_2 FC > 1 and \log_2 FC < -1 are considered upregulated and downregulated genes, respectively.

Identification of hub genes and establishment of protein-protein interaction (PPI) network

The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (<https://cn.string-db.org/>) was employed to evaluate the PPI network of the DEGs. Cytoscape v.3.9.1 (<https://cytoscape.org/>) was employed to visualize the positions and relationships of the key DEGs in the PPI network. The Molecular Complex Detection (MCODE) plugin in Cytoscape was used to identify central

Li and Chen. Key pathogenesis of idiopathic CaOx renal calculi

clusters to help identify potential functional modules and provide new insights into the activating signaling pathways.

Construction of transcription factor (TF)-DEG-microRNA (miRNA) network

The ENCODE (<https://www.encodeproject.org/>) and MiRTarBase v.8.0 databases (https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2019/php/index.php) were used to acquire interaction data between the miRNAs-DEGs, and the TFs-DEGs. The DEGs displaying interactions with the TFs and miRNAs were chosen, after which the miRNAs and TFs regulating these DEGs were extracted. Cytoscape was used to visualize the integrated TF-DEG-miRNA network.

Gene set enrichment analysis (GSEA)

The Metascape online tool (<https://metascape.org/gp/index.html>) was employed to conduct the functional analysis of the DEGs. A GSEA was conducted to examine whether there were statistically significant differences in the biological expression of a predefined set of genes. By identifying common signaling pathways and regulatory network modules, this analysis provided insights into the biological differences between the different samples.

Data of study subjects

A retrospective analysis was conducted on the clinical information of 116 patients with idiopathic renal calculi composed of CaOx who underwent PCNL at General Hospital of Northern Theater Command from January 2020 to December 2022. These patients comprised the study group. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) meet the diagnostic criteria for urinary system stones as outlined in “Urology” by Jieping Wu (2004 edition) (9); (II) have confirmation that the main component of the postoperative stone specimens was CaOx based on an analysis with an infrared spectroscopy automatic analysis system; (III) be aged 18 years or older; (IV) have no history of gout, coronary heart disease, diabetes, autoimmune diseases, or hyperparathyroidism; and (V) have complete medical records. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had co-existing diseases that could cause urinary stones, such as renal tubular acidosis, gout, nephrocalcinosis, primary cystinuria,

hyperuricemia, or congenital urinary tract obstruction; (II) had severe acute urinary tract infection or gross hematuria; (III) had a severe trauma or surgical treatment within the past 6 months; (IV) had uncontrolled diabetes, liver or kidney dysfunction, hyperparathyroidism, cardiovascular diseases, cerebrovascular diseases, hematological diseases, autoimmune diseases, and/or malignant tumors; and/or (V) had severe mental or psychological disorders, or were non-cooperative with the follow-up. (VI) Merge chronic diseases that affect intestinal absorption and metabolism, such as Crohn's disease, chronic diarrhea, short bowel syndrome, history of intestinal surgery. A control group of 110 healthy adults undergoing routine physical examinations during the same period was selected. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of General Hospital of Northern Theater Command (No. 2020-3) and informed consent was taken from all the participants.

Enzyme-linked immunosorbent assay (ELISA) assay

Fasting venous blood (5 mL) was collected from the elbow of all the participants using procoagulant/separation gel vacuum blood collection tubes. The samples were centrifuged at 3,500 r/min for 10 minutes at 4 °C to obtain the serum, which was then stored at -80 °C. The expression levels of the key DEGs in the serum were measured using ELISA kits (Shanghai Zhenke Bio-Technology Co., Ltd., Shanghai, China).

Statistical analysis

GraphPad Prism 7.0 software (<https://www.graphpad-prism.cn/>) was used for the graphical plotting and statistical analysis. In the analysis of the DEGs, *t*-tests were used to determine the *P* values and adjusted *P* values, with the *P* values adjusted by the false discovery rate. The categorical data are presented as the number of cases (%). The groups were compared using the χ^2 test. The Kolmogorov-Smirnov test was used to assess the normal distribution of the continuous data. Independent sample *t*-tests were applied to compare the normally distributed data, and the data are presented as the mean \pm standard deviation (SD). The non-normally distributed data are expressed as the median and interquartile range [M (P25, P75)], and were compared using the Mann-Whitney *U* test. A binary logistic regression analysis was used to conduct the multivariate analysis. A *P* value less than 0.05 was considered

statistically significant.

Results

Data normalization and identification of DEGs

We analyzed the gene expression of the GSE73680 dataset from the GEO database, focusing on the DEGs between RPs from CaOx stone-forming kidney papillae and normal kidney papillae tissues. Preprocessing included normalizing the data and performing cross-comparisons to remove technical and systemic variability. A principal component analysis (PCA) was performed to evaluate the biological variability between the samples. The PCA plot revealed unique gene expression profiles (*Figure 1A*), and the box plot illustrated the gene expression range for each sample (*Figure 1B*), which indicated the data suitability for further analysis. The raw data were robustly normalized to ensure the reliability of the downstream analyses. The limma package was used in R to identify the DEGs that met the following criteria: $|\log FC| > 1$ and $P < 0.05$. In total, 276 upregulated and 538 downregulated genes were identified. The volcano plot of the DEGs (*Figure 1C*), and the heatmap (*Figure 1D*) revealed substantial differences in gene expression between the two groups.

Construction of PPI network and TF-DEG-miRNA network

Using the STRING database, we constructed a PPI network to illustrate the associations among the proteins encoded by the DEGs (*Figure 2A*). The majority of proteins encoded by the DEGs showed high interconnectivity with other proteins. The module analysis with MCODE identified the most notable module in the PPI network, which contained three genes (*Figure 2B*). The DEGs in this module were interleukin 11 (*IL-11*), interleukin 16 (*IL-16*), and interleukin 32 (*IL-32*). Among these, *IL-11* was significantly differentially expressed between the two groups based on the GEO database (*Figure 2C*). To explore the functional roles of the DEGs, we explored the possible regulatory relationships between the TFs and DEGs, and also between the miRNAs and DEGs. Through a network analysis using the miRTarBase database, pairs of miRNA-DEGs were identified. The identification of potential regulatory links between the DEGs and TFs was based on the analysis of the TF binding site data. The genomic coordinates were provided by ENCODE (*Figure 2D*).

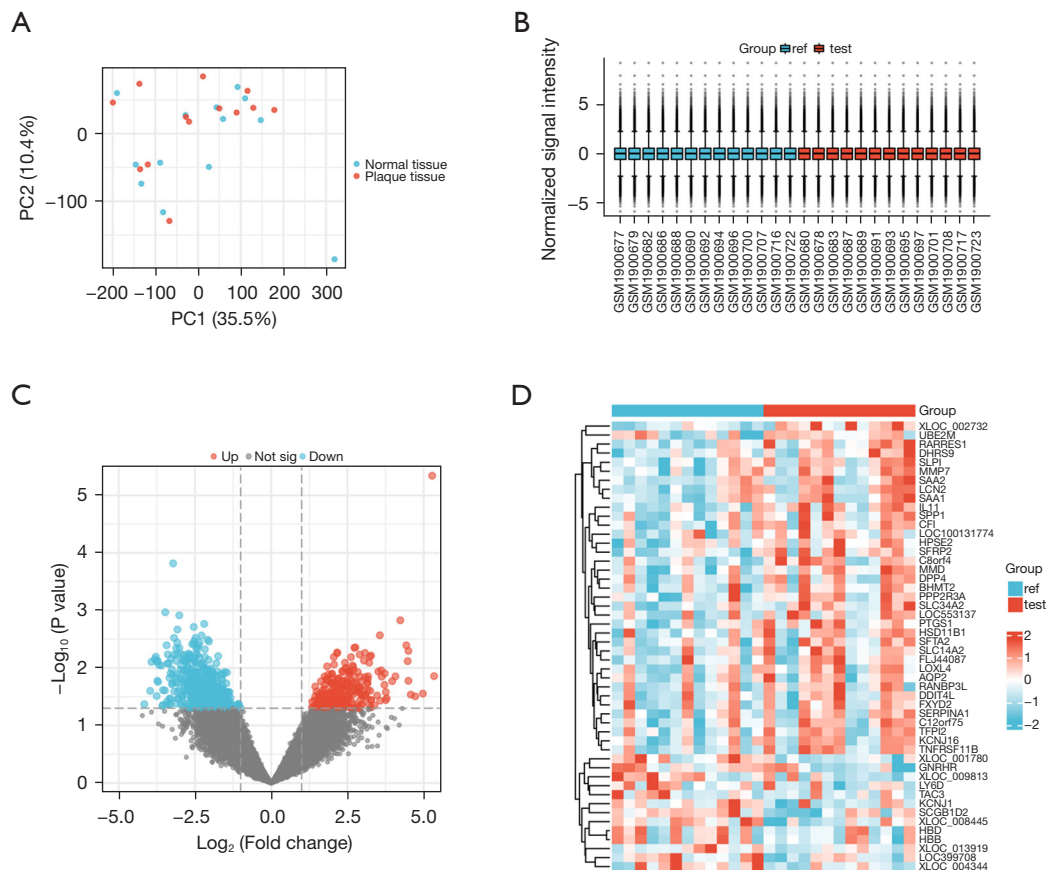


Figure 1 Data normalization and detection of DEGs. (A) PCA showing the distribution of all the samples. (B) Box plot comparing the expression values of all the samples. (C) Volcano plot displaying all the DEGs in the GSE73680 data set as examined by the limma package in R. (D) Heatmap of the DEGs, of which 276 were upregulated and 538 were downregulated. PC, principal component; ref, reference; sig, significant; DEGs, differentially expressed genes; PCA, principal component analysis.

Notably, *IL-11* is potentially regulated by 25 TFs and interacts with six miRNAs.

Prediction of signaling pathways based on the GSEA

We conducted a functional GSEA of *IL-11* using Metascape. The analysis revealed that *IL-11* influences the occurrence and progression of idiopathic renal calculi composed of CaOx by affecting chemokine expression, and the signaling pathways of the toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors [NOD-like receptors (NLRs)] (Figure 3).

Serum *IL-11* gene expression levels in the two study groups

The study included imaging results of kidney stones from

two patients as shown in Figure 4A. The ELISA results indicated that the *IL-11* serum levels of the study group (67.44 ± 13.15 pg/mL) were significantly increased compared to those of the control group (48.52 ± 14.41 pg/mL) ($P < 0.001$) (Figure 4B).

Analysis of factors influencing the occurrence of idiopathic renal calculi composed of CaOx

The univariate analysis showed that age, gender, body mass index (BMI), systolic blood pressure (SBP), total cholesterol (TC), low-density lipoprotein (LDL), and serum *IL-11* levels were significantly associated with the occurrence of idiopathic renal calculi composed of CaOx (all $P < 0.05$) (Table 1). The variables that were statistically significant in the univariate analysis were then included in the multivariate

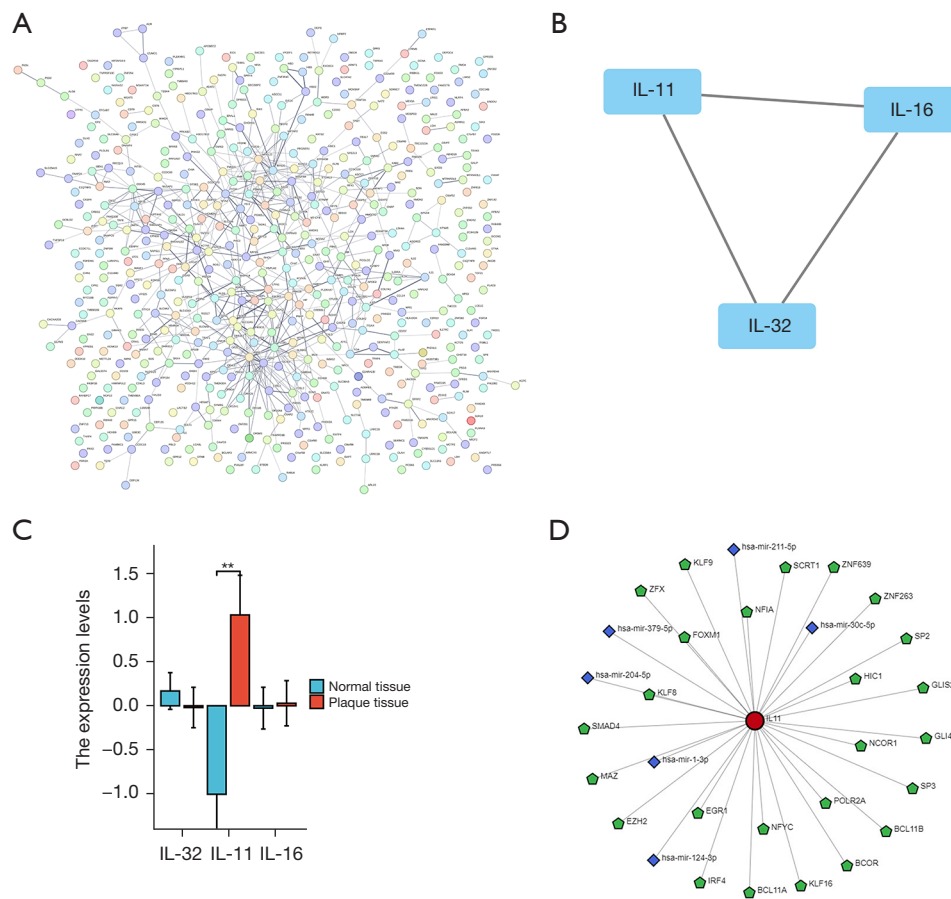


Figure 2 PPI network and key modules of DEGs. (A) PPI network of the DEGs constructed using STRING. (B) The most significant module was obtained from the PPI network using the MCODE plugin in Cytoscape. (C) Changes in the expression of the three DEGs between the two groups based on the GSE73680 microarray dataset. (D) Construction of the TF-DEG-miRNA network. **, $P < 0.001$. IL-11, interleukin 11; IL-16, interleukin 16; IL-32, interleukin 32; PPI, protein-protein interaction; DEGs, differentially expressed genes; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins; MCODE, Molecular Complex Detection; TF, transcription factor; miRNA, microRNA.

logistic regression model. The results indicated that gender, BMI, SBP, TC, and *IL-11* were independent risk factors for the occurrence of idiopathic renal calculi composed of CaOx (all $P < 0.01$) (Table 2).

Discussion

Recently, with the continuous advancement of molecular biology techniques, DNA microarrays, and next-generation sequencing technology, the investigation of DEGs of idiopathic renal calculi composed of CaOx at the transcriptome level and the analysis of key genes have become crucial methods for studying the risk factors and molecular mechanisms of this condition. Multiple studies

have shown that the abnormal transcriptional activity of certain genes has a major effect on the formation and progression of idiopathic renal calculi composed of CaOx (10,11). Screening the differential gene expression profiles related to idiopathic CaOx kidney stones and identifying the key genes involved in their development is essential for the diagnosis, prevention, and treatment of this condition. In this study, by analyzing the GSE73680 dataset and using bioinformatics techniques, we identified 276 upregulated and 538 downregulated DEGs. Using the STRING database to construct a PPI network, three key genes were initially identified: *IL-11*, *IL-16*, and *IL-32*.

Previous research has shown that the interleukin family plays several vital roles in urinary stone formation.

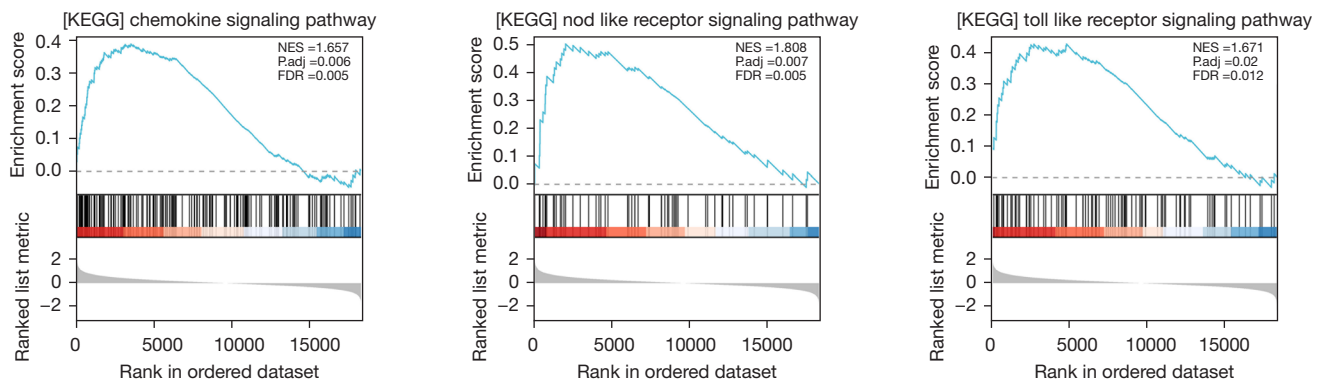


Figure 3 Statistically significant pathways identified in the GSEA. The gene sets used in the analysis were derived from the MSigDB focusing on biological processes. A total of 1,600 random sample permutations were conducted. KEGG, Kyoto Encyclopedia of Genes and Genomes; NES, normalized enrichment score; Padj, adjusted P value; FDR, false discovery rate; GSEA, gene set enrichment analysis; MSigDB, Molecular Signatures Database.

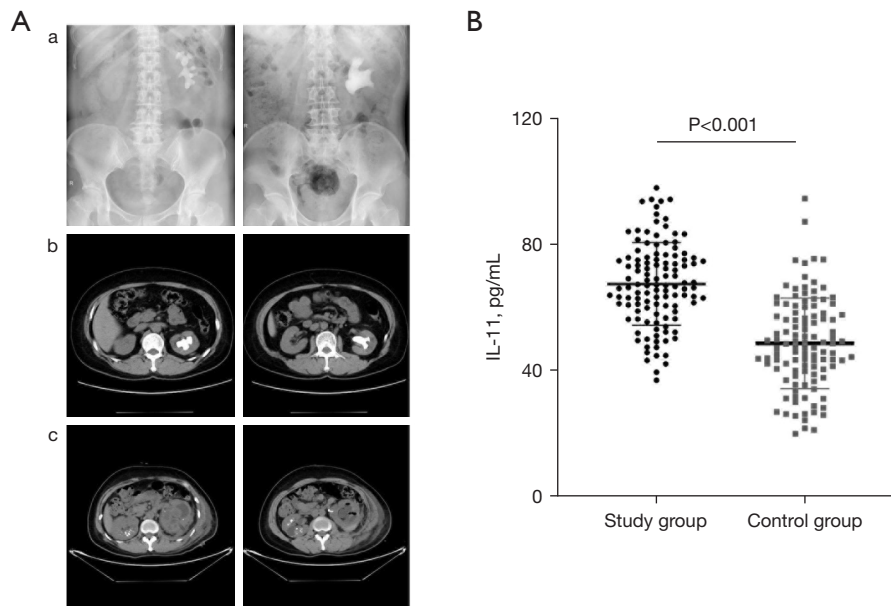


Figure 4 CT images and the serum IL-11 expression levels of the patients. (A) Imaging of patients with idiopathic renal calculi composed of CaOx: panel a, preoperative standing abdominal plain radiograph; panel b, preoperative CT scan; panel c, postoperative CT scan showing renal pelvis infection. (B) Serum expression levels of IL-11 in the two study groups. IL-11, interleukin 11; CT, computed tomography; CaOx, calcium oxalate.

Specifically, the interleukin family: (I) promotes inflammatory responses: interleukins can trigger both local and systemic immune responses, contributing to tissue damage in the urinary tract and chronic low-grade systemic changes; (II) regulates calcium ion metabolism: certain interleukins may influence the absorption, excretion, or transport of calcium ions in the body, thereby increasing

the risk of oxalate precipitates (such as oxalate) in the urine; (III) stimulates epithelial cell activation: when produced in the surrounding renal tissues, some interleukins can activate adjacent epithelial cells, enhancing their adhesive capacity required for nucleation and aggregation of crystal nuclei; and (IV) disrupts the fibrinolytic system balance: some interleukins can induce the deposition of various

Table 1 Univariate analysis

Variables	Study group (n=116)	Control group (n=110)	t/ χ^2	P value
Age (years)	55.57±5.68	54.03±5.49	2.071	0.04
Sex			5.583	0.02
Male	75	54		
Female	41	56		
BMI (kg/m ²)	23.02±1.04	22.34±0.87	5.317	<0.001
Smoking history			2.223	0.14
Yes	64	45		
No	52	55		
SBP (mmHg)	101.19±15.34	94.95±14.14	3.175	0.002
TC (mmol/L)	2.15±0.89	1.86±0.73	2.670	0.008
LDL (mmol/L)	2.10±0.81	1.87±0.61	2.401	0.02
IL-11 (pg/mL)	67.44±13.15	48.52±14.41	10.32	<0.001

Data are presented as mean ± standard deviation or n. BMI, body mass index; SBP, systolic blood pressure; TC, total cholesterol; LDL, low-density lipoprotein; IL-11, interleukin 11.

Table 2 Multivariate binary logistic regression analysis

Variables	Exp (B) (95% CI)	P value
Age	1.063 (0.996–1.134)	0.07
Sex (male)	2.884 (1.321–6.299)	0.008
BMI	2.147 (1.403–3.286)	<0.001
SBP	1.038 (1.011–1.066)	0.006
TC	1.526 (0.982–2.372)	0.06
LDL	1.118 (0.693–1.805)	0.65
IL-11	1.115 (1.080–1.151)	<0.001

Exp (B), exponential of the beta coefficient; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; TC, total cholesterol; LDL, low-density lipoprotein; IL-11, interleukin 11.

oxides, including the formation of calcium phosphate and other oxides, by interfering with the fibrinolytic system in an alkaline environment (12–14). The construction of the TF-DEG-miRNA network revealed that *IL-11* alone is subject to TF regulation and potential miRNA interactions. Taguchi *et al.* (15) conducted a genome-wide analysis and found that the transcriptional activity of *LCN2*, *IL-11*, *PTGS1*, *GPX3*, and *MMD* is upregulated in RP tissues, which aid in the development of idiopathic renal calculi composed of CaOx, compared to non-RP tissues.

The GSEA suggested that *IL-11* influences the occurrence and formation of idiopathic renal calculi composed of CaOx by affecting chemokine expression, and the signaling pathways of the TLR and NLR. These mechanisms are also supported by other studies in the context of kidney stones. For example, Gao *et al.* (16) used bioinformatics approaches to highlight the role of chemokine activity as a crucial pathway in kidney stone formation. Similarly, Olcucu *et al.* (17) demonstrated changes in subtypes of TLR in experimentally induced kidney stone disease, with real-time quantitative polymerase chain reaction showing a substantial decrease in expression of several TLRs, specifically TLR11 and TLR7. These findings are valuable for understanding the pathogenesis of idiopathic CaOx kidney stones. Current research on *IL-11* primarily focuses on its effects on kidney function and fibrosis. It has been observed that *IL-11* levels in the kidney increase with the progression of renal failure. Neutralizing *IL-11* can reduce epithelial-mesenchymal transition, fibrosis, and inflammation, thereby improving kidney function (18). Further, the excessive expression of *IL-11* can cause fibrosis in the kidneys and heart. Conversely, the deletion mutation of IL-11 receptor subunit alpha (*IL-11Ra*) can preserve organ functionality by preventing fibrosis (19). However, direct studies on *IL-11* and kidney stones are limited (20), indicating a need for further research and validation in this area.

Through a retrospective analysis comparing serum *IL-*

IL-11 expression levels between patients with idiopathic renal calculi composed of CaOx and healthy subjects, this study preliminarily discovered that the expression of *IL-11* was significantly upregulated in the serum of patients with idiopathic CaOx kidney stones. This suggests that *IL-11* might play an important part in the pathological process of this condition. Further analysis revealed that sex, BMI, SBP, TC, and the expression level of *IL-11* are independent risk factors for the occurrence of idiopathic renal calculi composed of CaOx. Study has shown that men are more prone to kidney stones than women (21), possibly because estrogen in women reduces calcium excretion, thereby lowering the risk of stone formation. Obesity increases the risk of kidney stones through various mechanisms, as excessive food intake can lead to metabolic imbalances of calcium, sodium, oxalate, and gastric acid, making obese individuals more susceptible to urinary stones (22). High blood pressure and high cholesterol can cause abnormal excretion of calcium and other minerals in the urine, promoting stone formation (23,24). *IL-11* plays a significant role in kidney fibrosis, which may alter normal kidney function and promote stone formation. Considering these findings, *IL-11* might serve as a diagnostic molecular marker and therapeutic target for idiopathic CaOx, offering a novel perspective for the diagnosis and treatment of this disease.

Conclusions

In summary, the development of idiopathic renal calcifications composed of CaOx is likely regulated by multiple factors. The identification of significant genes and related signal transduction pathways enhances our understanding of their molecular mechanisms. However, this study had certain limitations, including the analysis being restricted to single-center case data, and the lack of *in vivo* and *in vitro* mechanistic studies. Future research should involve multi-center, large-sample, prospective studies and validation through cellular or animal experiments to further explore and confirm the related findings.

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Footnote

Reporting Checklist: The authors have completed the

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Data Sharing Statement: Available at <https://tau.amegroups.com/article/view/10.21037/tau-24-302/dss>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tau.amegroups.com/article/view/10.21037/tau-24-302/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of General Hospital of Northern Theater Command (No. 2020-3) and informed consent was taken from all the participants.

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