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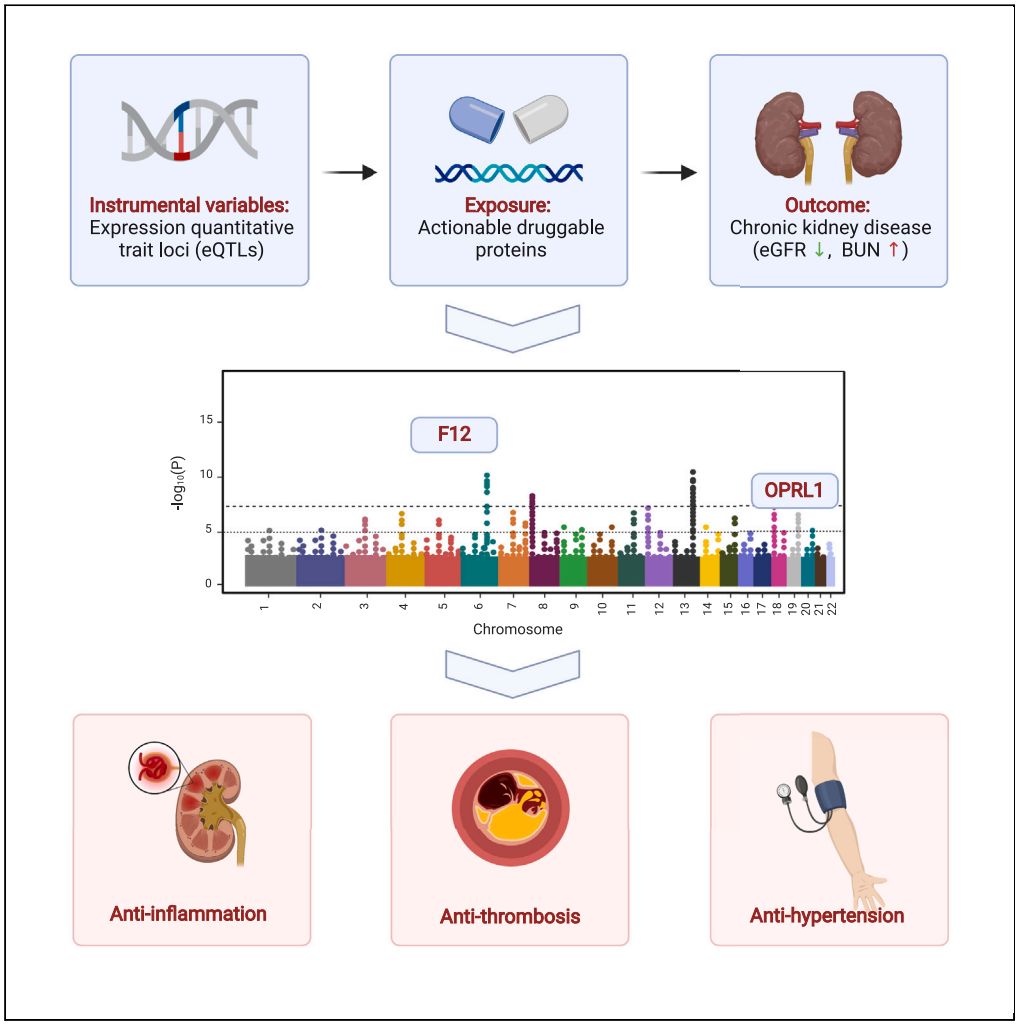

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Highlights

Druggable Mendelian randomization for chronic kidney disease was performed

Opioid receptor-like 1 has potential to restore renal function

F12 has potential to restore renal function

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Drug repurposing opportunities for chronic kidney disease

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SUMMARY

The development of targeted drugs for the early prevention and management of chronic kidney disease (CKD) is of great importance. However, the success rates and cost-effectiveness of traditional drug development approaches are extremely low. Utilizing large sample genome-wide association study data for drug repurposing has shown promise in many diseases but has not yet been explored in CKD. Herein, we investigated actionable druggable targets to improve renal function using large-scale Mendelian randomization and colocalization analyses. We combined two population-scale independent genetic datasets and validated findings with cell-type-dependent eQTL data of kidney tubular and glomerular samples. We ultimately prioritized two drug targets, opioid receptor-like 1 and F12, with potential genetic support for restoring renal function and subsequent treatment of CKD. Our findings explore the potential pathological mechanisms of CKD, bridge the gap between the molecular mechanisms of pathogenesis and clinical intervention, and provide new strategies in future clinical trials of CKD.

INTRODUCTION

As the most common and complicated renal disease, chronic kidney disease (CKD), also known as chronic kidney failure, is a destructive disease that causes persistent abnormalities in the renal structure or function for more than three months. Estimated glomerular filtration rate (eGFR) measurement is treated as an indicator for kidney function and helps to classify CKD patients into five stages indicative of disease severity, among which end-stage renal disease (ESRD) is the final and irreversible stage of CKD progression requiring persistent dialysis or even kidney replacement therapy.[1] Globally, CKD affects more than 800 million individuals and is responsible for one in 60 deaths,[2,3] while ESRD threatens approximately about 2 million patients.[4] More than two-thirds of CKD cases are caused by diabetes and hypertension, which are highly related to a combination of genetic and environmental factors.[5,6] Current treatments such as intensive blood pressure (BP) management and glycemic control can only slow the progression of CKD, but fail to cure it.[1] Moreover, patients with CKD are at high risk for multiple severe complications, including cardiovascular disease, anemia, uremic lung disease, and other systemic disorders,[7] which are reported to result in the failure of conventional CKD interventions.[8] Since the socioeconomic and healthcare burdens of CKD are tremendous, it is essential to develop new therapeutic approaches for delaying CKD progression, restoring kidney function and curing CKD.

Taking advantage of the rapid growth of human genetic resources and advances in genome-wide association study (GWAS) datasets, emerging research has sought to identify the genetic determinants of complex diseases and apply these genomic findings in drug target discovery.[9] Nelson and other studies have established that drug targets with genetic evidence support are more likely to be validated in clinical testing and reach market approval.[10,11] For example, large-scale DNA sequencing identified that PCSK9 variants were related to reduced plasma low-density lipoprotein cholesterol levels and decreased risk of coronary disease.[12] Soon after, the clinical benefits of monoclonal antibodies against PCSK9 for treating dyslipidemia were proved in large clinical programs.[13] In the field of nephrology, eQTLs of the APOL-1 have been found to be associated with an increased risk of progressive CKD and ESRD. Currently, the novel drug VX-147, which targets APOL1-mediated kidney disease, has entered the pivotal clinical trial stage.[14,15] These studies show great promise in drug development based on large-scale human genetics.

Mendelian randomization (MR) is a widely adopted genetic technique used in observational epidemiological studies to reveal the causal effects of predictable exposures (that is drug target gene expression) on complex disease-associated phenotypes and outcomes

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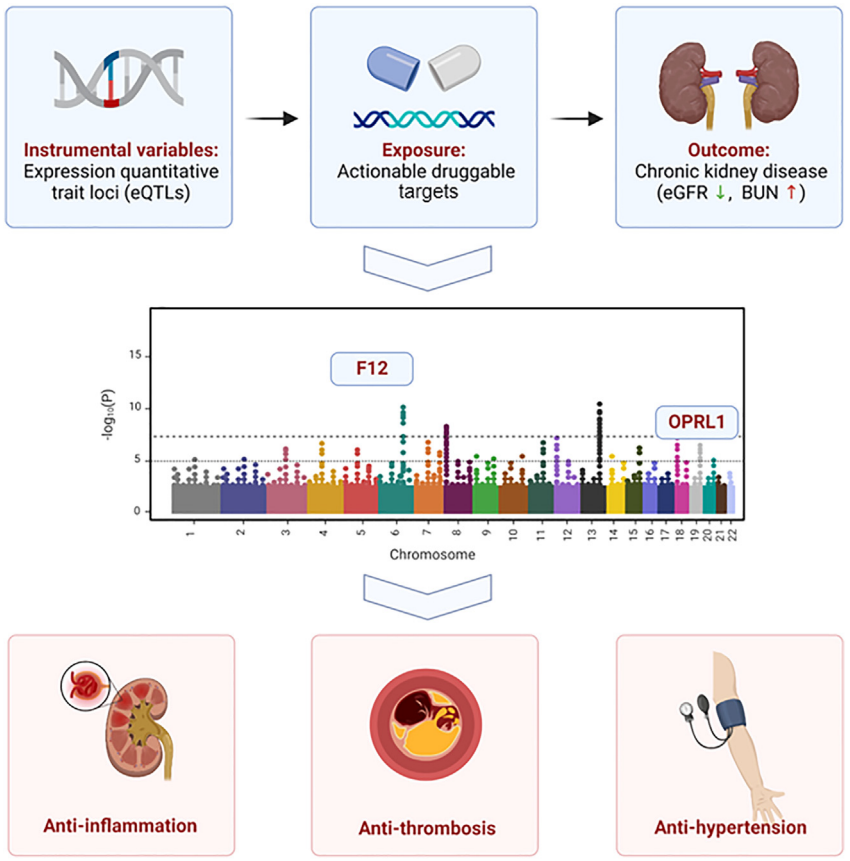

Figure 1. Study framework

This study utilized Mendelian randomization and colocalization analysis to reveal actionable druggable targets to cure chronic kidney disease. The expression levels of F12 and OPRL1 hold great potential in chronic kidney disease prevention and management, which might act through anti-inflammation, anti-thrombosis and anti-hypertension.

(that is kidney function assessments).[16] Since exposure-influencing genetic alleles are randomly allocated at conception according to Mendel's second law, the MR approach can mimic a randomized controlled trial (RCT) design without actual pharmacological intervention.[17] As a general feature of the human genome, some single-nucleotide polymorphisms (SNPs) acting in *cis* have been reported to affect the transcriptional activity or expression levels of encoded proteins, which are referred to as expression quantitative trait loci (eQTL). Since most genetic variants identified by GWAS are located in non-coding regions of the genome, the description of the eQTLs landscape across multiple human tissues by the Genotype-Tissue Expression (GTEx) project enable researchers to map SNP variants to causal genes expression.[18,19] Therefore, MR with eQTLs allows researchers to make inferences on the causal effects of the pharmacological modification of potential drug targets on disease-associated traits to mimic RCT studies.[20,21]

Herein, we investigated actionable druggable targets to improve renal function using large-scale MR and colocalization analyses. By combining two population-scale independent genetic datasets from the CKDGen Consortium and validated with cell-type-dependent eQTL data of kidney tubular and glomerular samples, we ultimately prioritized two drug targets, opioid receptor-like 1 (OPRL1) and F12, with potent genetic support for restoring renal function and subsequent treatment of CKD. Our findings explore the potential pathological mechanisms of CKD, bridge the gap between the molecular mechanisms of pathogenesis and clinical intervention, and provide a new strategy in future clinical trials of CKD.

RESULTS

Overall analysis framework

The overall design of this study was shown in Figure 1. First, suitable genetic instruments for actionable druggable targets were identified. Next, we designed discovery-validation protocol. CKD GWAS data were used in discovery phase and BUN-corrected eGFR were used in the validation phase. As described in our previous study, the BUN results should be opposite to those of eGFR, or the eGFR results would be violated and discarded in our study.[28] To make our results more robust and convincing, we performed following analyses for druggable targets that were significant in both the discovery and validation phases. First, colocalization was conducted using summary genetic data on

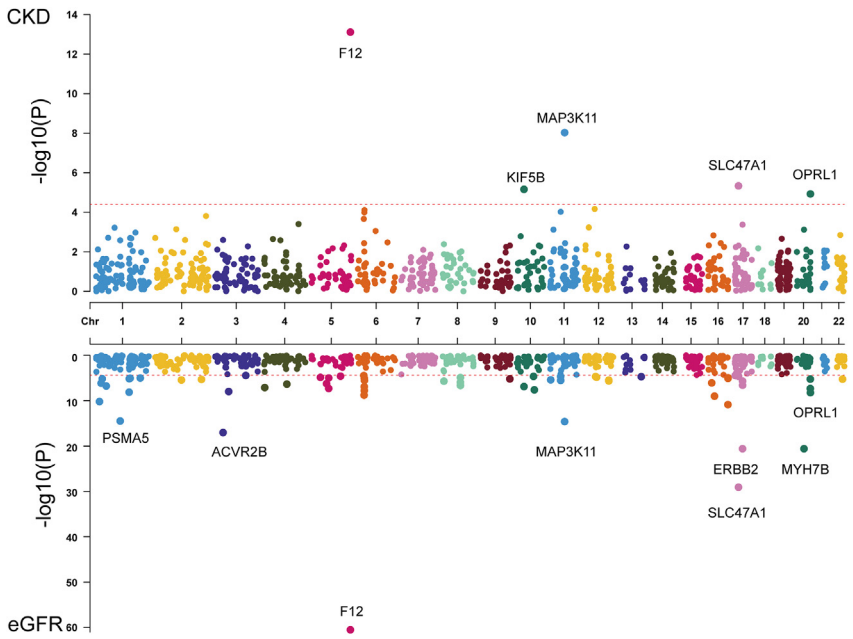

Figure 2. Miami plots of results from actionable druggable genome-wide MR analysis
The red dot line corresponds to $p = 0.000396$ for significant MR estimate. The gene with smallest p-value in both CKD and eGFR was F12.

gene expression from GTEx and a CKD GWAS to annotate the significant loci and prioritize actionable druggable targets. Second, we used glomeruli and tubule cell-type-dependent eQTLs to validate the consistency of MR estimates from GTEx data.

Mendelian randomization and colocalization with GTEx data

A comprehensive druggable two-sample MR was performed on CKD risk and kidney function, and 48 significant MR estimates and five actionable druggable targets for CKD risk were identified ($p < 3.96 \times 10\text{-}5$, Figure 2; Table S9). The MR estimates of GTEx *cis*-eQTL on eGFR and BUN are presented in Tables S10 and S11. In total, eight genes with strong evidence for an effect on CKD risk also showed strong evidence for a causal effect on eGFR with an opposing effect on BUN (Table 1). Strong evidence of colocalization (PP.H4 > 0.8) was found between the expressions of two significant genes (F12 and OPRL1) and CKD (Table 2). The MR estimates from expression levels of F12 in the esophageal mucosa on CKD and eGFR were significant, and colocalization reconfirmed their association. The OR for OPRL1 in testis, cultured fibroblasts cell, tibial nerve, skin not exposed to sun, stomach, and prostate were also significant and <1, suggesting reduced expression of OPRL1 as this is what the authors instrumented (Table 2). The regional association plots around rs35716097 (IV for F12) and rs4408777 (IV for OPRL1) in CKD were presented in Figure 3. No other gene expression was found to correlated with the eQTLs of F12 and OPRL-1.

Validation with cell-type-specific eQTL data of kidney tubular and glomerular samples

We identified cell-type-dependent eQTLs using the aforementioned criteria and the genetic instruments are listed in Tables S6 and S7. The significant MR estimates with cell-type-dependent eQTL data of kidney tubular and glomerular samples were largely consistent with MR estimates from GTEx data. MR results are shown in Tables S12 and S13. Notably, F12 remained the most significant candidate in both tubule and glomeruli (Figure 4). OPRL1 remained suggestively significant in eQTL of the glomerulus and CKD risk with a p value of 0.0006. No cell-type-dependent eQTL for OPRL1 was identified in tubules; therefore, MR estimates were lacking in the eQTL of OPRL1 in kidney tubules based on CKD risk.

Candidate drugs for F12 and OPRL-1

After identifying genes with strong evidence for a causal effect of expression on CKD risk, we searched the Drug Signatures Database (DSigDB, https://dsigdb.tanlab.org/DSigDBv1.0/) to identifying potential candidate drugs.[22] In total, 27 drugs or chemical targets were identified for F12 and 142 for OPRL-1 (Table S14).

DISCUSSION

CKD has been recognized as a major global public health problem, leading to a broad range of long-term complications including anemia, mineral bone disease, cardiac abnormalities, arterial disorders, etc.[23–25] The risk of these adverse events increases with worsening renal function, and they tremendously decrease the quality of life for patients with CKD. Novel, safe, and effective drugs are warranted for the treatment

Table 1. Significant ($p < 3.96 \times 10^{-5}$) MR results from eQTLs of Genotype-Tissue Expression project on chronic kidney diseases

Exposure	Odds ratio of CKD	*p* value of CKD	Beta effect on eGFR	*p* value of eGFR	Beta effect on BUM	Beta effect of eGFR opposite to BUN?
F12_Esophagus_Mucosa	0.592	7.65×10^{-14}	0.043	3.02×10^{-61}	−0.039	✓
MAP3K11_Adipose_Visceral_Omentum	1.282	9.36×10^{-9}	−0.011	2.35×10^{-12}	−0.021	×
MAP3K11_Brain_Cerebellum	1.214	9.36×10^{-9}	−0.009	2.35×10^{-12}	−0.017	×
MAP3K11_Breast_Mammary_Tissue	1.195	9.36×10^{-9}	−0.008	2.35×10^{-12}	−0.015	×
MAP3K11_Colon_Sigmoid	1.165	9.36×10^{-9}	−0.007	2.35×10^{-12}	−0.013	×
MAP3K11_Heart_Atrial_Appendage	1.289	9.36×10^{-9}	−0.012	2.35×10^{-12}	−0.022	×
MAP3K11_Pituitary	1.210	9.36×10^{-9}	−0.008	2.35×10^{-12}	−0.016	×
MAP3K11_Skin_Not_Sun_Exposed_Suprapubic	1.210	9.36×10^{-9}	−0.009	2.35×10^{-12}	−0.016	×
MAP3K11_Stomach	1.183	9.36×10^{-9}	−0.008	2.35×10^{-12}	−0.015	×
MAP3K11_Testis	1.262	9.36×10^{-9}	−0.011	2.35×10^{-12}	−0.020	×
MAP3K11_Adipose_Subcutaneous	1.162	9.97×10^{-9}	−0.007	2.10×10^{-13}	−0.013	×
MAP3K11_Artery_Aorta	1.161	9.97×10^{-9}	−0.007	2.10×10^{-13}	−0.013	×
MAP3K11_Artery_Coronary	1.182	9.97×10^{-9}	−0.008	2.10×10^{-13}	−0.014	×
MAP3K11_Artery_Tibial	1.138	9.97×10^{-9}	−0.006	2.10×10^{-13}	−0.011	×
MAP3K11_Colon_Transverse	1.247	9.97×10^{-9}	−0.011	2.10×10^{-13}	−0.019	×
MAP3K11_Esophagus_Gastroesophageal_Junction	1.126	9.97×10^{-9}	−0.006	2.10×10^{-13}	−0.010	×
MAP3K11_Esophagus_Mucosa	1.270	9.97×10^{-9}	−0.011	2.10×10^{-13}	−0.021	×
MAP3K11_Esophagus_Muscularis	1.152	9.97×10^{-9}	−0.007	2.10×10^{-13}	−0.012	×
MAP3K11_Muscle_Skeletal	1.250	9.97×10^{-9}	−0.011	2.10×10^{-13}	−0.019	×
MAP3K11_Nerve_Tibial	1.176	9.97×10^{-9}	−0.008	2.10×10^{-13}	−0.014	×
MAP3K11_Ovary	1.129	9.97×10^{-9}	−0.006	2.10×10^{-13}	−0.010	×
MAP3K11_Pancreas	1.139	9.97×10^{-9}	−0.006	2.10×10^{-13}	−0.011	×
MAP3K11_Prostate	1.198	9.97×10^{-9}	−0.009	2.10×10^{-13}	−0.016	×
MAP3K11_Skin_Sun_Exposed_Lower_leg	1.226	9.97×10^{-9}	−0.010	2.10×10^{-13}	−0.018	×
MAP3K11_Spleen	1.107	9.97×10^{-9}	−0.005	2.10×10^{-13}	−0.009	×
MAP3K11_Thyroid	1.112	9.97×10^{-9}	−0.005	2.10×10^{-13}	−0.009	×
MAP3K11_Whole_Blood	1.390	9.97×10^{-9}	−0.016	2.10×10^{-13}	−0.028	×
MAP3K11_Heart_Left_Ventricle	1.420	1.31×10^{-8}	−0.018	4.60×10^{-15}	−0.027	×
MAP3K11_Lung	1.207	4.96×10^{-8}	−0.009	6.93×10^{-12}	−0.017	×
MAP3K11_Small_Intestine_Terminal_Ileum	1.220	1.00×10^{-7}	−0.011	2.38×10^{-15}	−0.021	×
SLC47A1_Stomach	0.863	4.65×10^{-6}	0.013	3.46×10^{-29}	0.002	×
SLC47A1_Adipose_Visceral_Omentum	0.906	4.88×10^{-6}	0.009	1.24×10^{-29}	0.0009	×
SLC47A1_Heart_Atrial_Appendage	0.926	4.88×10^{-6}	0.007	1.24×10^{-29}	0.0007	×

(*Continued on next page*)

Table 1. *Continued*

Exposure	Odds ratio of CKD	*p* value of CKD	Beta effect on eGFR	*p* value of eGFR	Beta effect on BUM	Beta effect of eGFR opposite to BUN?
SLC47A1_Lung	1.203	5.90×10^{-6}	−0.017	1.99×10^{-29}	−0.002	×
SLC47A1_GTEx_Thyroid	0.923	5.90×10^{-6}	0.007	1.99×10^{-29}	0.0007	×
SLC47A1_Brain_Caudate_basal_ganglia	1.090	6.03×10^{-6}	−0.007	8.72×10^{-27}	−0.001	×
SLC47A1_Brain_Putamen_basal_ganglia	1.065	6.03×10^{-6}	−0.005	8.72×10^{-27}	−0.001	×
KIF5B_Testis	0.920	6.95×10^{-6}	0.003	1.27×10^{-7}	−0.004	✓
SLC47A1_Esophagus_Muscularis	0.919	7.12×10^{-6}	0.008	2.48×10^{-28}	0.0009	×
OPRL1_Cells_Cultured_fibroblasts	0.866	1.19×10^{-5}	0.007	5.66×10^{-9}	−0.009	✓
OPRL1_Nerve_Tibial	0.895	1.19×10^{-5}	0.006	5.66×10^{-9}	−0.007	✓
OPRL1_Skin_Not_Sun_Exposed_Suprapubic	0.880	1.19×10^{-5}	0.006	5.66×10^{-9}	−0.008	✓
OPRL1_Stomach	0.929	1.19×10^{-5}	0.004	5.66×10^{-9}	−0.005	✓
KIF5B_Cells_Cultured_fibroblasts	0.697	2.33×10^{-5}	0.015	3.31×10^{-6}	−0.016	✓
OPRL1_Prostate	0.882	3.07×10^{-5}	0.006	1.10×10^{-8}	−0.010	✓
SLC47A1_Adipose_Subcutaneous	0.886	3.34×10^{-5}	0.013	8.53×10^{-30}	0.0016	×
SLC47A1_Ovary	0.927	3.34×10^{-5}	0.008	8.53×10^{-30}	0.0010	×
SLC47A1_Skin_Sun_Exposed_Lower_leg	0.834	3.34×10^{-5}	0.019	8.53×10^{-30}	0.002	×
SLC47A1_Artery_Aorta	0.913	4.21×10^{-5}	0.010	2.7×10^{-29}	0.001	×
SLC47A1_Cells_Cultured_fibroblasts	0.957	4.21×10^{-5}	0.005	2.7×10^{-29}	0.0006	×

Table 2. Significant actionable druggable proteins

gene	tissue	OR_CKD	95% CI_CKD	pval_ckd	colocalization PP.H4
F12	Esophagus_Mucosa	0.592	0.516–0.679	7.65×10^{-14}	0.842 *
KIF5B	Testis	0.919	0.886–0.954	6.95×10^{-6}	0.705
OPRL1	Cell_Cultured_fibroblasts	0.867	0.812–0.925	1.19×10^{-05}	0.984*
OPRL1	Nerve_Tibial	0.895	0.852–0.940	1.19×10^{-5}	0.996*
OPRL1	Skin_Not_Sun_Exposed_Suprapubic	0.881	0.832–0.932	1.19×10^{-5}	0.918*
OPRL1	Stomach	0.929	0.898–0.960	1.19×10^{-5}	0.893*
KIF5B	Cell_Cultured_fibroblasts	0.696	0.589–0.823	2.33×10^{-5}	0.004
OPRL1	Prostate	0.882	0.832–0.936	3.07×10^{-5}	0.611

These genes were significant ($p < 3.96 \times 10\text{-}5$) MR results from eQTL of GTEx on chronic kidney diseases and also satisfied the standard that has opposite effect on eGFR and BUN.

of CKD and its complications. Therefore, we conducted large-scale MR and colocalization analyses to investigate the potential therapeutic efficacy of 1263 druggable protein-encoding genes as drug targets for CKD. Our study suggested two druggable target genes, OPRL1 and F12, should be prioritized for further evaluation for a possible role in treating CKD and improving renal function.

OPRL1 encodes the nociception (NOP) receptor or nociceptin/orphanin FQ (N/OFQ) receptor, a member of the seven transmembrane-spanning G protein-coupled receptor superfamily, whose ligands are largely endogenous opioid-related neuropeptides.[26] The N/OFQ-NOP receptor system has been implicated in a diverse range of physiological and pathological processes, including pain transmission, memory consolidation, immune modulation, and cardiovascular regulation.[27–29] In kidney tissue, NOP has been implicated to exert direct renal effects by downregulating aquaporin-2-mediated water reabsorption and inducing endogenous antioxidants-associated nephroprotection.[30,31] Furthermore, preclinical and pilot clinical studies also elucidated that the NOP receptor agonist, SER100 (Serodus, ASA, Oslo, Norway), induced vasodilatation, promoted diuresis, and decreased BP, partially through their orchestration of autonomic tone and locally prejunctional inhibition of noradrenergic neurotransmission.[32,33] As for N/OFQ, it is ubiquitously expressed throughout the central nervous system, especially in brain regions involved in autonomic and cardiovascular control.[27] Studies have detected decreased plasma N/OFQ in patients with cardiovascular disease, including acute coronary syndrome and chronic angina, suggesting a potential role in ischemic stress and following inflammatory responses.[34,35] Thus, in addition to the direct effect on renal, NOP and N/OFQ receptor systems can regulate renal function through the modulation of inflammation and blood pressure. Because of the short half-life and poor pharmacokinetics of peptide NOP receptor ligands, non-peptide NOP receptor agonists including, AT-039, AT-127, AT-090, and AT-403 (Astraea Therapeutics), are emerging as more suitable agents for the treatment of cardiovascular and renal diseases. Intravenous infusion of AT-039 was shown to cause sodium and potassium-sparing diuresis and decrease BP without affecting heart rates.[36] Given the principal role of anti-inflammation and anti-hypertensive treatment in targeting CKD progression,[37] the above-mentioned findings support our observation that genetically predicted OPRL1 expression levels are associated with CKD progression.

In addition, our results identified another drug candidate F12. The F12 gene encodes coagulation factor XII (FXII), which activates both pro-coagulant and pro-inflammatory contact systems.[38] Upon contact with negatively charged surfaces, FXII zymogen is converted to an activated form, FXIIa, which initiates the intrinsic blood coagulation cascade.[39] Apart from its central role in thrombosis, FXIIa exacerbates inflammation by activating the kallikrein-kinin system and promoting the formation of the inflammatory mediator, bradykinin.[39] Thus, targeting FXII is a promising therapeutic strategy for preventing thrombosis and concomitantly counteracting systemic inflammations. Irrespective of the many causes, patients with CKD are characterized by elevated pro-inflammatory properties that ultimately lead to renal fibrosis and dysfunction.[40] Since the most commonly used non-steroidal anti-inflammatory drugs are nephrotoxic to some extent,[1] we propose that targeting F12 may provide a cue to overcome this obstacle and prevent CKD progression. In contrast, patients with CKD exhibit features of hypercoagulability and are more susceptible to coagulopathy, for which direct oral anti-coagulants are highly recommended.[41] As such, targeting FXII could benefit patients with CKD by preventing thrombosis without compromising their hemostatic capacities.

Furthermore, our results indicated that MAP3K11 and SLC47A1 were significantly associated with CKD risk. Consistent results can be found in eGFR-based MR, but the results of BUN-based MR were not in the opposite direction to those of eGFR-based MR. Because the increased BUN levels and decreased eGFR levels suggest renal function deterioration, MR estimates of the same exposure on eGFR and BUN should be in opposite directions. As a result, in the current situation, MR estimates may be biased. In contrast, these two genes were found to be strongly associated with CKD risk in glomeruli and tubule cell-type-dependent eQTL analysis. Based on these findings, we suggest that more studies should be conducted to detect the effects of MAP3K11 and SLC47A1 on CKD risk.

CKD encompasses highly heterogeneous risk factors and primary disorders, making it an umbrella term for various disease states with genetic and phenotypic complexities. Groopman et al. conducted the largest exome sequencing study in more than 3,300 patients with CKD and identified that genetic variants could account for a significant number (~9%) of these patients.[42] In addition, previous GWAS in CKD has revealed approximately 300 genetic loci that are significantly associated with compromised renal function (decreased eGFR levels),[43] highlighting the value of human genetics for CKD pathogenesis and potential drug discovery. Although drug discovery is vital for the

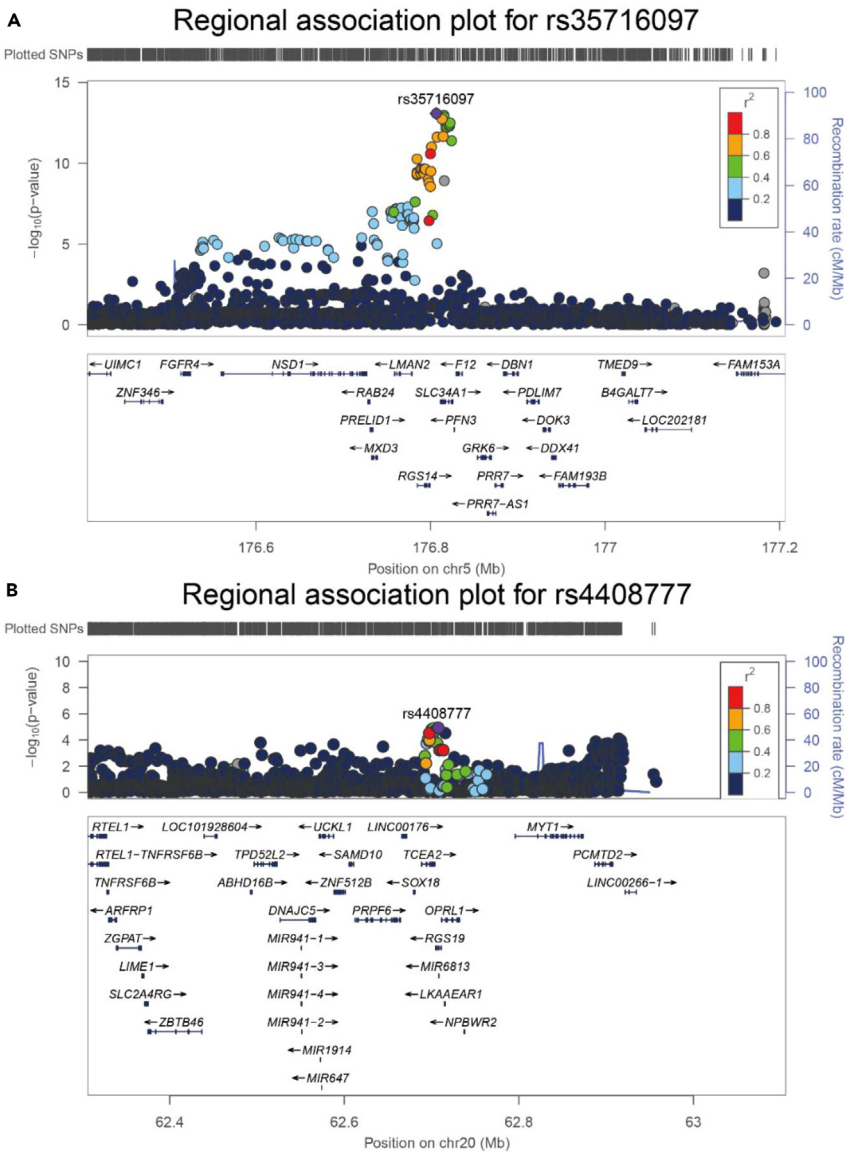

Figure 3. Regional association plots around (A) rs35716097 and (B) rs4408777 in CKD

Plots are produced in LocusZoom and show the most strongly associated SNP (presented as purple diamond). The color reflects LD correlation (r2) using 1000G EUR population as reference. The left y axis indicates -log10(*p* value) of SNPs and the x axis indicates the chromosomal positions of SNPs (GRCh37). The right y axis represents the genetic recombination rates.

treatment of CKD, the difficulty of achieving novel drug development has greatly increased owing to both the duration and costs involved, leading to a decrease in the overall success rate of translating discoveries to clinical practice.[44] Advances in GWAS have proven promising for drug repurposing, as GWAS reveals important biological insights into complex traits that are helpful in identifying compounds suitable for repurposing. Specifically, emerging druggable genome resource enables researchers to systematically investigate the causal effects of drug target genes expression on human disease phenotypes using MR analyses.[45] *Cis*-variants that act on the expression levels of drug target genes could mimic the on-target effects of pharmacological interventions, thereby serving as powerful instruments for inferring target-indication pairs.[20] As such, GWAS has been reported to double or triple the success rate of drug repurposing. For example, Gaziano et al. predicted repurposing opportunities for COVID-19 with druggable genome-wide MR, which prioritizes trials of drugs for the early management of COVID-19.[46] However, to the best of our knowledge, there has been no such exploration in CKD.

Given that CKD is widely recognized as a systemic disease affecting multiple organs, we conducted drug-target MR analyses using the GTEx Consortium *cis*-eQTLs across 49 human tissues combined with kidney-specific eQTL data provided by Sheng et al. to mimic medical exposures in the present study.[47] Focusing on *cis*-variants and their influence on druggable gene expression levels, we are the first

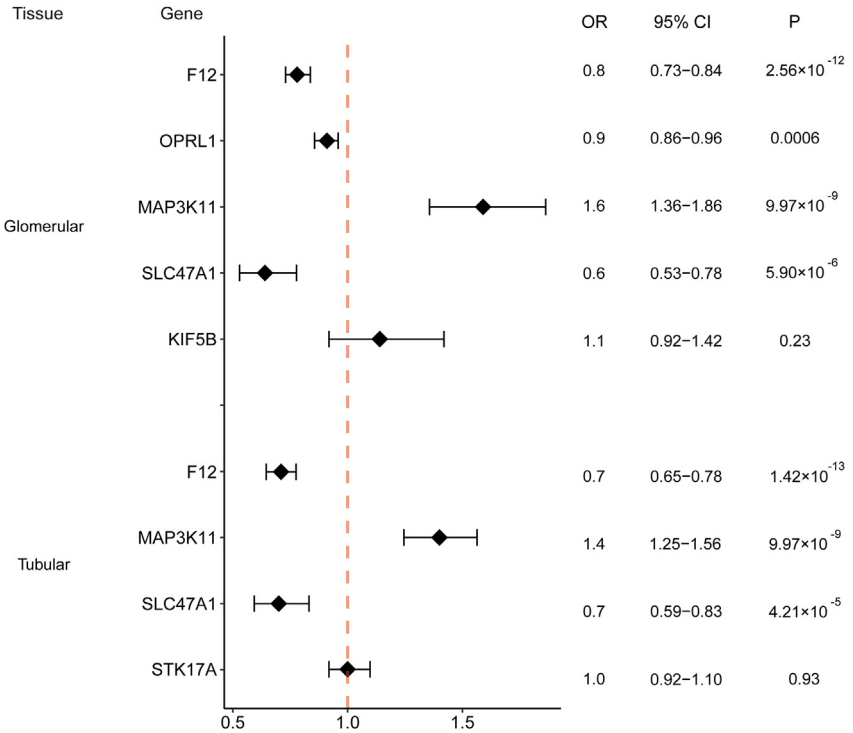

Figure 4. Forest plot of results from actionable druggable genome-wide MR analysis with glomeruli and tubule cell-type-dependent eQTL dataset
Genes included in this figure was those with PPH4 > 0.8 in colocalization analysis.

to implicate the causal role of nociception receptor OPRL1, and coagulation factor F12 in CKD progression using MR analyses. To our knowledge, the data used in this study were derived from the largest publicly available CKD GWAS to date. To reduce the possibility that genetic instruments are influenced by alternative disease pathways (that is horizontal pleiotropy), we restricted the proposed genetic instruments to variants acting in *cis* and excluded *trans*-eQTLs distal to the encoding genes. Furthermore, our application of both the discovery and validation cohorts also strengthened causal inference and avoided potential bias. Colocalization analyses further reduced the possibility of false positive conclusions resulting from the confounding effect of linkage disequilibrium. Based on the pivotal role of these MR study design and quality control methods in validating reliable causal inference,[48] we propose OPRL1 and F12 with robust genetic evidence as prioritized drug target genes for CKD treatment.

Limitations of the study

The interpretations and generalizations of our findings are limited by several factors. First, MR studies generally mimic rather than replace randomized trials. The unique features of genetic variants make it possible for MR studies to assess the impact of life-long, low-dose exposure on clinical outcomes of interest. In contrast, RCTs usually evaluate the therapeutic effects of comparably high-dose interventions over a relatively short duration of time, typically ranging from several months to five years.[49] Therefore, dedicated and strictly designed clinical trials with adequate power are warranted to investigate the safety and efficacy of potential small-molecule drugs targeting OPRL1 and F12 in treating patients with CKD. Second, we selected only *cis* instruments that are less prone to violating the MR horizontal pleiotropy assumption when compared with *trans*-eQTLs. However, this procedure might exclude some valid variants simultaneously, which may compromise the contributions of this research. To date, it remains challenging to decipher the underlying biological mechanisms of GWAS results using cell-type specific eQTL datasets. Because the GTEx database has low coverage of human kidney-specific eQTLs owing to the limited number of samples, we validated the drug candidate genes using the kidney compartment-based eQTL dataset generated by Susztak lab.[50] Nonetheless, we did not consider the possibility that genetic variants affected CKD progression via alternative pathways (that is epigenetic modifications). Third, only data based on participants of European ancestry were analyzed, and generalization to other ancestry needs further validation. Fourth, when performing MR, few genes had a sufficient number of genetic instruments to perform pleiotropy-robust methods, meaning the influence of horizontal pleiotropy could not be evaluated. Fifth, the use of summary genetic data meant we were only able to evaluate evidence for linear causal effects.

In summary, our eQTL-based MR analyses revealed that OPRL1 and F12 are causally associated with CKD risk and represent two genetically supported promising therapeutic targets for CKD treatment. We hope that these findings will help provide valuable insights into the genetic causes of CKD, enhance the current understanding of its pathological mechanisms, and improve the success rates of future clinical trials.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.109953.

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AUTHOR CONTRIBUTIONS

X.C. and R.N.S. designed the study. X.C. wrote the first draft of the manuscript and verified the underlying data. X.C., R.N.S., S.L.L., Z.D.X., and G.C.Y. conducted statistical analyses and participated in data interpretation. R.J.L., X.S.H., R.J.L., and J.H.W. played roles in acquisition of the data and analyses. All authors revised and approved the final manuscript. The guarantor (Y.N.H. and T.X.L.) confirms that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

DECLARATION OF INTERESTS

The author declared no conflicts of interest.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
CKDGen consortium	http://ckdgen.imbi.uni-freiburg.de/datasets/Wuttke_2019	
eQTL	https://www.gtexportal.org/	
Cell-type dependent eQTL	http://susztaklab.com/eQTLci/index.php	
Software and algorithms		
TwoSampleMR (version 0.5.6)	https://github.com/MRCIEU/TwoSampleMR	
coloc (version 5.2.3).	https://github.com/chr1swallace/coloc/tree/main/R	
DSigDB	https://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4_ctd&id=6108	
Locuszoom	https://my.locuszoom.org/	

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and codes should be directed to and will be fulfilled by the lead contact, Tianxin Lin (lintx@mail.sysu.edu.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- All data for this study were publicly available and usl could be found in Methods details. All code could be found in the github (XiongChen-SYSU/iSCIENCE github.com).
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Our study is computational science research.

Ethics committee approval

This study used publicly available de-identified data from participant studies that were approved by an ethical standards committee with respect to human experimentation. No separate ethical approval was required in this study.

METHODS DETAILS

Actionable druggable targets and instrument variables selection

In this study, exposures were set as the expression levels of actionable druggable targets. Previously, Gaziano et al. identified 1,293 actionable druggable targets from the ChEMBL database (Table S1).[46] Actionable druggable targets were defined as therapeutic targets of approved drugs and clinical candidates or potential targets of approved drugs. Among the 1,293 druggable targets, 531 were therapeutic targets of approved drugs, 381 were therapeutic targets of clinical candidates, and 351 were potential targets of approved drugs. Gaziano et al. also proposed conditionally-independent genetic variants related to the expression levels of the 1,263 druggable targets (eQTL) using raw data from 49 tissues from GTEx V8, which encompassed > 70 European ancestry individual samples.[46] In brief, the selection criteria of druggable targets-related eQTL were as follows: 1) removal of ambiguous SNPs: genotype missingness <0.05, minor allele frequency <0.01, and Hardy-Weinberg equilibrium <0.000001; 2) adjustment for sex, the first five principal components, PEER factors, sequencing platform, and protocol; 3) Genome-wide significance with a *p*-value $<5\times10^{-8}$; *Cis*-eQTLs were defined as genome-wide significant associations within 1Mb on either side of the encoded gene. These 1,293 druggable genes were evaluated for their causal effect on CKD risk and measures of kidney function,

using eQTLs as genetic instruments variables (IVs) in this study. The selected IVs were listed in Table S2. The r2 and F-statistics were calculated with following formula:

$$r2=beta^2/(beta^2+se^2*sample\ size)$$

$$F=r2*(sample\ size\ -1-k)/(1-r2)$$

k indicates the number of SNP, for calculating F-statistics for each SNP, k=1.

Mendelian randomization and colocalization

The exposure and outcome data were harmonised. For those with only one eQTL, Wald ratio was used to reveal the causal effect of druggable actionable targets on CKD risk. For those with more than one variant, random-effects inverse-variance-weighted MR was applied for primary analyses. Bonferroni correction for multiple MR tests was used and the significant *P*-value threshold was set as 3.96×10^{-5} (0.05 /1,263), although SNPs for some druggable targets were lacking in outcomes resulting in a number of analyzed genes less than 1,263.

To derive robust MR estimates, the following three assumptions should be satisfied: (i) IVs are strongly associated with exposure; (ii) IVs are independent of confounders; and (iii) IVs affect outcomes only through their effects on exposure and not through an alternative causal pathway.[51] The IVs were strongly associated with the actionable druggable targets with the inclusion criteria.

To ensure MR results were not biased by linkage disequilibrium, colocalization was performed for those genes with strong evidence for an effect in MR analyses, including opposite directions of effect in eGFR and BUN MR analyses. Colocalization was performed with default priors (probability of shared causal variant for trait 1 and trait 2 was $P1 = P2 = 1 \times 10^{-4}$, probability of shared causal variant across two traits was $P12 = 1 \times 10^{-5}$). A posterior probability for hypothesis 4 (PP.H4) > 0.8 was regarded as statistically significant.

Validation with cell-type-dependent eQTL data of kidney tubular and glomerular samples

Xin Sheng et al manually micro-dissected 659 kidney samples into glomerular and tubular compartments and performed RNA-seq as well as genotyping (356 tubules and 303 glomeruli: see Tables S6 and S7).[52] They used two different linear mixed effect models with sequencing batch effect and calculated Akaike's information criterion (AIC). Those SNP with FDR< 0.05 and AIC <0 were retained. Then, those SNP with linear regression P-value < 5E-05 were finally defined as eQTLs. In this study, we leveraged the significant cell-type-dependent eQTLs reported by Xin et al to conduct glomerular and tubular cell-type-dependent MR to estimate whether consistent significant estimates could obtained. Detailed information of the included IVs for cell-type-dependent eQTLs in CKD is presented in Table S8. The MR analysis procedures were consistent with aforementioned methods.

QUANTIFICATION AND STATISTICAL ANALYSIS

All analysis was conducted in R (version 4.2.1). MR analyses were conducted using the R package "TwoSampleMR" (version 0.5.6). Colocalization was performed using the "coloc" (version 5.2.3) R package. The power for MR analysis was estimated using an online tool.[53]