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ORIGINAL RESEARCH

Unraveling the Genetic Links Between Polycystic Kidney Disease and Hypertension Through ARL13B

Juan Chen[1,*], Lei Song[2,*], Shuqin Mei[1,*], Jing Huang[3], Lili Fu[1], Chenchen Zhou[1], Xiaohua Hu[1], Liming Zhang[1], Cheng Xue[1,3], Zhiguo Mao[1]

[1]Kidney Institute, Division of Nephrology, Shanghai Changzheng Hospital, Second Military Medical University (Naval Medical University), Shanghai, People's Republic of China; [2]Division of Nephrology, People's Hospital of Yangzhong City, Yangzhong, Jiangsu Province, People's Republic of China; [3]Department of Cellular Biology and Anatomy, Medical College of Georgia at Augusta University, Augusta, GA, USA

*These authors contributed equally to this work

Correspondence: Zhiguo Mao; Cheng Xue, Kidney Institute, Division of Nephrology, Shanghai Changzheng Hospital, 415 Fengyang Road, Shanghai, 200003, People's Republic of China, Fax +86-21-81885411, Email maozhiguo518@126.com; chengxia1568@126.com, cheng8568@gmail.com

Background: Autosomal dominant polycystic kidney disease (ADPKD), the most common inherited kidney disorder, is frequently accompanied by hypertension, with each condition potentially exacerbating the other. This study employs a bidirectional Mendelian randomization (MR) design to investigate the causal relationship between PKD and hypertension, alongside bioinformatics analyses to explore underlying genetic mechanisms.

Methods: Genetic data for PKD and hypertension were obtained from the International Epidemiology Unit (IEU) Genome-Wide Association Study (GWAS) database. A bidirectional MR analysis was performed using nucleotide polymorphisms (SNPs) strongly associated with PKD and hypertension. Genetic annotation and enrichment analysis of SNPs were conducted using the Functional Mapping and Annotation (FUMA) platforms. Gene expression differences between PKD and controls were studied using the GEO database and single-cell data analysis tools. Quantitative PCR analysis of ARL13B mRNA levels in normal renal tubular epithelial cells (RCTEC), renal cystic epithelial cells (WT9-12), and ADPKD kidney tissues.

Results: MR analysis demonstrated a causal effect of PKD on hypertension (IVW: P=0.038; OR=1.011; 95% CI: 1.001–1.021) and a reverse causal effect of hypertension on PKD (IVW: P=0.042; OR=1.195; 95% CI: 1.007–1.420). No significant heterogeneity or pleiotropy was detected. Genetic annotation identified 27 *PKD* genes closely associated with hypertension. Among them, functional enrichment analysis indicated *ARL13B* was involved in cilia morphology and dysfunction. Notably, RT-PCR results showed that ARL13B mRNA expression was significantly elevated in human ADPKD kidneys (P<0.001) and WT9-12 cells (P<0.05).

Conclusion: Our bidirectional MR study demonstrated a causal effect of PKD on hypertension and a reverse influence of hypertension on PKD progression. Elevated ARL13B expression in ADPKD suggested a possible involvement of cilia-related pathways in the development of renal hypertension.

Keywords: Mendelian randomization, polycystic kidney disease, hypertension, ARL13B, cilia dysfunction

Introduction

Polycystic kidney disease (PKD), particularly its most prevalent form—Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most common inherited kidney disorders, characterized by the progressive formation and enlargement of cysts in the kidneys.[1] This condition often leads to a decline in renal function and the eventual development of end-stage renal disease. Hypertension is the most frequent complication of ADPKD, typically emerging early in the course of the disease.[2] The traditional understanding suggests that cysts in ADPKD compress renal parenchyma, leading to renal ischemia and subsequent renin-angiotensin-aldosterone system (RAAS) activation, which in turn causes renal hypertension.[3,4]

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Despite this well-established clinical observation, the genetic mechanisms underlying the relationship between ADPKD and hypertension remain largely unexplored. Moreover, the potential bidirectional nature of this association —whether hypertension could also influence the development and progression of ADPKD—has not been thoroughly investigated. Previous studies[5–7] have primarily focused on the impact of ADPKD on hypertension, with limited evidence on the genetic predispositions that might mediate this interaction.

The objective of this study is to utilize a bidirectional Mendelian randomization (MR) approach to elucidate the causal relationships between ADPKD and hypertension. MR is an epidemiological method that uses genetic variants as instrumental variables (IVs) to infer causal relationships between modifiable exposures and outcomes. This method is built upon three key assumptions: (i) the genetic variants are robustly associated with the exposure; (ii) the genetic variants are not associated with any confounders of the exposure-outcome relationship; and (iii) the genetic variants influence the outcome only through the exposure, not via alternative pathways (ie, no horizontal pleiotropy).[8] A recent study investigated the association between lipid-lowering drug targets and the risk of cystic kidney disease,[9] but no research has yet applied an MR design to systematically explore the causal relationship between ADPKD and hypertension. By leveraging genetic data, we aim to identify whether there is a genetic basis for the association between ADPKD and hypertension and to explore if hypertension might have a reciprocal effect on the risk of developing ADPKD. This study seeks to provide new insights into the genetic interplay between these two conditions, potentially uncovering novel mechanisms and therapeutic targets.

Materials and Methods

Study Design

This study employs a bidirectional MR design to elucidate the causal effect between PKD and hypertension, and the reliability of the data was confirmed by sensitivity analysis. MR is based on three assumptions:[8] (i) genetic variation is strongly associated with exposure factors only; (ii) genetic variation has no effect on confounding factors other than exposure factors; and (iii) genetic variation regulates outcomes through exposure factors only.

For the genetic annotation and enrichment analysis of single nucleotide polymorphisms (SNPs) significantly associated with PKD, we utilized the Functional Mapping and Annotation (FUMA) platform (https://fuma.ctglab.nl/) and the WeiShengxin platform (https://www.bioinformatics.com.cn/). Subsequently, we utilized the GEO2R gene chip provided by National Center for Biotechnology Information (NCBI) online tools (https://www.ncbi.nlm.nih.gov/geo/geo2r/) and the single-cell data analysis tool published by Muto[10] (http://humphreyslab.com/SingleCell/) to study the gene expression differences between PKD and controls. The bidirectional Mendelian study design is shown in Figure 1.

Data Sources

Both PKD and hypertension data were obtained from the International Epidemiology Unit (IEU) Genome-Wide Association Study (GWAS) database (https://gwas.mrcieu.ac.uk/). The PKD data was obtained from the European cohort population (id: ebi-a-GCST90018904) with a total sample size of 355431 cases and 424 cases, and the hypertension data was obtained from the European cohort population (id: ebi-a-GCST90013916) with a total sample size of 407746 cases. The genetic summary statistics for PKD (ebi-a-GCST90018904) and hypertension (ebi-a-GCST90013916) were with case definitions based on International Classification of Diseases (ICD) diagnostic codes (PKD: ICD-10 Q61) and, for hypertension, a combination of ICD diagnostic codes and/or self-reported physician diagnoses. The GSE7869 microarray includes data from cysts of different sizes and controls, and we chose data from large cysts (greater than 50 mL, n=3) for comparison with controls (n=3).[11] Supplementary Table 1 provides data from all study cohorts. As this study used data from a publicly available database, no additional ethical approval consent was required.

Instrumental Variables Selection and MR Analyses

Mendelian randomization analysis was conducted to select SNPs that met the genome-wide significance threshold ($p < 5 \times 10^{-8}$ or $p < 5 \times 10^{-6}$). In the forward MR analysis with PKD as the exposure and hypertension as the outcome, we

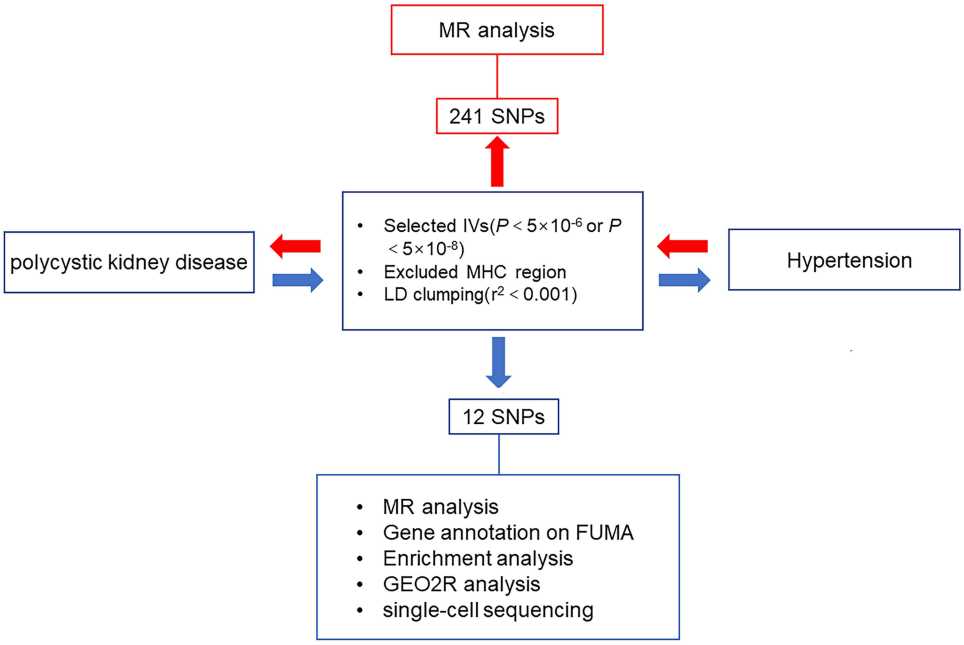

Figure 1 Description of the study design of the bidirectional MR analysis. The blue arrows represent the forward MR analysis, where PKD is the exposure factor and hypertension is the outcome factor. The red arrows represent the reverse MR analysis, with hypertension as the exposure factor and PKD as the outcome factor.
Abbreviations: IVs, Instrumental Variables; LD, Linkage Disequilibrium; MHC, Major Histocompatibility Complex; MR, Mendelian Randomization; SNPs, Single Nucleotide Polymorphisms.

adopted a significance threshold of $p < 5\times10^{-8}$. In the reverse MR analysis with hypertension as the exposure and PKD as the outcome, we used a significance threshold of $p < 5\times10^{-6}$. Linkage disequilibrium (LD) clumping was then applied to retain independent SNPs, using an LD threshold of $r^2 < 0.001$ and a clumping distance of 10,000 kb, based on the 1000 Genomes European reference panel. And F-values were calculated according to $F = R^2 \times (n-k-1)/ [K \times (1-R^2)]$, selecting instrumental variables with $F > 10$.[12] When the screened SNPs were harmonized with the outcome data, the palindromic SNPs with intermediate allele frequencies were excluded. Then the data were subjected to sensitivity analysis including Cochran's Q, funnel plot, MR-Egger regression to assess the heterogeneity and multiplicity of the data, and leave-one-out plots to analyze whether causality was greatly influenced by single SNP, and the analysis by using this method ensured that the results of the data were reliable and rigorous, and to reduce the influence of potential confounders.

Functional Annotation

Relevant genes were identified by annotating SNPs closely associated with ADPKD using FUMA online tool.

Functional Enrichment Analysis

Using the WeiShengxin website, enrichment, and pathway analyses were conducted on genes identified by the FUMA tool, and Manhattan plots were created to visually present the results of genome-wide association studies, revealing genes and pathways associated with specific diseases or phenotypes.

GEO2R Analysis and Single-Cell Sequencing

We used GSE7869 microarray data from GEO database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE7869) and single-cell data by KIT (https://humphreyslab.com/SingleCell/) from Humphreys lab to investigate mRNA expression differences between ADPKD and controls, as well as intracellular expression differences, with particular insight into ARL13B. Microarray data contained gene expression profiles from large renal cysts (>50 mL, n = 3) and adjacent normal renal tissues (controls, n = 3) from patients with ADPKD. Data analysis was performed using the GEO2R online tool, which utilizes the R programming language and the limma package to identify differentially expressed genes (DEGs)

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between experimental groups. The Benjamini & Hochberg (False Discovery Rate, FDR) method was applied to adjust for multiple testing. Genes with an adjusted $p < 0.05$ and an absolute log2 fold change ($\log_2$FC) > 1 were considered statistically significant and differentially expressed. We examined ARL13B expression specifically within the KIT snRNA-seq data, focusing on its cell-type–specific distribution across ADPKD samples. The results were visualized using UMAP clustering and expression plots.

Human Kidney Samples and Cell Lines

Human kidney tissues were obtained from Changzheng Hospital, including renal cortex specimens adjacent to cysts from ADPKD patients who underwent nephrectomy, and control samples from noncancerous kidney tissue (located >5 cm from tumor lesions) collected during nephrectomy for renal cell carcinoma. All tissue specimens were confirmed to be free of contamination and were snap-frozen in liquid nitrogen prior to analysis. Written informed consent was obtained from all participants, and the study was approved by the Ethics Committee of Changzheng Hospital (approval number: CZ2018-0619), in accordance with the Declaration of Helsinki.

The human immortalized renal cyst epithelial cell line WT9-12 was generously provided by Prof. Jing Zhou (Harvard University, Boston, MA, USA). Human renal tubular epithelial cell line RCTEC were used as non-cystic controls for WT9-12 cells.

Realtime PCR

RNA from cells or kidney tissues was isolated using TRIzol (Takara, Kyoto, Japan) and then reverse transcribed. The primer sequences were as follows: GAPDH, primer F, 5′-GGAAACTGTGGCGTGATG-3′ and primer R, 5′-TGGGTGTCGCTGTTGAAG-3′; ARL13B, primer F, 5′-AACGCATCCAAAAAGAGACAACA-3′ and primer R, 5′-TCTCGTAATTTTCGCACTCGTTC-3′. Real-time PCR was performed using SYBR Green PCR Master Mix (Vazyme, Nanjing, China) and the Rotor-Gene 3000A real-time PCR system (Corbett, Sydney, Australia) according to the manufacturer's instructions. In brief, the PCR amplification reaction mixture (20 mL) contained 2 mL cDNA, 0.4 mL F primer, 0.4 mL R primer, and 10 mL SYBR Green I. After initial denaturation at 95°C for 1 minute, the reaction was cycled 45 times. Each cycle consisted of denaturation at 95°C for 15 seconds and primer annealing and extension at 60°C for 31 seconds. Results are shown as the relative expression of ARL13B normalized to the expression of GAPDH. Real-time PCR was performed in triplicate for each experiment, and the average values were measured. Each experiment was repeated three times. Using the gene-specific efficiencies, mRNA relative expression folds were calculated as $2^{-\Delta\Delta}$ circle threshold.

Statistical Analysis

To investigate the causal relationship between PKD and hypertension, this study primarily employed the inverse-variance weighted (IVW) test, which better elucidates the causal effect between hypertension and PKD.[13] Four additional MR methods were applied to causality: MR-Egger, weighted median, simple mode, and weighted mode. Heterogeneity was tested using Cochrane's Q statistic, and sensitivity analysis was conducted using the leave-one-out method to assess the reliability and feasibility of the data results.[8] Pleiotropy was assessed using the intercept from the MR-Egger method and the MR-Presso test. ARL13B gene expression differences were *t*-tested and plotted by GraphPad Prism 8. MR analyses were conducted using R software (version 4.3.2), TwoSampleMR (version 0.6.1), the MR-Presso package (version 1.0.0), and the ieugwasr package (version 1.0.0), with a two-sided p-value < 0.05 considered significant. All estimates were expressed as odds ratios (OR).

Results

Causal Effects of PKD on Hypertension

The results of the MR analysis were detailed in Table 1 and depicted in Figure 2a. Using the Inverse Variance Weighted (IVW) method, a causal relationship between PKD and hypertension was established (P=0.038; OR=1.011; 95% CI: 1.001–1.021). Supplementary Table 2 lists the 12 SNPs derived from the PKD dataset. No significant heterogeneity was detected (IVW: P=0.831; MR-Egger: P=0.831) and no evidence of pleiotropy was found (MR-Egger regression: P=0.558; MR-PRESSO: P=0.558) as shown in Table 2. Figure 2b illustrated scatter

Table 1 MR Analysis of PKD on High Blood Pressure

Exposure	Outcome	Method	nSNPs	β	P	OR	OR_lci95	OR_uci95
Polycystic kidney disease	High blood pressure	MR Egger	10	0.015	0.120	1.015	0.998	1.032
		Weighted median	10	0.010	0.143	1.010	0.997	1.024
		Inverse variance weighted	10	0.011	**0.038**	**1.011**	**1.001**	**1.021**
		Simple mode	10	0.009	0.366	1.009	0.990	1.029
		Weighted mode	10	0.010	0.296	1.010	0.992	1.029

Notes: Bold font indicates the most significant result.
Abbreviations: nSNPs, number of SNPs used in MR; OR, odds radio; OR_lci95, upper 95% confidence intervals; OR_uci95, lower 95% confidence intervals.

plots of the causal effect estimates of each SNP on hypertension using different methods. The leave-one-out analysis, presented in Figure 2c, indicated that the causal effect of PKD is not driven by any single SNP. These findings suggest that PKD could be a potential risk factor for developing hypertension.

Reverse MR Analysis of Hypertension on PKD

We identified 241 SNPs strongly associated with hypertension (Supplementary Table 3). Considering the potential impact of hypertension on PKD, we conducted reverse MR analysis based on these SNPs. The MR analysis, as shown in Table 3 and Figure 2d, revealed a reverse causal effect of hypertension on PKD using the IVW method (P=0.042; OR=1.195, 95% CI: 1.007–1.420). There was no heterogeneity (IVW: P=0.858; MR-Egger: P=0.857) and pleiotropy (MR-Egger regression: P =0.352; MR-PRESSO: P=0.352) (Table 4). Figure 2e presented scatter plots from various methods, visualizing the causal effect estimates of each SNP on PKD. The leave-one-out analysis demonstrated that hypertension is not influenced by any single SNP (Figure 2f). These reverse findings suggest that hypertension may be a risk factor for PKD.

Gene Annotation

Genetic annotation of 12 lead SNPs screened for strong association with PKD based on MR analysis identified 27 mapped genes (Supplementary Table 4). At the genomic level, there were 12 independent loci significantly associated with PKD ($P < 5\times10^{-6}$), which were distributed on multiple chromosomes (Figure 3a and b). Based on human ADPKD GSE7869 microarray data, we screened and visualized expression changes in 27 key genes using a volcano plot. The results revealed significantly upregulated ARL13B expression ($\log_2$FC = 1.12, p<0.01) (Figure 3c).

Functional Enrichment Analysis

To explore the potential mechanisms by which PKD may lead to hypertension, 27 genes were analyzed using GO analysis tools. This analysis categorized the genes based on molecular function (MF), cellular components (CC), and biological processes (BP). The results suggested that these genes are involved in the DNA damage response and cilia movement at the bioprocess level. In terms of cellular components, they were associated with the calcium channel complex, non-motor cilia, motor cilia, and ion channel complexes (Figure 3c). In the analysis of cellular components (CC), we observed that genes were predominantly localized to cilia, nonmotile cilia, motile cilia, and cation channel complexes (Figure 3d). Notably, we found that a gene associated with ciliary motility, ARL13B, was significantly enriched in GO analysis. In the CC, ARL13B was associated with the localization of non-motile and motile cilia and may play a key role in regulating cilia function (Figure 3e); whereas on the BP side, ARL13B was involved in the localization of proteins to the ciliary membrane as well as the localization of proteins to non-motile cilia (Figure 3f).

GEO Analysis and Single-Cell Sequencing

As shown in Figure 4a, in human ADPKD GSE7869 microarray data, the mRNA level of ARL13B was significantly elevated in the ADPKD group compared with the normal human group. ARL13B may play a role in cilia formation and maintenance, and the pathogenesis of hypertension in PKD by cilia dysfunction. Therefore, we analyzed single-cell RNA sequencing data from human ADPKD and normal kidney tissues using transcriptomic and epigenomic datasets to further assess cell-specific expression of the ARL13B gene. ADPKD group cells were clustered and further divided into 15 cell

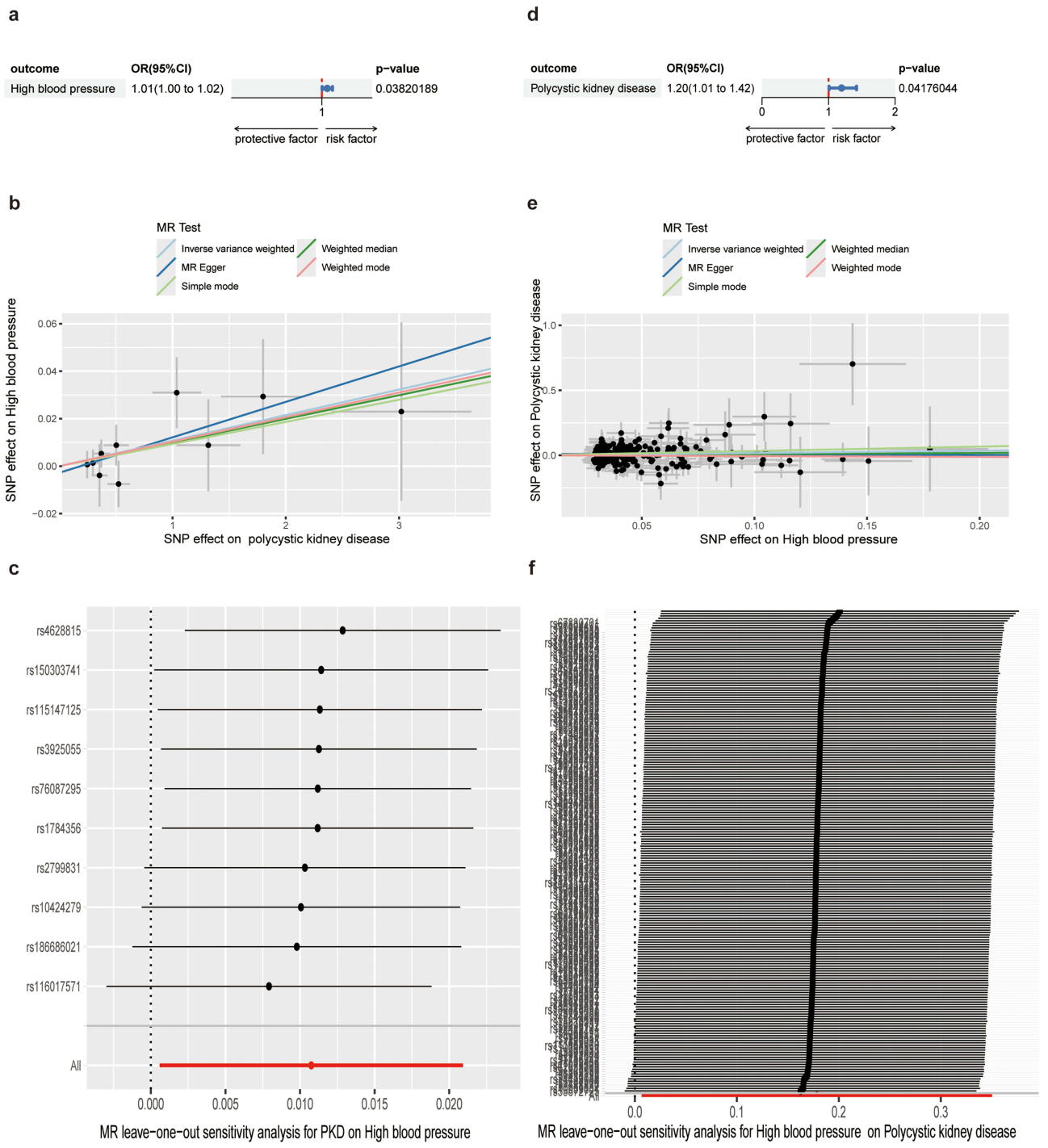

Figure 2 Bidirectional causal relationships between PKD and hypertension. (**a**) Forest plot showing the estimated causal effect of PKD on hypertension. (**b**) Forest plot showing the estimated causal effect of hypertension on PKD. (**c**) Scatterplot demonstrating the distribution of the causal effect of PKD on hypertension. (**d**) Scatterplot demonstrating the distribution of the causal effect of hypertension on PKD. (**e**) Leave-one-out plot analysis demonstrating the robustness of the causal effect of PKD on hypertension. (**f**) Leave-one-out plot analysis demonstrating the robustness of the causal effect of hypertension on PKD.

types (Figure 4b). The results showed that in the PKD group, ARL13B was expressed at high levels in a variety of cells compared with the normal group, including endothelial cells (ENDO), fibroblasts (FIB), leukocytes (LEUK), and Glomerular mural epithelial cells (PEC) (Figure 4c).

Table 2 Sensitivity Analysis of PKD on High Blood Pressure

Exposure	Outcome	Heterogeneity Test				Pleiotropy Test			
		IVW		MR-Egger		MR-Egger Regression		MR-PRESSO	
		Q	P	Q	P	Intercept	P	Outliers Number	P
Polycystic kidney disease	High blood pressure	4.658	0.863	4.283	0.831	−0.003	0.558	NA	0.862

Table 3 MR Analysis of High Blood Pressure on PKD

Exposure	Outcome	Method	nSNPs	β	P	OR	OR_lci95	OR_uci95
High blood pressure	Polycystic kidney disease	MR Egger	201	−0.042	0.869	0.959	0.586	1.570
		Weighted median	201	0.092	0.503	1.097	0.837	1.438
		Inverse variance weighted	201	0.178	**0.042**	**1.195**	**1.007**	**1.420**
		Simple mode	201	0.336	0.361	1.399	0.682	2.870
		Weighted mode	201	−0.062	0.817	0.940	0.557	1.587

Notes: Bold font indicates the most significant result.

Table 4 Sensitivity Analysis of High Blood Pressure on PKD

Exposure	Outcome	Heterogeneity Test				Pleiotropy Test			
		IVW		MR-Egger		MR-Egger Regression		MR-PRESSO	
		Q	P	Q	P	Intercept	P	Outliers Number	P
High blood pressure	Polycystic kidney disease	178.695	0.858	177.823	0.857	0.011	0.352	NA	0.844

Rt-qPCR Results

The mRNA levels of *ARL13B* gene were tested in RCTEC vs WT9-12 cells, and human normal vs ADPKD kidney tissues. As shown in Figure 4d and e, compared to normal renal tubular epithelial cells, ARL13B mRNA levels were significantly elevated in WT9-12 cells ($P < 0.001$) and also significantly elevated in human polycystic kidney tissue ($P < 0.05$).

Discussion

Our bidirectional MR study demonstrated a causal effect of PKD on hypertension and a reverse influence of hypertension on PKD progression. Single-cell analysis revealed that ARL13B was upregulated across multiple renal cell types in ADPKD, including endothelial cells, fibroblasts, leukocytes, and particularly parietal epithelial cells (PECs). Furthermore, bioinformatics analysis highlighted higher expression of *ARL13B* gene in ADPKD, suggesting that ARL13B might play a critical role in the development of renal hypertension by affecting cilia morphology. Notably, the lead SNPs identified in our MR analysis have not been previously reported in genome-wide association studies of PKD or hypertension. While this novelty reflects differences from general-population GWAS findings, it also highlights the possibility that PKD-related hypertension may involve disease-specific genetic mechanisms.

ADPKD is known to promote hypertension through multiple mechanisms.[14–16] Traditionally, it has been understood that the enlargement of cysts within the kidneys compresses the surrounding renal parenchyma, leading to renal ischemia. This ischemia triggers RAAS, a major regulator of blood pressure, resulting in hypertension.[17] Meanwhile, the mechanical pressure exerted by the cysts can directly compress blood vessels, further contributing to increased blood pressure.[1] Moreover, ADPKD advances as chronic kidney disease, increasing the risk of hypertension.[18] Renal fibrosis can further exacerbate hypertension by disrupting normal renal function and increasing systemic vascular resistance.[19,20] Other

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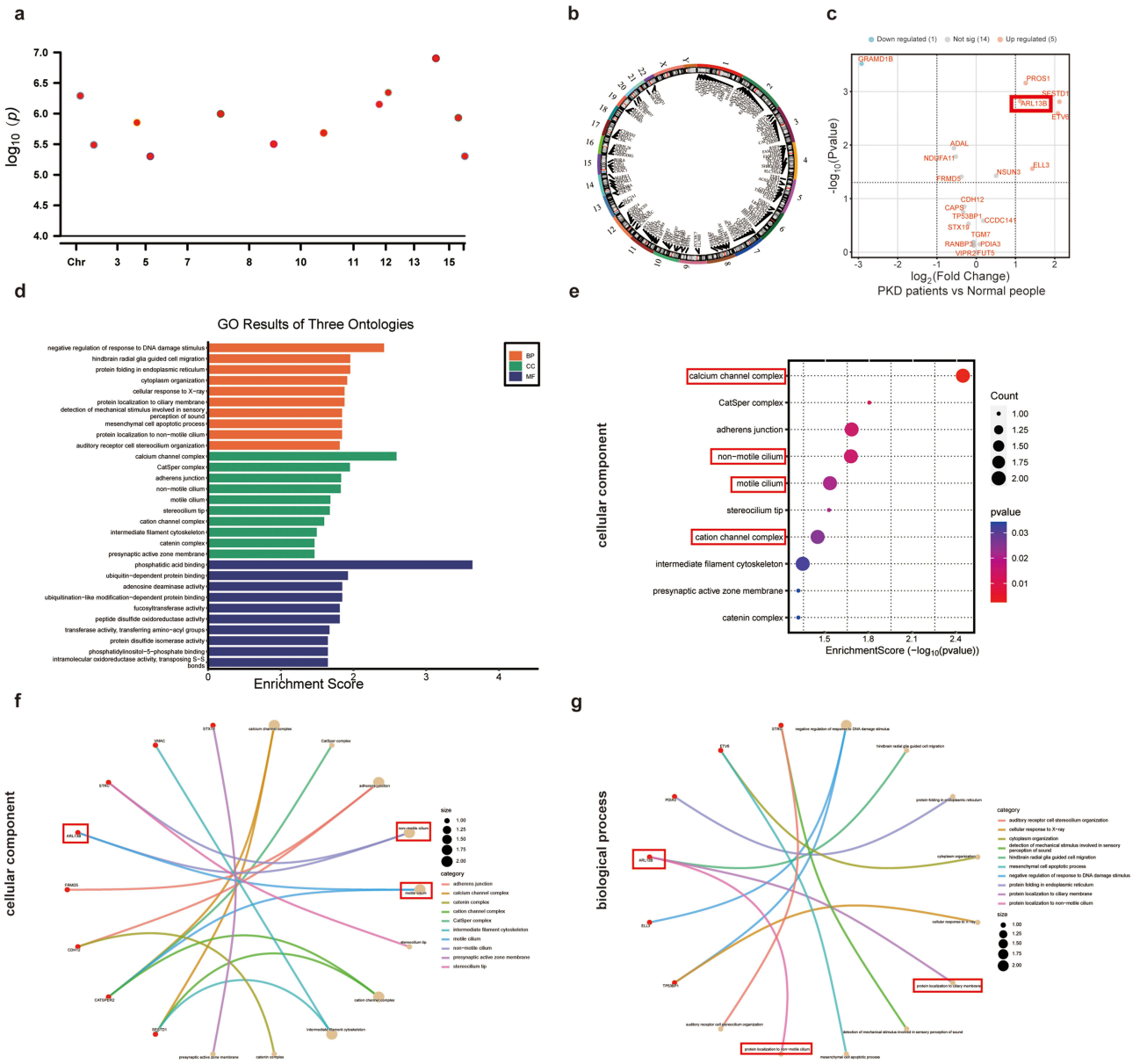

Figure 3 Gene annotation and Functional enrichment analysis. (**a**) A Manhattan plot of the 12 SNPs. (**b**) A chromosome ring plot for 27 genes. (**c**) Volcano plot of differentially expressed genes in human ADPKD (GSE7869). The plot displays 27 genes distributed by log2(fold change) versus –log10 (adjusted *P* value). Up-regulated genes (red, n = 5) include ARL13B, GRAMD1B, PROS1, SESTD1 and ETV6; down-regulated genes (blue, n = 1) and non-significant genes (gray, n = 14) are also indicated. (**d**) A Gene Ontology (GO) enrichment analysis plot of the 27 genes. (**e**) The cellular component of the enriched genes. (**f**) The cellular component network diagram of the enriched genes. (**g**) The biological process network diagram of the enriched genes.

contributing factors include the increased production of vasoconstrictive substances and impaired sodium excretion, which collectively drive the hypertensive state in ADPKD patients.[21]

Conversely, hypertension also influences the progression of ADPKD clinically. Elevated blood pressure can cause increased stress on the renal vasculature, potentially accelerating cyst growth and kidney damage.[22] Hypertension can exacerbate glomerular hyperfiltration and proteinuria, both of which are detrimental to kidney function.[23,24] This bidirectional relationship highlights the genetic susceptibility of hypertension in PKD. It underscores the importance of managing hypertension in ADPKD patients, as it is crucial not only for cardiovascular health but also for slowing the progression of kidney disease.

Notably, the lead SNPs instrumenting the causal effect of PKD on hypertension in our analysis are novel, as they have not been previously reported in large-scale GWAS of essential hypertension or PKD. These variants likely contribute to

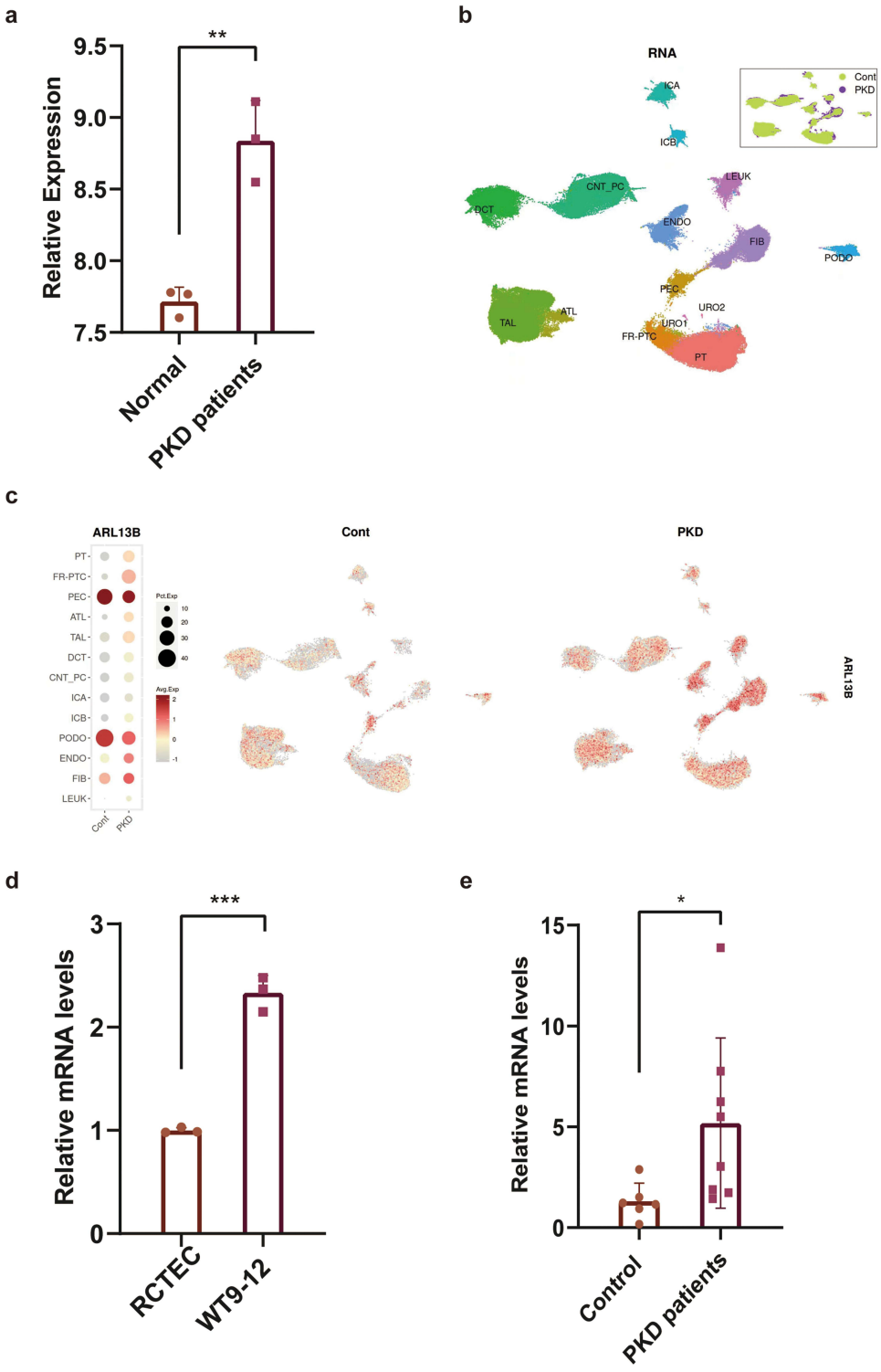

Figure 4 GEO analysis and single-cell sequencing map. (**a**) Differential expression of *ARL13B* gene in GSE7869 in human ADPKD group and control group. (**b**) UMAP visualization of single-nucleus RNA-seq data from human ADPKD and control kidney. Each dot represented a single nucleus, and clusters are colored by cell type identity. Cell types were assigned based on canonical marker genes: proximal tubule (*SLC34A1, LRP2*), distal convoluted tubule (*SLC12A3*), thick ascending limb (*UMOD, SLC12A1*), collecting duct/connecting tubule (*AQP2, ATP6V1G3*), intercalated cells (*ATP6V1B1, SLC4A1, SLC26A4*), parietal epithelial cells (*CLDN1, PAX8*), podocytes (*NPHS1, PODXL*), endothelial cells (*PECAM1, VWF*), fibroblasts (*COL1A1, DCN*), leukocytes (*PTPRC*), and urothelial cells (*UPK1A, KRT20*). (**c**) Clustering map of single cells in the ADPKD group. (**c**) Expression of ARL13B gene in human ADPKD kidney. (**d**) Quantitative PCR analysis of ARL13B mRNA levels in normal renal tubular epithelial cells (RTEC) and polycystic kidney cells (WT9-12). (**e**) Quantitative PCR analysis of ARL13B mRNA levels in human normal kidney tissues and polycystic kidney tissues. Results are presented as mean ± SEM. *: $P < 0.05$; **: $P < 0.01$; ***:$P < 0.001$.

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renal hypertension via PKD-specific mechanisms such as cyst expansion, renal parenchymal compression, and the aberrant signaling environment created by ciliary dysfunction—processes fundamentally distinct from those underlying primary hypertension. The fact that these SNPs map to genes enriched in cilia-related functions (eg, *ARL13B*) further supports their specificity to the ADPKD phenotype.

ARL13B is a gene known to play a critical role in the formation and maintenance of primary cilia, which are essential for cellular signaling and homeostasis in various tissues, including the kidneys.[25] In ADPKD, cilia dysfunction is a hallmark, and ARL13B's high expression in kidney endothelial cells suggests it may be involved in the pathogenesis of renal hypertension. Elevated expression of ARL13B can lead to cilia morphological abnormalities, such as increased cilia length and altered cilia structure.[26] These cilia abnormalities can disrupt mechanosensation and signal transduction in kidney cells, contributing to the development of hypertension. The increased length and abnormal structure of cilia can impair their normal function,[27] leading to dysregulated cellular signaling pathways involved in blood pressure regulation. This ciliary dysfunction can result in impaired fluid flow sensing and abnormal calcium signaling,[16,28] both of which are critical in maintaining vascular tone and blood pressure. As a cilia-localized small GTPase, ARL13B is essential for intraflagellar transport and modulates several key signaling cascades, including Hedgehog, Wnt, and calcium/cAMP pathways.[29] Dysregulation of these signals can impair fluid shear stress sensing and tubular flow regulation, leading to aberrant RAAS activation and sodium retention—both hallmarks of hypertensive pathology in ADPKD. Moreover, our single-cell RNA-seq analysis revealed that ARL13B is highly expressed in tubular epithelial cells, parietal epithelial cells (PECs), and fibroblasts, all of which possess primary cilia. In epithelial cells, altered ARL13B expression may disturb mechanosensation and promote cystic expansion. In fibroblasts, it may enhance pro-fibrotic signaling through defective ciliary control of growth factors. In PECs, which have regenerative capacity, ARL13B dysregulation may shift cell behavior toward inflammation or fibrosis, further contributing to a pro-hypertensive microenvironment.

Moreover, upregulated ARL13B in PECs suggests that ciliary dysfunction associated with ARL13B is not restricted to tubular epithelium but may represent a broader, kidney-wide phenomenon. The strong expression in PECs is especially noteworthy, as these cells possess progenitor-like properties and regenerative capacity.[30] Dysregulated ARL13B in PECs may interfere with cilium-dependent signaling, potentially driving aberrant proliferative or pro-fibrotic responses. While cysts originate mainly from tubular cells, PEC dysfunction could indirectly promote disease progression by fostering a fibrotic and inflammatory microenvironment.[31] Together with alterations in endothelial cells and fibroblasts, these changes provide a more comprehensive framework for understanding how ADPKD contributes to renal hypertension—beyond the classical RAAS—through pathways involving vascular dysfunction and fibrosis.

There are several limitations to consider. First, the study is based on data from European populations, which may limit the generalizability of the findings to other ethnic groups. Second, the MR analysis relies on the assumption that the selected SNPs are only associated with the exposure and not confounded by other factors, which, while statistically adjusted for, cannot be entirely ruled out. Another limitation was that the SNP–gene mappings were based on positional annotation rather than eQTL support, as no genome-wide significant eQTL associations were found for the lead SNPs in available databases. Additionally, the transcriptional regulation and functional analysis of ARL13B, while suggestive, require further experimental validation to confirm its role in ADPKD. Last, our MR analyses could not fully account for CKD stage, which is closely related to both PKD progression and hypertension. Future studies with stage-specific GWAS data will be necessary to disentangle the role of CKD as a potential confounder or mediator.

Conclusions

Our study provided new insights into the genetic relationship between PKD and hypertension, suggesting that ADPKD not only predisposes individuals to hypertension but may also be influenced by it. ARL13B may play a role in linking cilia function to renal hypertension in the context of ADPKD.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary Materials.

Ethics Approval and Informed Consent

The GWAS data for the articles were obtained from public databases and did not require additional informed consent and additional ethical consent. Informed consent was obtained from all subjects. The study was approved by the ethics review board of Changzheng Hospital (CZ2018-0619). The study abided by the Declaration of Helsinki principles. The cell lines used in this study have been approved by the Institutional Research Ethics Committee of Naval Medical University, Shanghai, China.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Juan Chen, Lei Song and Shuqin Mei are co-first authors for this study. The authors have no conflicts of interest to declare.

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