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Original Article

CDC42: unlocking a novel therapeutic target for primary sclerosing cholangitis through Mendelian randomization

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Abstract: Objectives: This study seeks to identify new drug targets for Primary Sclerosing Cholangitis (PSC), a condition currently lacking effective treatment, to improve survival without transplantation. Methods: We obtained summary statistics for 2,888 druggable genes and PSC from the eQTLGen Consortium and the FinnGen consortium, respectively. Through two-sample Mendelian randomization using the Inverse Variance Weighted (IVW) method, we identified genes associated with PSC at a False Discovery Rate (FDR) < 0.05. Further validation came from colocalization and Summary-data-based Mendelian Randomization (SMR) analyses, confirming the reliability of our results. Results: Five druggable genes were causally associated with PSC at FDR < 0.05. Subsequent colocalization and SMR analyses further confirmed that higher levels of CDC42 in plasma were associated with an increased risk of PSC (IVW method: Odds Ratio 1.319, 95% Confidence Interval 1.182-1.471, *P* = 6.85E-07, FDR = 0.002). Conclusions: Our research pioneered the identification of CDC42 as a target for slowing PSC progression. Our research not only uncovers a possible drug target but also provides direction for the development of therapeutics for PSC.

Keywords: M2 macrophages, causal relationship, single nucleotide polymorphism, druggable genes, cholangitis

Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disorder, marked by the deterioration of both intrahepatic and extrahepatic bile ducts, alongside fibrosis [1]. Statistical data reveal that the incidence rate of PSC stands at approximately 16.2 cases per 100,000 individuals, with Nordic countries reporting the highest occurrence rates, whereas significantly lower figures are noted in Asia [2-5]. The disease predominantly affects middle-aged men, particularly those aged between 30 to 40 years [4, 6]. Individuals diagnosed with PSC often experience a range of recurrent symptoms, including right upper quadrant pain, jaundice, cholestatic itch, and fatigue [1, 7, 8]. Not only are these symptoms persistent, but median survival from the point of diagnosis to either the event of liver transplantation or mortality due to related complications is estimated to be around 21.3 years [4]. This extended and recurring nature of PSC considerably deteriorates the patients' quality of life and imposes substantial burdens on both families and the broader society.

Despite considerable efforts, no singular medication or treatment strategy has been definitively proven to prolong the transplantation-free survival period for patients with PSC in clinical settings [1, 9]. Although hydrophilic bile acids, such as ursodeoxycholic acid, have been administered in the treatment of PSC and other similar cholestatic conditions across various countries, including Germany, Austria, and Switzerland [10], research indicates that these substances fail to enhance the transplantation-free survival rates of affected individuals [11-14]. Furthermore, the standard use of corticosteroids, immunosuppressants, biologics, and vancomycin is not typically advocated [1, 10]. Consequently, the search for pharmacological targets that may delay the onset or progression of PSC remains of paramount importance.

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By using the principle of random allocation of genetic variants at conception, Mendelian Randomization (MR) methodology serves as a natural experiment. This technique enables the investigation of causal connections between risk factors and disease outcomes, while significantly reducing the influence of confounding variables due to their randomized distribution [15]. MR analysis possesses the ability to uncover causal relationships with a level of precision akin to that of randomized controlled trials. Its benefits include a reduced risk of bias and the prevention of reverse causation errors [16].

In the realm of drug target MR analysis, expression quantitative trait loci (eQTLs), which are single nucleotide polymorphisms (SNPs) associated with variations in gene expression levels, act as instrumental variables (IVs) for exploring the effects of genes susceptible to pharmacologic manipulation. Specifically, cis-eQTLs situated in genomic regions proximal to the gene of interest are often selected due to their direct influence on the expression of that gene [17]. In this study, our goal is to navigate through a meticulously compiled database of genes with established drug-targeting capabilities [18], identifying those that code for drug targets or are linked with drug target proteins, to unveil potential therapeutic targets for PSC. Our aim is to utilize these identified drug targets as a strategy to prevent or slow down the progression of the disease.

Methods

Study design

The dataset employed in our analysis is publicly accessible and has been sanctioned by the pertinent institutional review boards. Consequently, this investigation did not necessitate a review by the ethical committee. Moreover, exhaustive details and specific sources of this data will be elucidated in the manuscript and its supplementary content.

In summary, our data collection encompassed cis-eQTLs linked with possible drug target genes from blood samples as the exposure variable, in conjunction with genome-wide association study (GWAS) data on PSC as the outcome, to execute a two-sample MR analysis. This endeavor aimed at probing the causal nexus between these drug target genes and PSC. For those genes that yielded significant MR analysis outcomes, we proceeded with colocalization analysis to determine whether the cis-eQTLs for these genes and PSC were influenced by identical causal variants. Ultimately, we applied the Summary-data-based Mendelian Randomization (SMR) technique to further substantiate the effect of expression level alterations in these possible drug target genes on the progression of PSC disease.

Source of data

Exposure data: Druggable genes are those that encode for proteins which can be targeted by drug-like small molecules, based on their sequence and structural similarities to the targets of existing drugs [18]. Finan et al. have catalogued a total of 4,479 such genes, offering a broad spectrum of targets for further investigation within this extensive collection of druggable genes [18].

Through an exploration within the eQTLGen Consortium, we pinpointed cis-eQTL data for 2,888 out of the 4,479 druggable genes, all derived from blood samples (Supplementary Table 1). This eQTL data is instrumental in identifying genetic variants that affect the expression levels of genes in blood, situated no more than 1 Mb away from the gene's central locus. Each variant accounted for has a minor allele frequency of over 0.01.

Outcome data: The GWAS summary statistics for PSC encompass 1,843 cases and an extensive control group of 361,641 individuals, encompassing a total of 21,305,253 SNPs. This information is sourced from the 10th edition of the detailed dataset released by the FinnGen consortium in 2023, available on their official website (www.finngen.fi).

IVs selection and data harmonization

Our study employed SNPs as IVs for a comprehensive two-sample bidirectional MR analysis. The robustness of MR analysis is predicated on three essential criteria: (1) a demonstrable linkage between SNPs and the exposure variable; (2) an assurance that SNPs are not entangled with any confounders affecting the exposure-outcome relationship; and (3) a direct pathway

through which SNPs influence the outcome exclusively through the exposure variable [19].

In our investigation, we applied strict selection criteria for SNPs to bolster the credibility of our results. Initially, our focus was on SNPs that reached genome-wide significance ($P < 5 \times 10^{-8}$) for detailed examination. To uphold the integrity of our chosen IVs, we meticulously excluded SNPs that were either palindromic or ambiguous [20]. Moreover, to amass a sufficient array of IVs for our study, we clustered SNPs based on linkage disequilibrium, employing a 10,000 kb window and an r^2 threshold below 0.1 [17]. The F-statistic was calculated using the formula [(N - K - 1)/K]/[R^2/(1 - R^2)], where K represents the number of genetic instruments and N denotes the sample size. This was done to quantitatively evaluate the variance each SNP explained. IVs with an F-statistic lower than 10 were deemed too weak and were subsequently excluded to preserve the rigor of our analysis [21]. Through a thorough literature review, we diligently assessed all phenotypes linked with the genetic instruments used, carefully removing any SNPs with possible confounding associations to safeguard the validity of our causal deductions.

Preliminary analysis - screening of genes

To elucidate the causal relationship between 2,888 druggable genes and PSC, we embarked on a two-sample MR analysis, positioning these genes as the exposure and PSC as the outcome. Our analysis was grounded in the Inverse Variance Weighted (IVW) method, which amalgamates meta-analysis techniques with Wald estimates for each SNP [22]. To enrich our analysis, we incorporated a range of supplementary MR techniques: Bayesian Weighted Mendelian Randomization (BWMR) [23], MR-Egger [24], Weighted Median [25], and Weighted Mode methods [26]. These methodologies cater to different validity assumptions and offer robust alternatives for generating MR estimates, thereby bolstering the comprehensiveness and dependability of our causal conclusions. To ensure the reliability of our findings, we applied corrections for the False Discovery Rate (FDR) to pinpoint significant MR results.

In our two-sample MR analysis, aimed at enhancing the reliability of our results, we adopted various strategies to mitigate heterogeneity stemming from differences in experimental setups, study demographics, and SNP variations. To evaluate this heterogeneity, we employed the IVW and MR-Egger methods. The heterogeneity of our genetic instruments was quantified using Cochrane's Q statistic, with a *P-value* > 0.05 indicating minimal heterogeneity, suggesting a consistent effect across the genetic instruments [27]. A core tenet of MR analysis is that the IVs should influence the outcome exclusively through the exposure. This necessitates the investigation of horizontal pleiotropy, which could confound the exposure-outcome relationship. To this end, we applied the MR-Egger intercept test, where a *P-value* > 0.05 signifies no significant pleiotropy, thus not compromising our causal inference [28]. Moreover, we utilized the MR-PRESSO test to detect and exclude outliers in the IVW analysis, thereby refining the accuracy of our estimates [29]. A "leave-one-out" analysis was conducted to determine the influence of each SNP on the exposure-outcome relationship [30]. Furthermore, we calculated the statistical power for each group of studies, excluding any results with less than 80% power to reduce the likelihood of Type II errors (https://sb452.shinyapps.io/power/) [31].

Colocalization analysis

Colocalization analysis was performed using the "coloc" package, designed to uncover shared SNPs between features, thereby shedding light on their biological interconnections. This package employs Bayesian methods to assess the probability of five specific, mutually exclusive scenarios: (1) no association with either the SNP or traits 1 and 2; (2) association with trait 1; (3) association with trait 2; (4) independent associations with both traits 1 and 2; (5) joint association with both traits 1 and 2. For each scenario, posterior probabilities for hypotheses H0 through H4 were calculated. A posterior probability (PP.H4) greater than 0.75 was deemed indicative of significant colocalization.

SMR analysis

Druggable genes that satisfy the colocalization analysis criteria are subsequently integrated into SMR analysis. SMR analysis, rooted in genetic principles, functions as a statistical

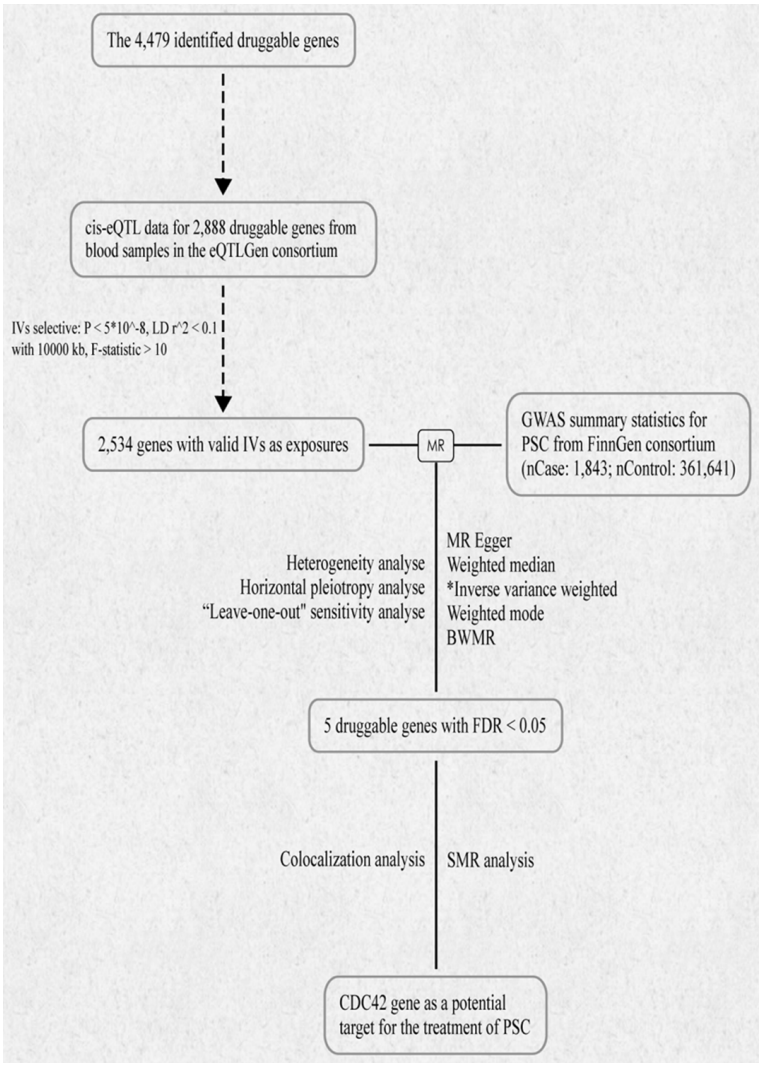

Figure 1. Schematic representation of the study design. Note: BWMR, Bayesian Weighted Mendelian Randomization; CDC42, Cell Division Cycle 42; eQTLs, Expression Quantitative Trait Loci; FDR, False Discovery Rate; GWAS, Genome-wide Association Study; IVW, Inverse Variance Weighted; LD, Linkage Disequilibrium; MR, Mendelian Randomization; PSC, Primary Sclerosing Cholangitis; SMR, Summary-data-based Mendelian Randomization.

method to investigate and corroborate the associations between genetic variations and phenotypes [32]. Employing the SMR approach alongside the complementary HEIDI test, the objective is to ascertain whether the effects of a SNP on a phenotype are mediated through changes in protein expression [32].

Statistical analysis

For our detailed analysis, we utilized R software (version 4.2.0, http://www.r-project.org) and the "Two-Sample MR" package (version 0.5.6) to perform the MR analysis [33].

Results

Figure 1 is a comprehensive schematic diagram of the study design. Our calculations verify that the statistical power of our MR analysis exceeds the 80% threshold, underscoring the robustness of our findings for detecting these associations.

MR analysis

Among the 4,479 druggable genes screened, cis-eQTL data for 2,888 genes were successfully sourced from the eQTLGen Consortium. Adhering to criteria for IVs selection and adjustments for linkage disequilibrium, we pinpointed 2,534 genes equipped with valid IVs for subsequent examination.

Leveraging the IVW method and prioritizing genes with an FDR < 0.05, we pinpointed 11 pertinent genes: C4B, C4A, BTN3A2, CDC42, FDFT1, SOAT1, AGER, AATK, CYP21A2, MC1R, and RIPK4. Subsequent scrutiny, however, revealed that C4B, C4A, BTN3A2, SOAT1, AGER, and CYP21A2 encountered challenges related to heterogeneity or horizontal pleiotropy.

Through meticulous selection, we identified that CDC42, FDFT1, AATK, MC1R, and RIPK4 may have causal relationships with the onset and progression of PSC (FDR < 0.05) (**Figure 2**). The rates of SNPs in PSC for these five drug target genes are 1.92E-06 (41/21,305,253), 5.26E-06 (112/21,305,253), 1.69E-06 (36/21,305,253), 1.64E-06 (35/21,305,253), and 5.63E-07 (12/21,305,253), respectively.

Specifically, CDC42 was significantly positively associated with the risk of PSC (IVW method: Odds Ratio (OR) 1.319, 95% Confidence Inter-

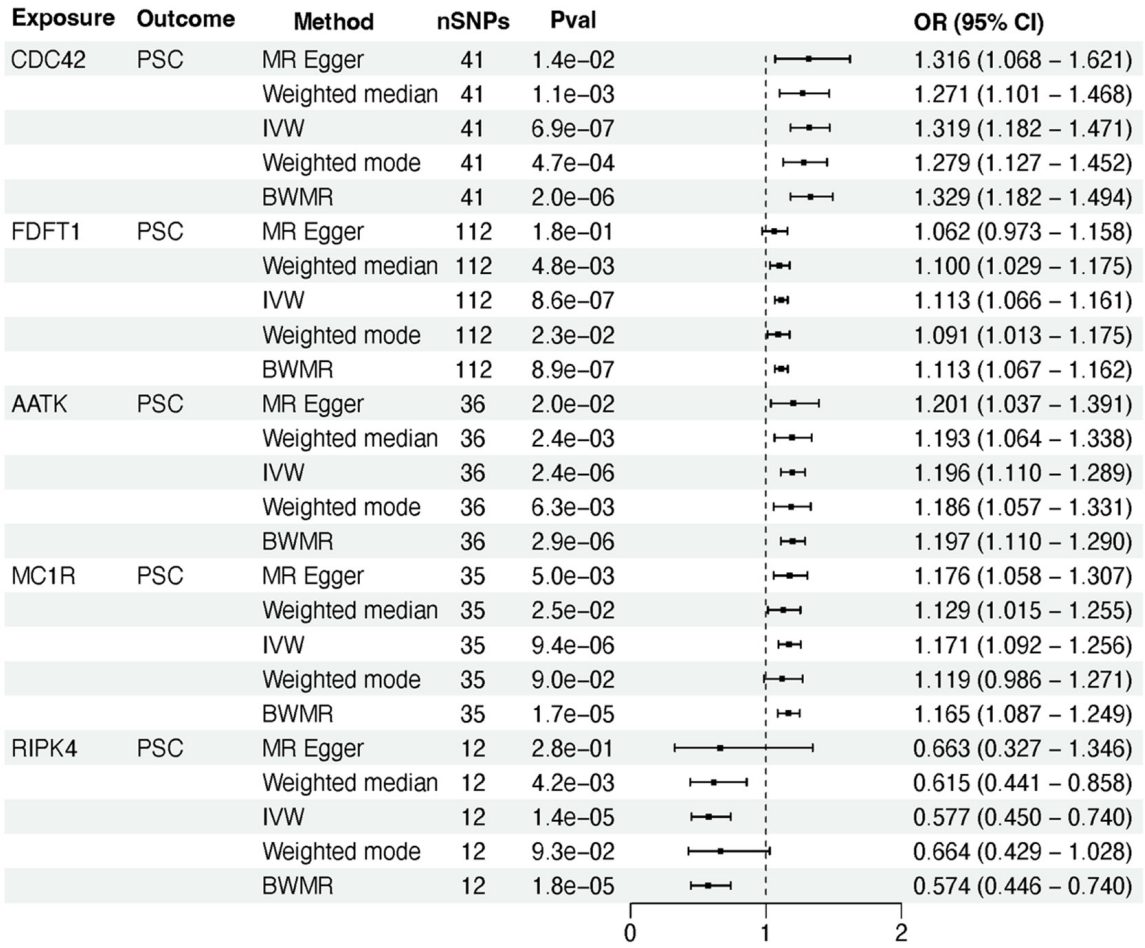

Figure 2. MR results linking 5 druggable genes on PSC. Note: AATK, Apoptosis-Associated Tyrosine Kinase; BWMR, Bayesian Weighted Mendelian Randomization; CDC42, Cell Division Cycle 42; CI, Confidence Interval; FDFT1, Farnesyl-Diphosphate Farnesyltransferase 1; IVW, Inverse Variance Weighted; MC1R, Melanocortin 1 Receptor; MR, Mendelian Randomization; nSNPs, Number of Single Nucleotide Polymorphisms; OR, Odds Ratio; PSC, Primary Sclerosing Cholangitis; RIPK4, Receptor-Interacting Serine/Threonine-Protein Kinase 4.

val (CI) 1.182-1.471, *P* = 6.85E-07); FDFT1 exhibited a significant positive correlation with PSC risk (IVW method: OR 1.113, 95% CI 1.066-1.161, *P* = 8.65E-07); AATK was significantly positively correlated with PSC risk (IVW method: OR 1.196, 95% CI 1.110-1.289, *P* = 2.37E-06); MC1R was significantly positively associated with PSC risk (IVW method: OR 1.171, 95% CI 1.092-1.256, *P* = 9.43E-06); RIPK4 showed a significant negative correlation with PSC risk (IVW method: OR 0.577, 95% CI 0.450-0.740, *P* = 1.41E-05). The characteristics of SNPs linked to the aforementioned five genes and PSC in the MR analysis are extensively documented in Supplementary Table 2. To further affirm the robustness of these findings, confirmatory analysis was also conducted using MR Egger, Weighted Median, Weighted Mode, and BWMR methods. The results of these analyses, in terms of significance levels and directionality, essentially support the reliability of the IVW method findings (Supplementary Table 3).

Furthermore, to bolster the reliability of the MR analysis outcomes, heterogeneity analysis, horizontal pleiotropy analysis, and "leave-one-out" sensitivity analyses were executed. The results affirm that the MR findings concerning the aforementioned five candidate druggable genes and PSC are consistently robust (Supplementary Table 4; Supplementary Figure 1).

Colocalization analysis

Through MR analysis, significant causal relationships between five druggable genes and

Table 1. Results of colocalization

Exposure	Outcome	nSNPs	PP.H0.abf	PP.H1.abf	PP.H2.abf	PP.H3.abf	PP.H4.abf
CDC42	PSC	40	8.57E-306	0.195	8.79E-308	0.001	0.803
FDFT1	PSC	112	0	0.816	0	0.007	0.178
AATK	PSC	36	0	0.776	0	0.003	0.221
MC1R	PSC	37	0	0.885	0	0.003	0.112
RIPK4	PSC	12	8.10E-60	0.936	8.51E-63	0.001	0.063

Note: AATK, Apoptosis-Associated Tyrosine Kinase; CDC42, Cell Division Cycle 42; FDFT1, Farnesyl-Diphosphate Farnesyltransferase 1; MC1R, Melanocortin 1 Receptor; PSC, Primary Sclerosing Cholangitis; RIPK4, Receptor-Interacting Serine/Threonine-Protein Kinase 4; SNPs, Single Nucleotide Polymorphisms.

Table 2. Results of the SMR analysis for the druggable gene CDC42

Exposure	Outcome	b_SMR	se_SMR	p_SMR	p_HEIDI	nsnp_HEIDI
CDC42	PSC	0.349	0.104	8.32E-04	1.90E-01	20

Note: SMR, Summary-data-based Mendelian Randomization; CDC42, Cell Division Cycle 42; PSC, Primary Sclerosing Cholangitis.

PSC were identified. Subsequently, a colocalization analysis was conducted to evaluate the probability of shared causal variants between cis-eQTLs and PSC. This analysis indicated a probable shared causal variant linking susceptibility to PSC with the CDC42 gene (CDC42: PP.H4 = 0.803), underscoring a strong association. However, for the other druggable genes such as FDFT1, AATK, MC1R, and RIPK4, with PP.H4 values of 0.178, 0.221, 0.112, and 0.063 respectively, all below 0.75, the evidence for colocalization with PSC progression appears to be insufficient (**Table 1**).

SMR analysis

Building upon our findings, CDC42 emerged as a promising drug target for reducing the risk associated with PSC. To strengthen the robustness of our conclusions, we engaged in SMR analysis. The outcomes of this analysis further confirmed a significant causal relationship between CDC42 and PSC, and a consistent direction of effect. Moreover, the results from the HEIDI test, with *P*-values at 0.190, suggest the absence of pleiotropy. These findings reinforce the notion that CDC42 serves as a strategic therapeutic target for mitigating PSC risk (**Table 2**).

Discussion

Primary sclerosing cholangitis (PSC) is characterized by inflammation and fibrosis of the bile ducts and liver, leading to impaired bile production or flow and ultimately resulting in progressive liver dysfunction [1]. Additionally, PSC significantly increases the risk of cholangiocarcinoma [34]. Currently, no medication has been proven to effectively improve the survival rate of patients without a need for transplantation [1]. While liver transplantation offers significant benefits for advanced disease, approximately 25% of patients experience a recurrence of the disease post-transplantation [35]. Hence, there is an urgent need to identify new therapeutic targets to improve the prognosis for patients with PSC. In this study, we collected GWAS data for 2,525 druggable genes from the eQTLGen Consortium and employed MR analysis to explore therapeutic targets for PSC. The reliability of our findings was further confirmed through colocalization analysis and SMR analysis. After a series of rigorous analyses, we ultimately identified the CDC42 gene as the most promising therapeutic target for the treatment of PSC. Although our initial screening had identified FDFT1, AATK, MC1R, and RIPK4 as candidate drug targets for the treatment of PSC, they were excluded from further consideration because they did not pass subsequent colocalization analyses and SMR analyses.

CDC42, short for Cell Division Cycle 42, is a small GTPase that toggles between an active state when bound to GTP and an inactive state when bound to GDP, serving as a molecular switch in various cellular physiologic processes [36]. CDC42 plays a crucial role in orchestrating cell polarization, cytoskeleton remodeling, cell adhesion, migration, and proliferation [37-39]. A plethora of studies have highlighted the

intimate connection between CDC42 and inflammatory responses. Additionally, CDC42, through its interaction with downstream proteins such as ACK1, influences tumor cell dynamics - including proliferation, adhesion, and migration - by modulating the JAK/STAT signaling pathway [40-42]. Myeloid deletion of CDC42 has been demonstrated to reduce liver damage, oxidative stress, hepatocyte apoptosis, and necrosis induced by hepatic ischemia-reperfusion injury [36]. Moreover, CDC42 deletion hinders M1 macrophage polarization and decreases the expression of inflammatory cytokines like tumor necrosis factor-alpha, Interleukin (IL)-1β, and IL6 [36]. At the same time, it promotes M2 macrophage polarization, enhancing anti-inflammatory effects and increasing the secretion of anti-inflammatory cytokines, including IL13 and soluble Tumor Necrosis Factor Receptor 1 [36]. An increasing body of evidence suggests that interactions between inflammatory proteins and PSC exist, where aberrant inflammatory responses can lead to tissue damage, a key pathogenic mechanism in autoimmune diseases [43]. Studies indicate that IL-17-mediated mucosal immunity is involved in the pathophysiology of PSC [44]. Additionally, elevated levels of inflammatory markers such as tumor necrosis factor-alpha, interferon-gamma, and IL8 are often observed in PSC patients [45]. Monocytes/macrophages are considered vital regulators of regional immunity, regeneration, and fibrosis in the liver, playing a significant role in the pathogenesis of PSC [46]. Li et al. observed a prevalence of activated macrophages in the livers of PSC patients, predominantly M1 polarized, associated with an increase in Notch signaling [47]. Therefore, CDC42 deficiency mitigates M1 macrophage polarization and fosters M2 polarization, reducing the infiltration of inflammatory factors into the bile ducts and liver, possibly alleviating the progression of PSC.

Concurrently, fibrosis of the bile ducts and liver is a hallmark of PSC [1]. Studies highlighting CDC42's role in driving the transdifferentiation of cardiac fibroblasts to myofibroblasts during post-myocardial infarction fibrosis support this perspective [48]. Additionally, the activation of fibroblasts by CDC42 is deemed crucial, underscoring its significant pathogenic role in renal fibrosis [49]. Research demonstrates that inhibiting CDC42 activity can mitigate renal fibrosis [49]. Hence, by alleviating inflammation and decelerating fibrosis progression, CDC42 inhibitors emerge as promising agents in PSC treatment. This indicates that targeting CDC42 not only can dampen the inflammatory response associated with PSC but might also forestall or slow the fibrotic transformation in the liver and bile ducts, presenting a novel therapeutic pathway for PSC patients. Numerous CDC42 inhibitors have been developed, among which the most frequently utilized include: ML141, a potent, selective, and non-covalent inhibitor of CDC42 GTPase [50]; CASIN, which selectively curtails CDC42 activity, thereby affecting cell division [51]; and ZCL278, a compound that specifically blocks the interaction between CDC42 and its effector, intersectin, playing a pivotal role in actin assembly and endocytosis [52]. Currently, these drugs are primarily designated for research purposes. Their transition into clinical settings, especially for conditions like PSC, remains under exploration.

Our research unveils profound implications. For individuals predisposed genetically, the early detection and targeting of CDC42 may be a strategy for preempting PSC onset. Diverging from conventional pathways in drug discovery, leveraging genetic insights to identify CDC42 as a therapeutic target accelerates the pinpointing of efficacious interventions, streamlining the drug development process both in terms of time and financial investment. Furthermore, therapeutic approaches focused on CDC42, informed by distinct genetic markers, pave the way for tailored treatment regimens for PSC patients. Such personalized strategies stand to significantly enhance treatment outcome and elevate the quality of life for those affected.

Our study has several limitations. First, although we identified a possible link between CDC42 and PSC through MR analysis, colocalization analysis, and SMR analysis, suggesting CDC42 as a potential target for drug development, these findings were limited to large-scale data analysis and lack experimental validation. We plan to validate these findings in future studies by constructing animal models. Secondly, our data primarily originate from European populations, which may limit the generalizability of our findings. Moreover, despite our efforts to address linkage disequilibrium, plei-

otropy, and heterogeneity, we cannot fully ensure that each SNP site strictly adheres to the assumption that the instrumental variable affects the outcome only through the exposure. Unidentified confounding factors may inevitably affect our results. However, despite these limitations, our findings still offer significant insight for further analysis of the mechanisms involved.

Conclusion

We show a connection between CDC42 and PSC for the first time, suggesting that drugs targeting CDC42 may slow the progression of PSC in patients. Furthermore, our study delves into the underlying mechanisms, proposing that CDC42 inhibitors may alleviate the disease's progression by inhibiting the polarization of M1 macrophages and promoting the polarization of M2 macrophages, thereby reducing the infiltration of inflammatory factors and slowing the development of fibrosis.

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Disclosure of conflict of interest

None.

Abbreviations

PSC, Primary Sclerosing Cholangitis; MR, Mendelian Randomization; eQTLs, Expression Quantitative Trait Loci; SNPs, Single Nucleotide Polymorphisms; IVs, Instrumental Variables; GWAS, Genome-wide Association Study; SMR, Summary-data-based Mendelian Randomization; IVW, Inverse Variance Weighted; BWMR, Bayesian Weighted Mendelian Randomization; FDR, False Discovery Rate; OR, Odds Ratio; CI, Confidence Interval; IL, Interleukin.

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Supplementary Table 2. The characteristics of SNPs associated with 5 genes and PSC ($P < 5*10^{-8}$) in the MR analysis

Exposure	Outcome	SNPs	EA	OA	EAF	BETA	SE	P	Samplesize	F-Statistics
CDC42	PSC	rs10157126	C	T	0.185	0.057	0.010	2.52E-08	31567	31.041
CDC42	PSC	rs10799745	A	G	0.155	0.082	0.011	1.16E-13	31567	55.074
CDC42	PSC	rs10917051	A	C	0.671	-0.059	0.009	1.86E-11	29723	45.114
CDC42	PSC	rs12030578	T	C	0.171	0.119	0.011	1.74E-29	31684	127.120
CDC42	PSC	rs12035094	T	G	0.024	0.459	0.027	4.37E-65	29543	290.243
CDC42	PSC	rs12035401	G	A	0.880	-0.144	0.013	5.94E-29	28588	124.680
CDC42	PSC	rs12093861	G	A	0.595	0.166	0.008	3.78E-93	31684	419.105
CDC42	PSC	rs12118516	A	C	0.061	-0.124	0.018	3.50E-12	27627	48.381
CDC42	PSC	rs12125201	T	A	0.212	-0.061	0.010	3.22E-10	31562	39.531
CDC42	PSC	rs12131703	T	C	0.124	-0.071	0.012	3.57E-09	31569	34.840
CDC42	PSC	rs1256341	C	T	0.280	-0.062	0.009	2.12E-12	31684	49.367
CDC42	PSC	rs12740670	T	G	0.058	0.160	0.018	1.74E-19	28943	81.515
CDC42	PSC	rs139286514	A	G	0.060	-0.131	0.019	1.38E-11	23479	45.692
CDC42	PSC	rs141779913	A	G	0.013	0.550	0.092	2.48E-09	4559	35.543
CDC42	PSC	rs146131710	G	A	0.038	0.289	0.022	1.13E-38	27867	169.152
CDC42	PSC	rs148963741	T	C	0.022	-0.256	0.032	1.27E-15	23073	63.953
CDC42	PSC	rs149413568	T	C	0.040	-0.133	0.023	4.86E-09	25288	34.242
CDC42	PSC	rs16826249	T	C	0.063	-0.150	0.017	4.50E-19	29791	79.632
CDC42	PSC	rs17427572	T	C	0.072	-0.132	0.016	1.50E-16	28943	68.167
CDC42	PSC	rs2035449	G	T	0.243	0.061	0.009	6.74E-11	31355	42.592
CDC42	PSC	rs2473290	T	C	0.757	0.351	0.009	1.00E-200	31568	1430.980
CDC42	PSC	rs2501299	C	T	0.363	0.278	0.008	1.00E-200	30077	1072.413
CDC42	PSC	rs2744751	A	C	0.375	0.096	0.008	2.96E-31	31561	135.213
CDC42	PSC	rs28462103	T	C	0.056	-0.185	0.017	9.96E-27	31565	114.526
CDC42	PSC	rs28468423	A	G	0.193	-0.113	0.015	1.32E-13	13868	54.811
CDC42	PSC	rs28617726	A	G	0.074	0.109	0.015	9.46E-13	31567	50.952
CDC42	PSC	rs35182048	C	T	0.030	0.147	0.025	4.12E-09	27308	34.567
CDC42	PSC	rs4654773	A	G	0.163	0.104	0.011	9.26E-22	31300	91.863
CDC42	PSC	rs4654995	T	C	0.353	-0.084	0.009	4.14E-19	24675	79.796
CDC42	PSC	rs4655022	T	C	0.772	0.122	0.009	1.02E-37	31569	164.768
CDC42	PSC	rs60718161	G	A	0.872	-0.066	0.012	3.12E-08	31565	30.631
CDC42	PSC	rs67504988	T	G	0.653	-0.081	0.008	4.61E-22	31683	93.242
CDC42	PSC	rs72647442	A	G	0.114	-0.111	0.012	7.86E-19	31565	78.527
CDC42	PSC	rs72649403	T	G	0.234	-0.076	0.009	7.46E-16	31569	65.005
CDC42	PSC	rs72665339	A	G	0.199	-0.185	0.010	1.38E-76	31355	343.024
CDC42	PSC	rs74778002	A	G	0.020	0.285	0.050	8.93E-09	10340	33.055
CDC42	PSC	rs7519770	A	G	0.019	0.243	0.029	5.29E-17	31196	70.223
CDC42	PSC	rs7556412	C	T	0.654	0.114	0.009	6.13E-37	27397	161.210
CDC42	PSC	rs760916	G	T	0.043	0.164	0.020	1.07E-16	31231	68.832
CDC42	PSC	rs78665342	A	G	0.017	0.243	0.037	7.12E-11	20976	42.484
CDC42	PSC	rs79364962	A	G	0.052	0.162	0.018	4.18E-19	30727	79.783
FDFT1	PSC	rs10108205	T	C	0.089	-0.169	0.015	4.26E-28	26066	120.771
FDFT1	PSC	rs10109101	C	T	0.163	-0.169	0.012	2.47E-46	26272	204.231
FDFT1	PSC	rs1043180	T	C	0.120	0.424	0.013	1.00E-200	26280	997.435
FDFT1	PSC	rs10903342	C	A	0.441	-0.342	0.009	1.00E-200	26380	1522.679
FDFT1	PSC	rs111399861	T	G	0.064	-0.254	0.018	1.69E-45	25947	200.402

FDFT1	PSC	rs112860567	C	G	0.127	-0.144	0.015	8.00E-23	21099	96.702
FDFT1	PSC	rs113135411	G	A	0.061	-0.139	0.018	2.50E-14	26276	58.090
FDFT1	PSC	rs113225536	T	C	0.031	0.168	0.026	1.31E-10	24479	41.290
FDFT1	PSC	rs116858126	A	G	0.017	0.530	0.043	1.32E-35	16858	155.101
FDFT1	PSC	rs116966174	T	C	0.025	0.218	0.029	5.73E-14	24419	56.460
FDFT1	PSC	rs117096501	T	G	0.018	0.274	0.046	2.47E-09	13554	35.557
FDFT1	PSC	rs117273263	T	C	0.014	0.625	0.096	6.14E-11	3987	42.753
FDFT1	PSC	rs117423839	T	C	0.055	-0.185	0.020	1.04E-19	23384	82.534
FDFT1	PSC	rs117537300	A	G	0.058	-0.169	0.019	7.18E-19	25245	78.703
FDFT1	PSC	rs117602022	C	T	0.031	0.191	0.030	1.28E-10	19028	41.341
FDFT1	PSC	rs117728931	C	T	0.017	0.279	0.047	2.24E-09	13594	35.752
FDFT1	PSC	rs11774454	T	C	0.042	-0.140	0.023	2.20E-09	22691	35.785
FDFT1	PSC	rs11774712	C	T	0.037	0.187	0.025	2.83E-14	22978	57.843
FDFT1	PSC	rs11777870	A	C	0.325	-0.152	0.010	5.54E-49	21412	216.367
FDFT1	PSC	rs11778235	T	C	0.084	0.203	0.017	5.04E-31	21341	134.151
FDFT1	PSC	rs11783694	C	T	0.727	-0.078	0.010	3.18E-14	24179	57.614
FDFT1	PSC	rs11787390	T	C	0.060	-0.177	0.018	6.46E-22	26277	92.572
FDFT1	PSC	rs118105989	T	C	0.015	0.367	0.050	1.21E-13	13369	54.990
FDFT1	PSC	rs118117906	C	A	0.110	-0.140	0.014	4.21E-23	25613	97.977
FDFT1	PSC	rs118151985	T	C	0.018	0.251	0.039	7.99E-11	19433	42.256
FDFT1	PSC	rs11998044	A	G	0.060	-0.122	0.020	1.02E-09	22021	37.279
FDFT1	PSC	rs12156245	C	A	0.185	-0.124	0.011	2.94E-28	26066	121.508
FDFT1	PSC	rs12546026	C	A	0.598	-0.128	0.009	4.90E-46	25939	202.870
FDFT1	PSC	rs1293300	T	C	0.019	-0.843	0.035	9.82E-131	21964	591.807
FDFT1	PSC	rs1299525	T	C	0.448	-0.314	0.009	1.00E-200	26395	1283.806
FDFT1	PSC	rs13267199	A	G	0.023	0.253	0.036	1.17E-12	17772	50.534
FDFT1	PSC	rs137933629	T	C	0.014	0.312	0.050	5.73E-10	13915	38.410
FDFT1	PSC	rs139003069	G	T	0.016	0.461	0.038	1.49E-34	22323	150.292
FDFT1	PSC	rs140592384	T	C	0.015	0.281	0.041	7.89E-12	19725	46.792
FDFT1	PSC	rs141111503	C	T	0.018	-0.712	0.035	3.29E-90	22257	405.575
FDFT1	PSC	rs144176129	A	C	0.022	0.524	0.034	2.82E-54	20208	240.636
FDFT1	PSC	rs146183035	C	T	0.026	-0.177	0.028	3.71E-10	24411	39.256
FDFT1	PSC	rs147406237	T	C	0.021	0.257	0.035	2.42E-13	19734	53.627
FDFT1	PSC	rs148811125	G	A	0.020	0.344	0.056	8.14E-10	8164	37.719
FDFT1	PSC	rs148856205	T	C	0.018	0.314	0.041	3.03E-14	16996	57.709
FDFT1	PSC	rs149129569	A	G	0.021	0.501	0.072	3.00E-12	4657	48.667
FDFT1	PSC	rs150460423	C	A	0.046	-0.252	0.022	2.86E-30	23385	130.700
FDFT1	PSC	rs150480084	A	G	0.019	0.320	0.054	3.06E-09	9191	35.141
FDFT1	PSC	rs17153454	A	G	0.757	-0.231	0.011	4.16E-95	21781	428.078
FDFT1	PSC	rs17795704	A	C	0.035	0.203	0.024	1.22E-17	26062	73.123
FDFT1	PSC	rs1809356	T	C	0.052	0.137	0.020	4.20E-12	26066	48.030
FDFT1	PSC	rs183165894	T	G	0.022	0.261	0.040	6.12E-11	14583	42.778
FDFT1	PSC	rs1864586	T	C	0.350	-0.141	0.009	1.71E-53	26066	237.056
FDFT1	PSC	rs189983844	G	A	0.034	0.274	0.029	7.38E-22	18933	92.312
FDFT1	PSC	rs1961893	G	T	0.016	-0.818	0.041	5.78E-89	19275	399.863
FDFT1	PSC	rs2196295	A	G	0.672	-0.140	0.009	2.79E-51	26395	226.901
FDFT1	PSC	rs2253946	G	A	0.122	-0.177	0.014	5.79E-36	23184	156.737
FDFT1	PSC	rs2294140	G	C	0.397	-0.081	0.009	8.27E-20	26382	82.977
FDFT1	PSC	rs2409750	C	A	0.843	-0.163	0.012	4.12E-41	25567	180.308

FDFT1	PSC	rs2572410	T	A	0.395	-0.135	0.009	6.31E-51	25728	225.280
FDFT1	PSC	rs2686207	T	C	0.965	0.291	0.030	4.40E-22	16395	93.333
FDFT1	PSC	rs2736335	A	G	0.181	0.178	0.011	1.43E-55	26277	246.584
FDFT1	PSC	rs2740434	A	G	0.288	-0.216	0.010	2.25E-112	26395	507.436
FDFT1	PSC	rs28416371	G	A	0.027	0.180	0.028	2.50E-10	23299	40.027
FDFT1	PSC	rs34765821	C	G	0.103	-0.161	0.014	5.81E-29	25947	124.726
FDFT1	PSC	rs35097563	C	T	0.022	0.344	0.039	1.80E-18	14931	76.890
FDFT1	PSC	rs35365998	A	G	0.016	0.397	0.063	3.66E-10	7848	39.277
FDFT1	PSC	rs3779664	A	G	0.840	0.449	0.012	1.00E-200	26395	1431.984
FDFT1	PSC	rs3802168	A	G	0.038	0.413	0.025	1.46E-60	21394	269.480
FDFT1	PSC	rs4307299	C	T	0.565	0.145	0.009	5.28E-61	26395	271.507
FDFT1	PSC	rs4566991	G	A	0.319	0.293	0.010	1.00E-200	25333	947.949
FDFT1	PSC	rs4841496	A	C	0.063	-0.137	0.018	1.15E-13	24876	55.091
FDFT1	PSC	rs4841560	A	C	0.106	-0.266	0.015	1.15E-74	24788	334.205
FDFT1	PSC	rs55908105	T	C	0.021	0.230	0.036	1.63E-10	18703	40.866
FDFT1	PSC	rs56076833	A	G	0.013	-0.638	0.050	2.20E-37	15128	163.235
FDFT1	PSC	rs56138616	G	A	0.213	-0.205	0.011	1.00E-82	26276	371.220
FDFT1	PSC	rs57956255	A	G	0.020	0.322	0.038	1.67E-17	17950	72.490
FDFT1	PSC	rs58868609	T	G	0.032	0.160	0.025	9.39E-11	26018	41.941
FDFT1	PSC	rs59446076	T	G	0.724	-0.170	0.010	6.44E-68	26186	303.228
FDFT1	PSC	rs62490741	A	G	0.045	0.225	0.025	6.09E-20	19142	83.584
FDFT1	PSC	rs62490931	T	C	0.107	0.181	0.014	3.68E-37	25938	162.224
FDFT1	PSC	rs62495702	T	C	0.029	0.422	0.027	1.63E-53	23850	237.159
FDFT1	PSC	rs7010927	T	C	0.181	0.307	0.011	5.39E-162	26276	735.563
FDFT1	PSC	rs7015879	A	T	0.826	-0.270	0.011	1.41E-121	26274	549.734
FDFT1	PSC	rs71518504	A	G	0.907	-0.165	0.015	7.05E-28	26277	119.773
FDFT1	PSC	rs71518537	C	T	0.019	-0.905	0.059	2.55E-52	7714	231.628
FDFT1	PSC	rs73196883	A	G	0.061	0.268	0.020	5.56E-41	21763	179.710
FDFT1	PSC	rs73201420	T	C	0.068	-0.456	0.018	4.23E-136	23384	616.476
FDFT1	PSC	rs73201424	A	G	0.081	0.190	0.016	1.23E-31	25613	136.950
FDFT1	PSC	rs73203483	G	A	0.096	0.263	0.015	2.69E-70	26277	314.159
FDFT1	PSC	rs73207298	C	T	0.023	0.348	0.032	2.47E-28	22667	121.853
FDFT1	PSC	rs7386288	T	C	0.766	-0.198	0.010	2.46E-81	26066	364.832
FDFT1	PSC	rs7386860	A	G	0.070	0.209	0.020	1.33E-24	18455	104.820
FDFT1	PSC	rs74302411	A	G	0.029	0.370	0.028	5.54E-40	22921	175.142
FDFT1	PSC	rs74525991	T	C	0.051	-0.138	0.021	3.07E-11	23850	44.130
FDFT1	PSC	rs74573986	A	G	0.024	0.176	0.031	8.21E-09	22975	33.221
FDFT1	PSC	rs7462014	A	C	0.075	0.178	0.017	6.20E-27	26395	115.463
FDFT1	PSC	rs75220994	T	C	0.076	0.179	0.018	1.36E-22	21370	95.651
FDFT1	PSC	rs75364663	C	A	0.059	0.188	0.019	8.98E-24	26058	101.043
FDFT1	PSC	rs75819332	T	G	0.041	0.137	0.022	3.96E-10	26277	39.131
FDFT1	PSC	rs75930610	T	G	0.022	-0.194	0.033	2.76E-09	22369	35.343
FDFT1	PSC	rs75987312	T	C	0.042	-0.164	0.023	2.00E-12	22691	49.478
FDFT1	PSC	rs76837891	G	A	0.037	-0.224	0.026	4.11E-18	21328	75.257
FDFT1	PSC	rs77416525	C	T	0.064	0.158	0.018	6.81E-19	26276	78.816
FDFT1	PSC	rs77743132	G	T	0.166	-0.156	0.012	1.58E-40	26280	177.630
FDFT1	PSC	rs77968590	T	C	0.028	-0.217	0.028	1.44E-14	22828	59.179
FDFT1	PSC	rs78161669	T	C	0.023	-0.189	0.034	2.38E-08	19751	31.153
FDFT1	PSC	rs7817160	G	A	0.138	-0.380	0.013	4.41E-196	26066	892.328

FDFT1	PSC	rs7818169	T	C	0.229	-0.078	0.010	5.93E-14	26066	56.390
FDFT1	PSC	rs7828656	A	C	0.369	-0.111	0.009	2.40E-34	25999	149.346
FDFT1	PSC	rs7833185	T	C	0.075	0.180	0.017	3.20E-25	23905	107.644
FDFT1	PSC	rs78389655	T	G	0.089	-0.167	0.015	4.10E-27	25728	116.283
FDFT1	PSC	rs78867821	A	G	0.055	-0.539	0.020	1.14E-165	24788	752.454
FDFT1	PSC	rs79433440	C	T	0.023	0.323	0.047	5.90E-12	10174	47.355
FDFT1	PSC	rs79523920	A	C	0.059	-0.185	0.019	8.15E-22	24095	92.114
FDFT1	PSC	rs79740149	C	T	0.042	-0.443	0.026	1.98E-63	17907	282.622
FDFT1	PSC	rs804289	C	A	0.332	-0.559	0.009	1.00E-200	25942	3596.771
FDFT1	PSC	rs8191620	A	C	0.033	-0.796	0.026	1.00E-200	23849	962.954
AATK	PSC	rs111411640	A	G	0.076	-0.347	0.022	2.24E-55	14629	245.678
AATK	PSC	rs11150780	G	A	0.296	0.110	0.010	4.85E-26	22110	111.390
AATK	PSC	rs113314481	A	G	0.021	0.272	0.040	7.92E-12	15371	46.781
AATK	PSC	rs116445173	T	C	0.034	0.215	0.030	3.63E-13	17520	52.832
AATK	PSC	rs11650195	C	T	0.447	-0.057	0.010	9.54E-09	20829	32.930
AATK	PSC	rs11650279	T	C	0.025	0.288	0.044	4.13E-11	10730	43.545
AATK	PSC	rs11650745	C	T	0.092	0.164	0.020	7.97E-16	14328	64.869
AATK	PSC	rs116858312	T	C	0.035	0.222	0.033	2.05E-11	13596	44.921
AATK	PSC	rs117002938	G	A	0.029	0.312	0.030	4.12E-25	19874	107.145
AATK	PSC	rs117202000	A	C	0.016	-0.384	0.058	4.08E-11	9115	43.562
AATK	PSC	rs118001767	G	A	0.017	0.400	0.052	9.34E-15	11454	60.021
AATK	PSC	rs12953216	A	G	0.126	0.159	0.018	1.26E-19	14839	82.141
AATK	PSC	rs138955069	A	G	0.022	-0.409	0.042	5.49E-22	12659	92.886
AATK	PSC	rs140089573	T	C	0.057	-0.242	0.023	1.39E-26	18214	113.860
AATK	PSC	rs146409760	C	T	0.021	-0.297	0.043	4.69E-12	13091	47.807
AATK	PSC	rs147729628	A	G	0.034	0.257	0.035	1.88E-13	12532	54.124
AATK	PSC	rs2659017	A	G	0.027	0.363	0.036	1.11E-23	14337	100.617
AATK	PSC	rs2725417	A	G	0.195	0.379	0.013	1.03E-174	17599	794.033
AATK	PSC	rs34156191	C	T	0.052	-0.315	0.026	1.43E-34	15480	150.354
AATK	PSC	rs34564603	C	T	0.395	0.222	0.018	1.30E-36	6781	159.685
AATK	PSC	rs35603697	A	G	0.030	-0.309	0.034	2.60E-19	14731	80.708
AATK	PSC	rs35663354	G	T	0.460	0.126	0.011	8.30E-33	17950	142.299
AATK	PSC	rs35867081	A	G	0.474	0.223	0.011	5.23E-99	18035	446.001
AATK	PSC	rs4076037	A	G	0.295	-0.112	0.011	4.37E-23	18702	97.903
AATK	PSC	rs4969238	C	T	0.659	-0.069	0.011	5.38E-10	17919	38.530
AATK	PSC	rs4969258	T	C	0.604	-0.440	0.011	1.00E-200	17184	1594.068
AATK	PSC	rs59763245	A	G	0.062	-0.360	0.022	4.59E-62	18245	276.357
AATK	PSC	rs62075320	A	G	0.093	-0.272	0.020	3.66E-41	14502	180.528
AATK	PSC	rs6565559	G	A	0.415	-0.104	0.012	2.56E-18	14502	76.192
AATK	PSC	rs72634319	G	C	0.052	-0.236	0.034	2.53E-12	8870	49.013
AATK	PSC	rs74002072	T	C	0.025	0.422	0.042	1.20E-23	11563	100.451
AATK	PSC	rs8069265	C	T	0.411	0.217	0.010	9.84E-107	21158	481.507
AATK	PSC	rs8073182	T	C	0.510	0.110	0.011	2.11E-24	17226	103.906
AATK	PSC	rs9895719	T	C	0.023	-0.314	0.049	2.15E-10	8943	40.313
AATK	PSC	rs9903399	C	T	0.210	-0.097	0.013	5.41E-13	16743	52.041
AATK	PSC	rs9915393	G	C	0.241	0.083	0.011	1.18E-13	21657	55.039
MC1R	PSC	rs11076664	A	G	0.173	-0.103	0.011	6.69E-21	29122	87.950
MC1R	PSC	rs113849132	A	G	0.051	-0.113	0.019	1.01E-09	29985	37.294
MC1R	PSC	rs11646910	A	G	0.117	-0.142	0.012	3.41E-30	31238	130.358

MC1R	PSC	rs117896335	T	C	0.019	0.603	0.034	1.88E-72	23931	324.049
MC1R	PSC	rs12447797	T	C	0.075	0.264	0.019	2.73E-44	20297	194.871
MC1R	PSC	rs12932427	A	G	0.033	0.885	0.056	5.50E-56	4950	248.410
MC1R	PSC	rs186650642	T	C	0.019	1.209	0.097	7.45E-36	2944	156.151
MC1R	PSC	rs1946482	C	T	0.133	-0.133	0.012	3.96E-30	31683	130.059
MC1R	PSC	rs2279350	T	C	0.872	-0.067	0.012	2.15E-08	31683	31.349
MC1R	PSC	rs28630471	G	A	0.279	0.297	0.009	1.00E-200	30817	1095.393
MC1R	PSC	rs2883067	G	A	0.250	-0.059	0.009	2.41E-10	30617	40.097
MC1R	PSC	rs2911266	T	C	0.296	-0.081	0.009	3.71E-20	30746	84.565
MC1R	PSC	rs3114908	T	C	0.669	0.076	0.008	2.61E-19	31355	80.714
MC1R	PSC	rs34427386	A	G	0.014	-0.286	0.045	1.39E-10	17839	41.173
MC1R	PSC	rs408800	T	G	0.124	-0.117	0.013	1.42E-19	27523	81.900
MC1R	PSC	rs4238834	T	C	0.349	-0.126	0.009	5.16E-49	30062	216.511
MC1R	PSC	rs56331811	C	T	0.201	0.104	0.012	1.09E-18	22531	77.886
MC1R	PSC	rs56361264	A	G	0.272	0.068	0.011	1.62E-09	19960	36.381
MC1R	PSC	rs57276429	T	C	0.119	-0.136	0.012	2.00E-28	31683	122.276
MC1R	PSC	rs62054623	G	A	0.070	0.663	0.016	1.00E-200	30021	1717.889
MC1R	PSC	rs62068511	G	A	0.577	0.069	0.008	8.69E-17	29992	69.243
MC1R	PSC	rs62068681	A	G	0.119	0.539	0.013	1.00E-200	27779	1692.271
MC1R	PSC	rs7191934	T	C	0.070	0.724	0.017	1.00E-200	25823	1762.906
MC1R	PSC	rs7198060	C	T	0.219	0.100	0.012	6.03E-18	21723	74.505
MC1R	PSC	rs7200842	G	A	0.450	0.195	0.008	6.98E-131	31599	592.520
MC1R	PSC	rs73277907	T	C	0.030	0.236	0.031	2.65E-14	18136	57.976
MC1R	PSC	rs74466939	T	C	0.100	0.318	0.014	3.32E-113	27979	511.266
MC1R	PSC	rs7498985	A	G	0.430	0.155	0.008	1.05E-80	30729	361.946
MC1R	PSC	rs76180276	T	C	0.037	0.599	0.024	1.00E-136	23980	619.361
MC1R	PSC	rs77733403	C	T	0.165	-0.149	0.012	6.71E-38	27179	165.602
MC1R	PSC	rs78319320	A	G	0.061	-0.116	0.018	2.78E-10	25971	39.822
MC1R	PSC	rs8044136	G	C	0.400	0.154	0.010	8.28E-56	21653	247.668
MC1R	PSC	rs8047204	G	A	0.629	0.226	0.008	7.95E-164	31231	743.987
MC1R	PSC	rs8049644	C	T	0.667	0.097	0.009	4.61E-29	30208	125.190
MC1R	PSC	rs9921599	T	C	0.152	-0.072	0.013	1.94E-08	23479	31.554
MC1R	PSC	rs9923267	G	C	0.357	-0.089	0.010	4.08E-20	23409	84.368
MC1R	PSC	rs9929800	C	G	0.425	-0.086	0.008	4.16E-26	31232	111.690
RIPK4	PSC	rs116954548	C	T	0.065	0.115	0.017	3.42E-12	30077	48.429
RIPK4	PSC	rs13052067	T	C	0.715	-0.049	0.009	3.77E-08	31017	30.259
RIPK4	PSC	rs28360603	A	G	0.592	-0.062	0.008	2.18E-14	31355	58.358
RIPK4	PSC	rs2838103	C	T	0.247	0.110	0.009	6.16E-33	31684	142.903
RIPK4	PSC	rs3018511	T	G	0.279	-0.060	0.009	2.86E-11	30716	44.268
RIPK4	PSC	rs4919938	G	A	0.445	-0.062	0.010	1.01E-09	19772	37.292
RIPK4	PSC	rs4919944	A	C	0.329	0.146	0.008	1.41E-66	31684	297.092
RIPK4	PSC	rs62216195	G	A	0.044	0.129	0.019	3.61E-11	31352	43.811
RIPK4	PSC	rs6586239	C	G	0.845	-0.126	0.011	1.01E-29	31100	128.198
RIPK4	PSC	rs7278103	A	C	0.108	-0.074	0.013	1.34E-08	30902	32.267
RIPK4	PSC	rs8126818	T	G	0.137	0.065	0.012	3.85E-08	30436	30.219
RIPK4	PSC	rs9982898	A	G	0.781	-0.112	0.011	8.80E-23	22531	96.516

Note: EA, effect allele; OA, other allele; EAF, effect allele frequency; SNPs, single nucleotide polymorphisms; MR, Mendelian Randomization; CDC42, Cell Division Cycle 42; FDFT1, Farnesyl-Diphosphate Farnesyltransferase 1; AATK, Apoptosis-Associated Tyrosine Kinase; MC1R, Melanocortin 1 Receptor; RIPK4,Receptor-Interacting Serine/Threonine-Protein Kinase 4.

Supplementary Table 3. MR Results Linking 5 druggable genes on PSC

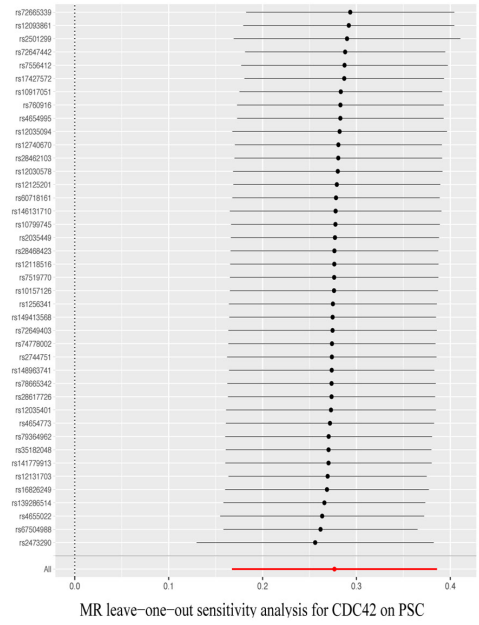
Exposure	Outcome	method	nsnp	b	se	pval	or	or_lci95	or_uci95
CDC42	PSC	MR Egger	41	0.275	0.106	1.38E-02	1.316	1.068	1.621
		Weighted median	41	0.240	0.073	1.06E-03	1.271	1.101	1.468
		Inverse variance weighted	41	0.277	0.056	6.85E-07	1.319	1.182	1.471
		Weighted mode	41	0.246	0.065	4.67E-04	1.279	1.127	1.452
		BWMR	41	0.284	0.060	1.96E-06	1.329	1.182	1.494
FDFT1	PSC	MR Egger	112	0.060	0.044	1.82E-01	1.062	0.973	1.158
		Weighted median	112	0.095	0.034	4.84E-03	1.100	1.029	1.175
		Inverse variance weighted	112	0.107	0.022	8.65E-07	1.113	1.066	1.161
		Weighted mode	112	0.087	0.038	2.30E-02	1.091	1.013	1.175
		BWMR	112	0.107	0.022	8.88E-07	1.113	1.067	1.162
AATK	PSC	MR Egger	36	0.183	0.075	1.98E-02	1.201	1.037	1.391
		Weighted median	36	0.177	0.058	2.44E-03	1.193	1.064	1.338
		Inverse variance weighted	36	0.179	0.038	2.37E-06	1.196	1.110	1.289
		Weighted mode	36	0.171	0.059	6.27E-03	1.186	1.057	1.331
		BWMR	36	0.180	0.038	2.88E-06	1.197	1.110	1.290
MC1R	PSC	MR Egger	35	0.162	0.054	5.05E-03	1.176	1.058	1.307
		Weighted median	35	0.121	0.054	2.55E-02	1.129	1.015	1.255
		Inverse variance weighted	35	0.158	0.036	9.43E-06	1.171	1.092	1.256
		Weighted mode	35	0.113	0.065	9.02E-02	1.119	0.986	1.271
		BWMR	35	0.153	0.035	1.67E-05	1.165	1.087	1.249
RIPK4	PSC	MR Egger	12	-0.411	0.361	2.82E-01	0.663	0.327	1.346
		Weighted median	12	-0.486	0.170	4.18E-03	0.615	0.441	0.858
		Inverse variance weighted	12	-0.550	0.127	1.41E-05	0.577	0.450	0.740
		Weighted mode	12	-0.409	0.223	9.35E-02	0.664	0.429	1.028
		BWMR	12	-0.555	0.129	1.80E-05	0.574	0.446	0.740

Note: MR, Mendelian Randomization; nSNPs, Number of Single Nucleotide Polymorphisms; or, odds ratio; or_lci95, 95% Lower Confidence Interval; or_uci95, 95% Upper Confidence Interval. BWMR, Bayesian Weighted Mendelian Randomization; LRP11, Low-Density Lipoprotein Receptor-Related Protein 11; NECTIN2, Nectin Cell Adhesion Molecule 2; LTA, Lymphotoxin-alpha; LTBR, Lymphotoxin-beta Receptor; TNFRSF14, Tumor Necrosis Factor Receptor Superfamily Member 14; TNFRSF13B, Tumor Necrosis Factor Receptor Superfamily Member 13B; TNFRSF9, Tumor Necrosis Factor Receptor Superfamily Member 9.

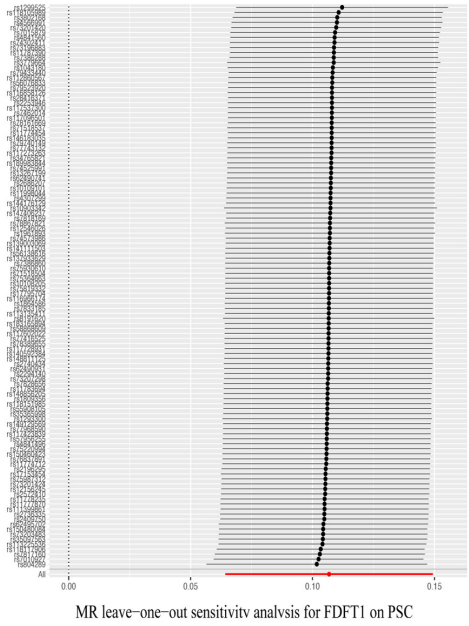
Supplementary Table 4. Heterogeneity and Pleiotropy in MR Analyses.

Exposure	Outcome	Methods	nSNPs	Heterogeneity			Horizontal Pleiotropy		
				Q	Q Degrees of Freedom	Q *P*-value	MR-Egger regression		
							Egger intercept	SE	*P*-value
CDC42	PSC	MR Egger	41	49.819	39	0.115	0.000	0.016	0.983
		Inverse variance weighted	41	49.819	40	0.137			
FDFT1	PSC	MR Egger	112	80.715	110	0.984	0.014	0.011	0.228
		Inverse variance weighted	112	82.182	111	0.982			
AATK	PSC	MR Egger	36	33.770	34	0.479	-0.001	0.016	0.952
		Inverse variance weighted	36	33.773	35	0.527			
MC1R	PSC	MR Egger	35	27.155	33	0.753	-0.001	0.012	0.929
		Inverse variance weighted	35	27.163	34	0.791			
RIPK4	PSC	MR Egger	12	6.095	10	0.807	-0.014	0.034	0.689
		Inverse variance weighted	12	6.265	11	0.855			

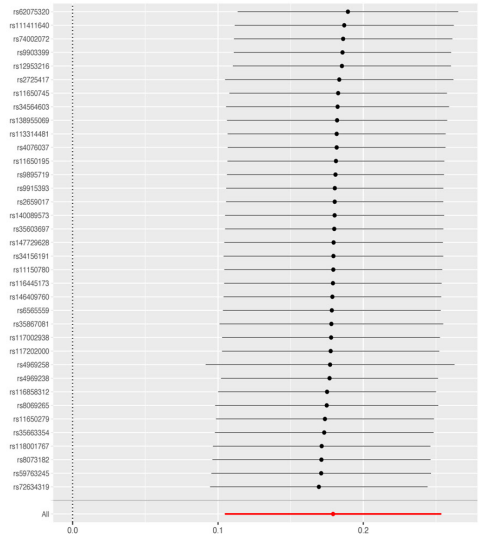
Note: SNPs, single nucleotide polymorphisms; MR, Mendelian randomization; CDC42, Cell Division Cycle 42; FDFT1, Farnesyl-Diphosphate Farnesyltransferase 1; AATK, Apoptosis-Associated Tyrosine Kinase; MC1R, Melanocortin 1 Receptor; RIPK4,Receptor-Interacting Serine/Threonine-Protein Kinase 4.



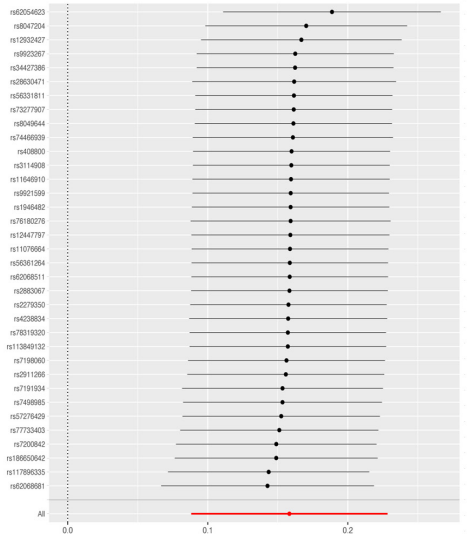
MR leave–one–out sensitivity analysis for CDC42 on PSC



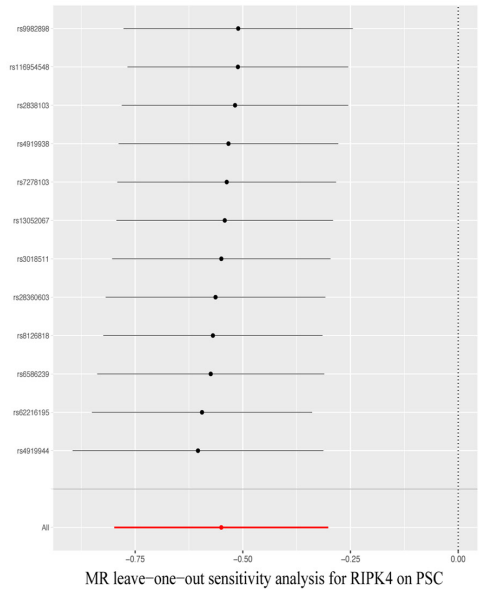
MR leave–one–out sensitivity analysis for FDFT1 on PSC



MR leave–one–out sensitivity analysis for AATK on PSC



MR leave–one–out sensitivity analysis for MC1R on PSC



MR leave–one–out sensitivity analysis for RIPK4 on PSC

Supplementary Figure 1. MR leave-one-out sensitivity analysis for 5 druggable genes on PSC. Note: MR, Mendelian Randomization; CDC42, Cell Division Cycle 42; FDFT1, Farnesyl-Diphosphate Farnesyltransferase 1; AATK, Apoptosis-Associated Tyrosine Kinase; MC1R, Melanocortin 1 Receptor; RIPK4, Receptor-Interacting Serine/Threonine-Protein Kinase 4.