Whole Transcriptome-wide Analysis Combined With Summary Data-Based Mendelian Randomization Identifies High-Risk Genes for Cholelithiasis Incidence

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INTRODUCTION: **Cholelithiasis is influenced by various factors, including genetic elements identified in genomewide association studies, but their biological functions are not fully understood.**

METHODS: **Analyzing data from the Finngen database with 37,041 cholelithiasis cases and 330,903 controls, this study combined SNP data from GTEx v8 and linkage disequilibriums data from the 1000 Genomes Project. Using the Transcriptomewide Association Studies FUSION protocol and summary data-based Mendelian randomization analysis, it investigated the relationship between gene expression and cholelithiasis, using colocalization tests and conditional analyses to explore causality.**

RESULTS: **The study identified genes associated with cholelithiasis in the liver and whole blood, such as LINC01595, TTC39B, and UGT1A3, with several showing colocalization traits. Notably, RP11-378A13.1 and adenosine deaminase acting on RNA (ADAR) were significantly associated with the disease in both tissues.**

DISCUSSION: **This research provides insights into the genetic underpinnings of cholelithiasis, highlighting the significant role of gene expression in its development. It establishes new gene associations and identifies potential genetic markers for the disease.**

KEYWORDS: cholelithiasis; gene expression; TWAS; Mendelian randomization

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B278; http://links.lww.com/CTG/B279; http://links.lww.com/CTG/B280; http://links.lww.com/CTG/B281

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INTRODUCTION

Gallstone disease is a relatively common ailment worldwide and a major cause of hospitalization. The prevalence of gallstone disease varies across the globe: approximately 10%–15% in the United States and Europe, 3.9% in Japan, 4% in South Korea, and 7% in China (1–4). Moreover, the incidence of gallstone disease is steadily increasing, making it the second most common primary reason for hospital admissions related to gastrointestinal, hepatic, and pancreatic diseases in the United States (5). In addition, gallstone disease is considered one of the costliest diseases worldwide. For instance, in the United States alone, more than 700,000 gallbladder removal surgeries are performed annually at a cost of approximately $6.5 billion (6,7). Furthermore, gallstone disease is associated with an elevated risk of other conditions such as pancreatitis, gallbladder cancer, and type 2 diabetes (8–10).

The causes of gallstone formation are multifactorial, resulting from factors such as cholesterol oversaturation in the gallbladder, inappropriate bile salt concentrations, and defects in gallbladder epithelial contractility. These factors stem from a complex interplay of dietary, hormonal, and genetic factors (11). Genetic factors play an important role in the pathogenesis of gallstones. The prevalence of gallstone disease varies significantly among different countries and ethnic groups. Even within the same ethnic group, individuals with gallstone disease have a significantly higher

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likelihood of developing gallstones in comparison with their first-degree relatives compared with controls (12). These studies emphasize the role of genetic factors in the pathogenesis of gallstone disease.

Previous studies have identified many genetic factors associated with gallstone formation. In the case of cholesterol gallstones, genetic factors play the following roles. ABCG5/ABCG8 is a heterodimeric protein that functions as a cholesterol transporter within the bile canalicular network, directly influencing the cholesterol content in bile (13). A specific missense mutation in the *ABCG8* gene (D19H), where histidine replaces aspartic acid, leads to an elevated cholesterol concentration in bile (13). Although substantial data center around this variant, another mutation involving the same protein exists: ABCG5 R50C, in which cysteine replaces arginine at position 50, resulting in increased transport activity and decreased cholesterol absorption (14). ABCB4 can participate in the genetic risk of gallstone disease by promoting the generation of cholesterol-supersaturated bile. On the other hand, ABCB11 plays an important role in regulating the transfer of bile components across the membrane, with the mechanisms not yet fully elucidated (15). In the case of bilirubin gallstones, genes play the following roles. The protein encoded by the *UGT1A1* gene plays a crucial role in the glucuronidation of bilirubin (16). Its mutation leads to an increase in unconjugated bilirubin, which has poor water solubility, creating nucleation sites for cholesterol crystal formation and ultimately contributing to stone formation (16). ABCC2 serves as a transporter for bilirubin and bile salts and is prominently expressed on the apical membranes of both hepatocytes and gallbladder cholangiocytes. Its mutation can also lead to the formation of gallstones (17). Finally, genetic factors can also influence gallstone formation by affecting miRNAs. Notably, miR-210 exhibits increased expression in gallbladders containing gallstones, and this miRNA targets the *ATP11A* gene, which encodes an ABC (adenosine triphosphate [ATP]-binding cassette) transporter (18). ABC transporters are crucial in determining the cholesterol content in bile, thereby affecting the lithogenic potential of bile (18). In summary, genetic factors play an important role in the pathogenesis of gallstone disease; therefore, further research on the genetic aspects of gallstone formation is essential for the treatment and prevention of gallstones.

With the rapid rise of genomewide association studies (GWAS), numerous genes associated with gallstone disease have been discovered. However, GWAS alone cannot provide exact information about causative variations, genes, cell types, and tissues involved. By contrast, Transcriptomewide Association Studies (TWAS) make use of databases that specify disease-relevant cell types and tissues, along with detailed information on tissue-specific gene expression, offering findings that are more biologically explanatory and relevant (19). TWAS combines results from Expression Quantitative Trait Loci (eQTL) with GWAS summary data to examine genes whose expression is likely to be regulated and linked to disease risk (20).

In this experiment, we will use TWAS to identify genes with biological relevance to gallstone disease and use summary data-based Mendelian randomization (SMR) to establish causal relationships between these genes and the disease. This research endeavor aims to enhance our comprehension of the genetic mechanisms underlying gallstone disease and offer new insights into its prevention and treatment.

METHODS

Study design data sources

Figure 1 shows the flowchart of this study. In summary, we obtained the gene expression data from peripheral blood and liver, as well as the GWAS data for gallstones. Through TWAS combined with colocalization analysis, we identified genes associated with the occurrence of gallstones in both peripheral blood and liver. Subsequently, using SMR analysis, we identified genes with causal relationships to the occurrence of gallstones in peripheral blood and liver, respectively. Finally, we intersected the genes obtained from TWAS, colocalization analysis, and SMR analysis in both peripheral blood and liver, and the genes passing all the tests were considered the core genes identified in this study. This analysis used the following data sources: (i) gallstone disease whole-genome association data from the Finngen database, comprising 37,041 cases and 330,903 controls; (ii) single nucleotide polymorphisms (SNPs) weight set data for liver and whole blood from GTEx v8; and (iii) linkage disequilibrium (LD) reference data from the 1000 Genomes Project. SNP weights indicate the association between SNPs and their related gene expression. The GWAS data for 37,041 cases and 330,903 controls were downloaded from the Finngen database (https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_K11_CHOLELITH.gz). SNP weight sets for liver and whole blood were obtained from the TWAS FUSION official website (http://gusevlab.org/projects/fusion/#reference-functional-data). Finally, the European LD reference data from Phase Three of the 1000 Genomes Project, including 489 individuals, were obtained from the FUSION website (http://gusevlab.org/projects/fusion/).

Transcriptomewide association study and colocalization

FUSION, a suite of programs for performing TWAS and Regulatory Trait Concordance analysis, was used. FUSION models the genetic component of functional/molecular phenotypes and analyzes components related to disease using summary statistics from GWAS. TWAS analysis was conducted using the default settings of the TWAS FUSION protocol. In addition, colocalization tests, which provide data on shared causal variants between predicted functional features and features, were used as an alternative approach to TWAS. Colocalization analysis was performed to evaluate the colocalization status of genes by calculating posterior probabilities of genetic and functional correlations generated by different causal SNPs and shared causal SNPs (PP4). Colocalization was performed using the colocal R package for all genes that met transcriptomewide significance ($P < 0.05$) and within a 0.5-Mb window. A strict Bonferroni-corrected study-level significance threshold was set at $P = 0.05/$number of genes. The significance thresholds for these genes were $P < 1.34 \times 10^{-5}$ (liver) and $P < 6.15 \times 10^{-6}$ (peripheral blood).

Conditional analysis

Conditional and joint analyses were conducted using the FUSION software to confirm whether the significant signals identified in the transcriptomewide analysis were due to multiple associated features or conditionally independent. This method assesses the impact of all important features within each locus when considering the predicted expression of other features in the region. The method can determine which features represent joint significance, referred to as joint significant, and which do not,

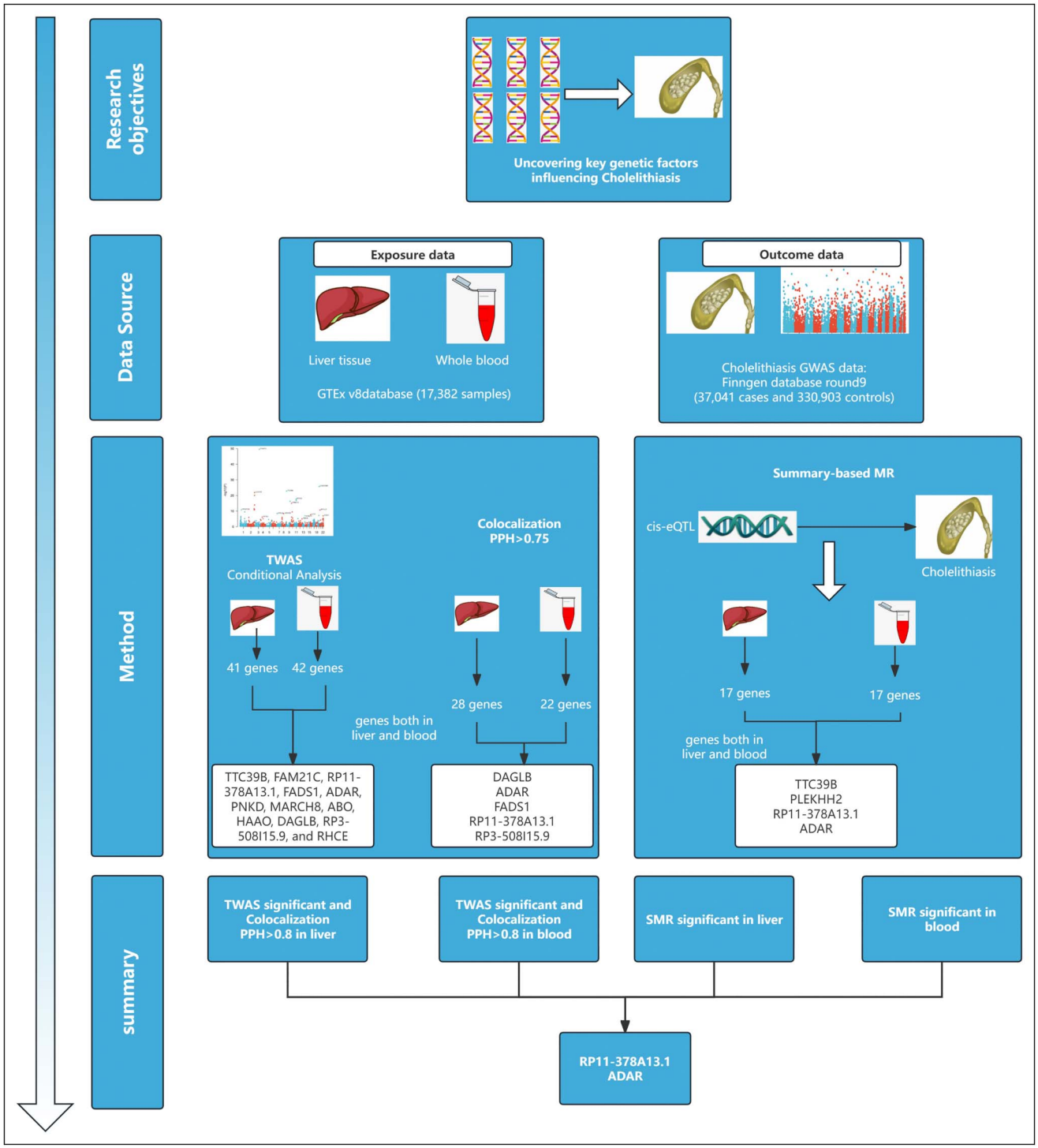

Figure 1. The flowchart of this study. eQTL, Expression Quantitative Trait Loci; GWAS, genomewide association studies; MR, mendelian randomization; PPH, posterior probability of heterogeneity; SMR, summary data-based Mendelian randomization; TWAS, Transcriptomewide Association Studies.

referred to as marginally significant. The "FUSION.post process.R" script was used for post-processing and generating numerous conditional output plots and summary statistics.

SMR analysis

SMR analysis was used to observe genes causally related to gallstone disease, prioritizing functionally relevant genes within GWAS loci. SMR combines GWAS and eQTL summary statistics data and uses Mendelian randomization principles to assess pleiotropic correlations between gene expression and a feature at a locus driven by shared variants. In SMR analysis, cis-eQTL genetic variants were used as instrumental variables for gene expression. SMR analysis was conducted separately for gene expression in liver and peripheral blood. eQTL data for blood and

liver were downloadable online (https://yanglab.westlake.edu.cn/software/smr/#DataResource). Heterogeneity in dependent instruments tests were performed to assess the presence of LD in identified associations. The genomewide significance level for SMR tests was defined as 0.05/number of probes. The significance values for these probes were $P < 1.99 \times 10^{-5}$ (liver) and $P < 7.21 \times 10^{-6}$ (peripheral blood), with probes lacking significant evidence of heterogeneity (P_HEIDI $\geq$ 0.05) being retained.

Ethics statement

The data used in this study are sourced from public databases; therefore, further ethical review is not required.

RESULTS

Transcriptomewide significant genes

A total of 71 differentially expressed genes were identified in the liver and whole blood. In liver, 41 differentially expressed genes were found ($P < 1.34 \times 10^{-5}$), including 18 upregulated and 23 downregulated genes (see Figure 2a, Supplementary Table S1, http://links.lww.com/CTG/B278). In whole blood, 42 differentially expressed genes were discovered ($P < 6.15 \times 10^{-6}$), with 21 upregulated and 21 downregulated genes (see Figure 2b, Supplementary Table S1, http://links.lww.com/CTG/B278). Notably, 12 genes were found to be differentially expressed in both liver and peripheral blood, including *TTC39B*, *FAM21C*, *RP11-378A13.1*, *FADS1*, adenosine deaminase acting on RNA (*ADAR*), *PNKD*, *MARCH8*, *ABO*, *HAAO*, *DAGLB*, *RP3-508I15.9*, and *RHCE*.

Colocalization analysis

Of the 71 genes, 45 were considered colocalized based on their high PP4 content (PP4 $>$ 0.75). In liver, the significant feature TTC39B was observed to explain all signals at its locus (PP4 = 1) (see Supplementary Table S2, http://links.lww.com/CTG/B279).

Conditional analysis

Many significant features were found to be located within the same locus (defined as a 0.5-Mb window). Conditional analysis of these 71 significant features revealed 50 jointly significant features and 21 marginally significant features (see Supplementary Table S3, http://links.lww.com/CTG/B280), indicating that many identified genes were associated with gallstone disease as they shared coexpression with these 50 independent features.

SMR analysis

In liver, our SMR analysis identified 17 unique genes with pleiotropic associations with gallstone disease (see Supplementary Table 4, http://links.lww.com/CTG/B281), with LINC01595, UGT1A3, P_SMR = 6.85×10^{-10}, and RPL17P11 ranking as the top 3 genes. In peripheral blood, our SMR analysis identified 17 unique genes with pleiotropic associations with gallstone disease (see Supplementary Table 4, http://links.lww.com/CTG/B281), with FAM21C, RP11-378A13.1, and TTC39B ranking as the top 3 genes. We found 4 genes that were pleiotropically associated with gallstone disease in both liver and peripheral blood, including *TTC39B*, *PLEKHH2*, *RP11-378A13.1*, and *ADAR*.

Summary of results

In liver, 16 genes exhibited significant correlations in both TWAS and SMR analyses. These genes included *LINC01595*, *TTC39B*, *UGT1A3*, *FADS3*, *ABO*, *RPL17P11*, *RP11-378A13.1*, *SPTLC3*, *ADAR*, *UBXN2B*, *LITAF*, *TMEM147*, *JOSD1*, *NIPAL1*, *PLEKHH2*, and *DLG5*. Of these 16 genes, 12 were colocalized (PP4 $>$ 0.75) and shared joint significant features, including *TTC39B*, *UGT1A3*, *FADS3*, *ABO*, *RP11-378A13.1*, *SPTLC3*, *ADAR*, *LITAF*, *TMEM147*, *JOSD1*, *NIPAL1*, and *DLG5*.

In peripheral blood, 13 genes exhibited significant correlations in both TWAS and SMR analyses, including *TTC39B*, *FAM21C*, *FAM8A1*, *RP11-378A13.1*, *ADAR*, *PNKD*, *ARNTL*, *OR13A1*, *HAAO*, *DAGLB, H1F0, DCLK2*, and *ORMDL3*. Four of these genes were colocalized (PP4 $>$ 0.75) and shared joint significant features, including *RP11-378A13.1*, *ADAR*, *DAGLB*, and *H1F0*.

RP11-378A13.1 and *ADAR* were found to meet all analysis thresholds in both liver and peripheral blood, suggesting a strong association with gallstone disease (Figure 1).

DISCUSSION

In the past decade, cholelithiasis has emerged as a significant global health issue. The role of genetics in the pathogenesis of cholelithiasis has also been widely discussed. Scholars in previous research have already identified the role of genes in the occurrence of cholelithiasis. For instance, in the study by Helen H. Wang et al., it was found that the cholecystokinin A receptor gene is associated with an increased risk of cholelithiasis (21). In addition, some researchers have reported the role of the ABCG5 and ABCG8 genes in cholelithiasis, where their overexpression can increase the cholesterol content in the gallbladder, thereby leading to an increased incidence of cholelithiasis (22).

In recent years, with the rapid rise of GWAS, researchers have discovered a large number of genes associated with cholelithiasis through GWAS. For example, Fairfield et al. identified 75 genetic loci associated with the risk of cholelithiasis through GWAS, including 46 newly discovered loci; Bustos et al. found the role of *TRAF3* in the onset of cholelithiasis through GWAS, whereas Krawczy et al. discovered the role of the *rs12532734* gene in pediatric cholelithiasis (14,23,24).

The GWAS era has, to some extent, been successful because thousands of genetic loci have been statistically confirmed to be associated with diseases and traits, with a considerable number of these loci being well-validated, indicating genuine associations (25). However, GWAS also has certain limitations. First, because of the presence of LD, some variant types are coinherited with the most strongly disease-associated variants, forming a haplotype, making it challenging to distinguish their individual associations. Second, more than 90% of disease-associated variants are located in non–protein-coding regions of genes, often far from known genes (25).

TWAS, conducted on the foundation of GWAS, can to some extent address these limitations. TWAS fully leverages an eQTL expression reference panel containing both expression and genotype data to seek gene-trait correlations within GWAS data sets (25). This experiment represents the first TWAS study on cholelithiasis. In this study, we analyzed GWAS data from the Finngen database, including 37,041 cases and 330,903 controls. We extensively explored different tissue types to thoroughly characterize identified associations, revealing the genetic components of cholelithiasis transcriptome expression. After conducting 4 key steps: transcriptomewide significant genes, colocalization analysis, conditional analysis, and SMR analysis, we found that *RP11-378A13.1* and *ADAR* simultaneously met all analysis thresholds in both liver and whole blood, indicating a strong association with the occurrence of cholelithiasis.

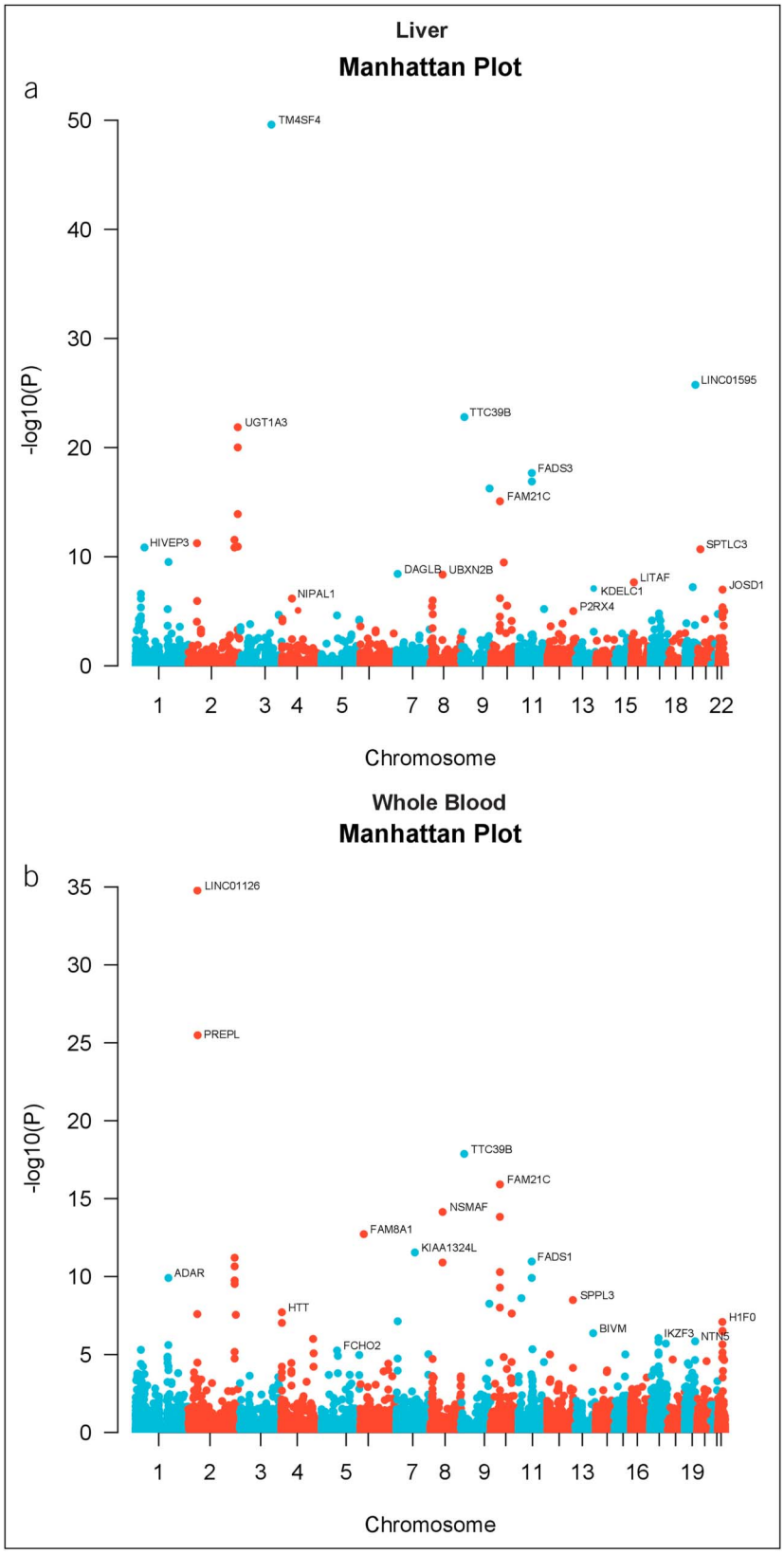

Figure 2. Differentially expressed genes identified in the liver **(a)** and whole blood **(b)**.

The *RP11-378A13.1* gene is responsible for encoding a long noncoding RNA. Long noncoding RNA functions through alternate splicing and gene fusions (26). Through alternate splicing, a single precursor mRNA can generate different mRNA isoforms, greatly increasing the diversity of proteins encoded by the genome (26). Gene fusion involves merging complete or partial sequences of 2 or more different genes into a single chimeric gene or transcript, thereby generating many new genes (27). The association between *RP11-378A13.1* and cholelithiasis has been discovered for the first time. Previous research has shown that *RP11-378A13.1* plays a role in certain diseases, such as cardiovascular disease, osteoporosis, and lung adenocarcinoma (26,28,29).

In cardiovascular disease, *RP11-378A13.1* is believed to increase the risk of cardiovascular disease by raising systolic blood pressure and increasing cholesterol levels in the blood. High cholesterol levels are a well-known contributing factor to cholelithiasis. When there is an excess of cholesterol in the liver, it can potentially enhance the expression of the bile acid transporter Abcg5/g8 by activating LXRα, leading to increased cholesterol excretion in bile. Excessive cholesterol in bile can then lead to the formation of cholesterol gallstones. Therefore, *RP11-378A13.1* may increase the risk of cholelithiasis by influencing cholesterol metabolism (28,30–32).

In osteoporosis, *RP11-378A13.1* is associated with the expression of *TMBIM1*. Abnormal *TMBIM1* expression can affect apoptosis in osteoclasts, leading to osteoporosis (27). In addition, *TMBIM1* is an important gene that controls fat production. Dysregulation of its expression can lead to pathological fat cell production, and high lipid levels can raise the risk of cholelithiasis. Therefore, *RP11-378A13.1* may affect lipid metabolism through its influence on TMBIM1, further increasing the risk of cholelithiasis (33,34).

In lung adenocarcinoma, *RP11-378A13.1* shows reduced expression. It is associated with immune and defense functions, and its reduced expression may be related to the development of lung adenocarcinoma (26). The specific role of *RP11-378A13.1* in the pathogenesis of cholelithiasis remains unknown and requires further experimental investigation.

The *ADAR* gene is responsible for encoding an enzyme called adenosine deaminase acting on RNA, which can convert adenosine in double-stranded RNA into inosine (35). Within the *ADAR* family, ADAR1 and ADAR2 are biologically active. When *ADAR1* is overexpressed in cells, it can edit mRNA, resulting in the recoding of specific mRNA molecules. In addition, increased *ADAR1* can lead to reduced expression of the retinoic acid–inducible gene I (36). RIG-I–like RNA helicases are receptors distributed in immune cells that can recognize molecules released by microbes and damaged cells (37). In a study by Lyu et al., it was observed that the expression of RIG-I–like receptors was significantly reduced in cholelithiasis patients (38). Therefore, *ADAR* may increase the risk of cholelithiasis by lowering retinoic acid–inducible gene I expression. Previous research has also indicated that ADAR plays a significant role in tumor development and immune therapy (39).

Our experiment has several advantages. First, causal relationships discovered through Mendelian randomization (MR) are not influenced by confounding factors, reducing bias compared with traditional observational studies. Second, our experiment benefits from a large sample size, using cholelithiasis whole-genome association data from the Finngen database, including 37,041 cases and 330,903 controls. Such a substantial sample size provides strong evidence for potential causal relationships. Last, our samples are exclusively from European populations, reducing heterogeneity.

However, our experiment also has limitations. First, the GWAS data we used were solely from European populations and may not be applicable to other populations. Second, our samples do not distinguish the severity of the disease, which could potentially impact the study. Last, we used SMR analysis to explore the causal association between specific genes and gallstone incidence. Although SMR analysis is a powerful tool for identifying potential causal links, it is not without limitations. The results of SMR analysis should be interpreted with caution because they may be influenced by various biases inherent in the observational data, such as selection bias, confounding factors, and reverse causality. Reverse causality refers to the possibility that gallstone incidence may influence the expression or function of the genes in question rather than the other way around. Although SMR analysis attempts to mitigate this issue by adjusting for known risk factors and using directionality tests, it cannot entirely eliminate the risk of reverse causality. Given these limitations, we acknowledge that the causal associations identified in our study warrant further validation through prospective, randomized controlled trials. Such trials would provide more robust evidence to support or refute the causal links between specific genes and gallstone incidence, thereby enhancing the clinical relevance and translational potential of our findings.

In conclusion, our experiment demonstrates a causal relationship between the RP11-378A13.1 and *ADAR* genes and the development of cholelithiasis. These newly discovered genes will aid in more effectively identifying high-risk populations for cholelithiasis through genetic screening and assist researchers in gaining a deeper understanding of the disease's pathogenesis at the genetic level.

CONFLICTS OF INTEREST

Guarantor of the article: Enjun Gao, MD.

Specific author contributions: X.L.: conceptualization, methodology, and data curation; H.W.: writing—original draft, writing—review and editing; Z.X.: writing—review and editing; L.L.: writing—review and editing; Y.H.: writing—review and editing; Z.M.: data curation; J.L.: data curation; J.Y.: data curation; Z.D.: formal analysis; Y.Z.: visualization; T.L.: visualization; C.H.: validation and funding acquisition; D.X.: validation and funding acquisition; L.W.: project administration and supervision; E.G.: project administration and supervision.

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Potential competing interests: None to report.

Ethics approval and consent to participate: The data used in this study are sourced from public databases, therefore further ethical review is not required.

Consent for publication: Not applicable.

Patient Anonymity and Informed Consent: Not applicable.

Availability of data and materials: The data sources used in this study are specified in the Material and Methods section.

Study Highlights

WHAT IS KNOWN

✓ Cholelithiasis is a common disease
✓ Cholelithiasis is influenced by genes

WHAT IS NEW HERE

✓ Genes associated with cholelithiasis are identified

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