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Diagnostic Yield of Whole Exome Sequencing in Adult-onset Cholestatic Liver Disease

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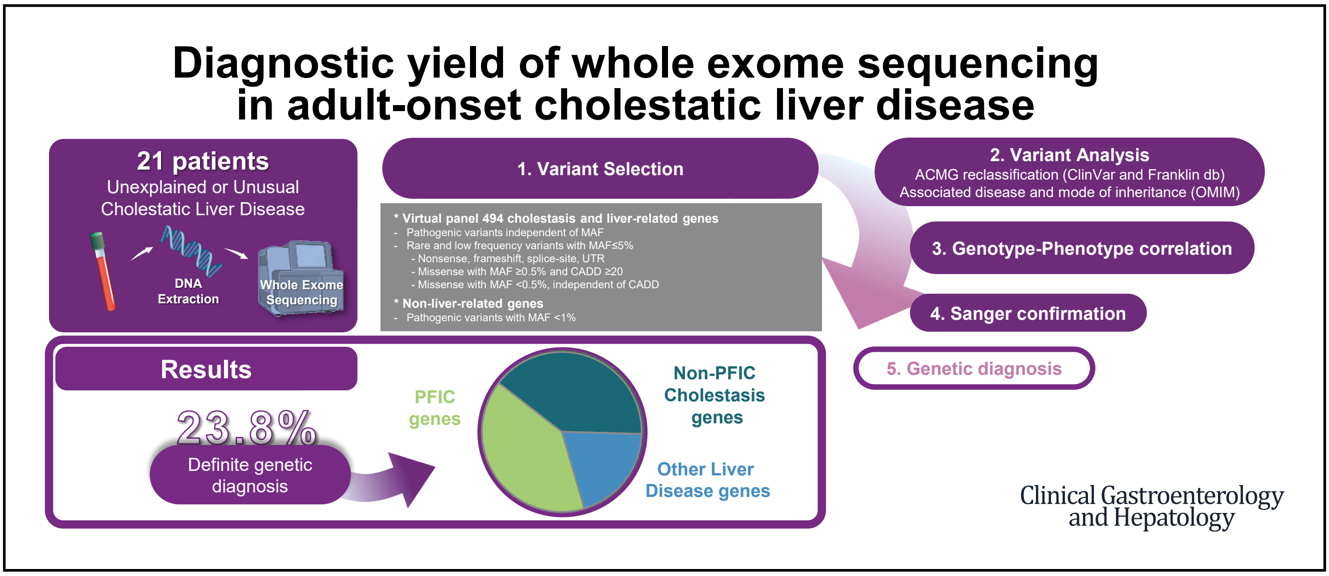

BACKGROUND & AIMS: **Cholestatic liver diseases are a heterogeneous group of conditions that can remain unexplained despite a comprehensive diagnostic assessment. Genetic disorders may underlie many of these unexplained adult-onset cholestasis cases. However, genetic testing in adults has been focused on genes linked to progressive familial intrahepatic cholestasis (PFIC). This study evaluated the diagnostic utility of whole exome sequencing (WES) by targeting a broader set of genes beyond PFIC genes.**

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Abbreviations used in this paper: ACMG, American College of Medical Genetics; AD, autosomal dominant; ALP, alkaline phosphatase; ANOVA, analysis of variance; AR, autosomal recessive; B/LB, benign/likely benign; CADD, Combined Annotation Dependent Depletion; CAP, controlled attenuation parameter; FDR, false discovery rate; gnomAD, Genome Aggregation Database; GGT, gamma glutamyl transferase; GWAS, genome-wide association study; HPO, Human Phenotype Ontology; IBD, inflammatory bowel disease; LPAC, low phospholipid-associated cholelithiasis; MAF, minor allele frequency; MRCP, magnetic resonance cholangio-pancreatography; MRI, magnetic resonance imaging; NGS, next-generation sequencing; OMIM, Online Mendelian Inheritance in Man database; PFIC, progressive familial intrahepatic cholestasis; P/LP, pathogenic/likely pathogenic; PSC, primary sclerosing cholangitis; SD, standard deviation; SLD, steatotic liver disease; UDCA, ursodeoxycholic acid; UTR, untranslated region; VUS, variants of uncertain significance; WES, whole exome sequencing.

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METHODS: Adults with unexplained cholestatic liver disease from one tertiary center underwent WES. Pathogenic and rare damaging variants in candidate cholestatic and liver disease genes were prioritized, and genotype-phenotype correlations were conducted.

RESULTS: Twenty-one patients with three distinct cholestatic phenotypes (recurrent lithiasis, intrahepatic cholestasis, and primary sclerosing cholangitis with unusual features) were included. WES yielded a genetic diagnosis of inherited cholestatic or liver disorder mimicking the cholestatic phenotype in 5 cases (23.8%). *ABCB4* was the causative gene in 2 cases (40.0%), whereas genes outside the PFIC spectrum (*ABCC2*, *PPOX*, *APOB*) accounted for the other 3 (60.0%).

CONCLUSION: This study highlights the value of WES in the diagnostic workup of adult-onset cholestatic liver disease and expands our understanding of its genetic landscape, paving the way for larger-scale studies.

Keywords: Genetic Cholestasis; Next-generation Sequencing; Primary Sclerosing Cholangitis; Progressive Familial Intrahepatic Cholestasis.

Cholestatic liver diseases are a heterogenous group of disorders characterised by impaired bile flow at the intra- or extrahepatic level, leading to biliary and liver fibrosis. Although pathogenic and rare damaging variants in various genes are well-recognized contributors in up to 25% of unexplained child-onset cholestatic liver disease,[1–5] genetic testing in adults with unexplained cholestasis remains uncommon or targeted to a limited number of genes, despite recommendations.[6]

Progressive familial intrahepatic cholestasis (PFIC) refers to rare pediatric cholestatic liver diseases caused by pathogenic and rare damaging variants in genes involved in canalicular transport and biliary epithelial barrier function.[7,8] Although traditionally associated with autosomal recessive (AR) inheritance, heterozygous variants in PFIC genes, such as *ABCB4*, have been linked to late-onset cholestatic conditions, including low phospholipid-associated cholelithiasis (LPAC), intrahepatic cholestasis of pregnancy, drug-induced liver injury, and biliary cirrhosis.[3,9–12] Indeed, 21% to 32% of patients with unexplained or atypical cholestatic liver disease have been found to harbor heterozygous variants in PFIC genes, suggesting these may act as disease modifiers.[13,14] Beyond PFIC, other cholestasis- and liver disease-related genes, including those associated with ciliopathies, mitochondrial hepatopathies, bile acid synthesis defects, alpha-1-antitrypsin deficiency,[1] and metabolic disorders[2] are well-documented in pediatrics, but their role in adult-onset cholestatic liver disease is poorly understood.

This study investigates the diagnostic yield of whole exome sequencing (WES) and its utility in 3 distinct cholestatic phenotypes in adults.

Methods

Study Cohort

Adult patients with cholestatic liver disease followed at the Gastroenterology Department of San Gerardo University Hospital from September 2022 to December 2023 were included. Cholestatic liver disease was defined by persistent or intermittent elevated serum alkaline phosphatase (ALP) with or without gamma-glutamyltransferase (GGT) for at least 6 months. Patients lacking a definitive diagnosis despite comprehensive assessment (Supplementary Table 1) and without prior genetic diagnoses underwent WES. Based on clinical phenotype, different subgroups of patients were identified: recurrent biliary lithiasis, intrahepatic cholestasis, and primary sclerosing cholangitis (PSC) with unusual features. Recurrent biliary lithiasis was defined as repeated formation of intra- and/or extrahepatic gallstones despite cholecystectomy, and intrahepatic cholestasis was defined as unexplained persistent or intermittent biochemical cholestasis without biliary obstruction, not meeting criteria for any chronic liver disease after liver biopsy. PSC was diagnosed via magnetic resonance cholangio-pancreatography (MRCP) and/or liver biopsy after excluding secondary causes of sclerosing cholangitis.[15] Unusual features included the absence of inflammatory bowel disease (IBD) in patients without radiological abnormalities (small duct PSC) or with nontypical radiological abnormalities (exclusive involvement of extrahepatic bile ducts or exclusive minimal radiological abnormalities in the intrahepatic bile ducts).[16] Advanced chronic liver disease was evaluated using liver biopsy or transient elastography (FibroScan) with ≥11 kPa defining advanced fibrosis (≥F3). Clinical data were collected from electronic charts, and probands-only WES was conducted following written informed consent. A sex- and ethnicity-matched group of 266 Italian healthy blood donors without clinical and biochemical evidence of cholestatic or liver disease was used as the control cohort. The study adhered to the Declaration of Helsinki and was approved by the local ethics committee (EC 125_2018bis).

DNA Isolation and WES

Genomic DNA was isolated from peripheral whole blood and quantified by a Qubit 2.0 analyzer using the Qubit dsDNA BR Assay Kit (Thermo-Fisher). Genomic

DNA libraries were enriched for WES by the SureSelect Human All Exon v8 kit, according to manufacturer instructions (Agilent, Cernusco sul Naviglio). Sequencing was performed on the NextSeq 2000 platform (Illumina).

Variant Prioritization and Interpretation

Data processing, variant calling, annotation, and quality control were performed as described previously.[17] Sequencing mean depth was 200×, with more than 96% of targets covered at 20× depth. Variants affecting protein function were prioritized, excluding those in intergenic or intronic regions. A virtual panel of 494 cholestasis- and liver disease-associated genes (Supplementary Table 2) was created based on Online Mendelian Inheritance in Man (OMIM) database, Orphanet, the Human Phenotype Ontology (HPO) database, and literature.[18,19] For these, we selected: (1) pathogenic variants according to ClinVar, as annotated by ANNOVAR, regardless of minor allele frequency (MAF) in the Genome Aggregation Database (gnomAD); (2) rare/low-frequency (MAF <5%) functional variants, including variants of uncertain significance (VUS) and benign/likely benign (B/LB), meeting one of the following: (1) nonsense, frameshift, splice-site, or untranslated region (UTR) variants; (2) missense variants with a MAF>0.5% and a combined annotation dependent depletion (CADD) score ≥20; (3) missense variants with a MAF <0.5%, regardless of CADD. For all other genes, only pathogenic variants with MAF <1% were considered. Different filters for autosomal dominant (AD) (MAF ≤0.1%) and AR (MAF ≤1%) inheritance were applied due to the different mode of disease transmission. When a single rare variant was detected in a gene causing an AR disease, all variants in that gene were reviewed independent of MAF for the specific patient. Prioritized variants were classified using American College of Medical Genetics (ACMG) guidelines.[20] Genotype-phenotype correlations were conducted matching molecular data with clinical findings. Only variants associated with the phenotype were considered diagnostic and confirmed by Sanger sequencing. A flowchart of variant prioritization and interpretation is shown in Supplementary Figure 1. Combining genetic findings with clinical data, 3 different diagnostic outcomes were defined (Table 1).

Statistical Analysis

Descriptive statistics were presented as number and proportion for categorical variables and mean and standard deviation (SD) for continuous variables. Group differences were assessed using 1-way analysis of variance (ANOVA), Mann-Whitney test, and Fisher's exact test as appropriate. Variant frequencies were compared between patients and controls using χ^2 tests adjusted for false discovery rate (FDR). Statistical analyses were performed in JMP Pro 16.0 Statistical Analysis Software (SAS Institute), and figures were created with GraphPad Prism (version 10.0; GraphPad Software, Inc). $P < .05$ (2-tailed) was considered significant.

Results

Study Population

From an initial number of 682 patients with adult-onset cholestatic liver disease, 24 unrelated patients were identified, after excluding established causes of cholestatic liver disease. Of these, 21 consented to undergo WES (Supplementary Figure 2). The study cohort included 3 cholestatic phenotypes: 2 patients (9.5%) with recurrent biliary lithiasis, 7 (33.3%) with intrahepatic cholestasis, and 12 (57.1%) with PSC with unusual features. The mean age at disease presentation was 33.7 years (SD, 11.4 years), and at genetic analysis, 42.8 years (SD, 10.8 years). The female-to-male ratio was 1:1, and 33.3% of patients had a first-degree relative with cholestatic liver disease. None had advanced chronic liver disease. Clinical and histological details are provided in Table 2, Supplementary Table 3, and Supplementary Table 4.

Variants Detection

WES identified 277 pathogenic or rare/low frequency damaging variants across 155 of the 494 genes

Table 1. Definition of Diagnostic Outcomes

Diagnostic outcome	Definition
Definite genetic diagnosis	Presence of pathogenic variants consistent with the clinical phenotype and mode of inheritance
Possible contribution to clinical phenotype	Presence of rare damaging[a] VUS in genes involved in disease pathogenesis
Negative	Absence of variants in genes associated with clinical phenotype

CADD, combined annotation dependent depletion; MAF, minor allele frequency; UTR, untranslated region; VUS, variant of uncertain significance.
[a]Nonsense, frameshift, splice-site, or UTR variants with a MAF <5% OR missense variants with a MAF 5% to 0.5% and a CADD score ≥20 OR missense variants with a MAF <0.5%, independent of CADD.

Table 2. Study Population Characteristics and Diagnostic Yield of WES in the Overall Cohort and in Each Phenotype

	Overall (N = 21)	Recurrent lithiasis (n = 2)	Intrahepatic cholestasis (n = 7)	PSC with unusual features (n = 12)	*P* value
Age at disease onset, *years*	33.3 (10.8)	29.0 (11.3)	35.7 (10.7)	32.6 (11.5)	.623
Age at genetic test, *years*	42.8 (10.8)	38.5 (0.7)	47.1 (9.0)	41.0 (12.1)	.429
Time from disease onset to genetic test, *years*	9.5 (5.8)	9.5 (10.6)	11.4 (6.9)	8.4 (4.5)	.643
Male sex	10 (47.6%)	1 (50.0%)	2 (28.6%)	7 (58.3%)	.659
Cholestatic liver disease in first-degree relatives	7 (33.3%)	1 (50.0%)	2 (28.6%)	4 (33.3%)	1.000
Pruritus	3 (14.3%)	0 (0.0%)	2 (28.6%)	1 (8.3%)	.653
ALP, *IU/L*	220 (147)	104 (3)	208 (99)	246 (175)	.350
GGT, *IU/L*	210 (181)	61 (13)	284 (233)	191 (148)	.204
TBIL, *mg/dL*	1.5 (1.8)	0.4 (0.2)	2.5 (2.8)	1.0 (0.7)	.163
TCol, *mg/dL*	188 (44)	154 (69)	194 (55)	190 (34)	.739
Liver biopsy	17 (81.0%)	1 (50.0%)	7 (100%)	9 (75.0%)	.190

NOTE: Data are presented as number (%) or mean (standard deviation).
NOTE: Unadjusted differences between the groups were evaluated using the 1-way ANOVA for normally distributed variables, Mann-Whitney test for non-normally distributed variables, and Fisher's exact test for categorical variables.
NOTE: Normal values: ALP <115 IU/L; GGT <50 IU/L; TBIL <1 mg/dL; TCol <200 mg/dL.
ALP, alkaline phosphatase; GGT, gamma-glutamyltrasferase; PSC, primary sclerosing cholangitis; TBIL, total bilirubin; TCol, total cholesterol; WES, whole exome sequencing.

analyzed (Supplementary Table 5). Most variants (87.7%) were unique to individual patients, with 98.5% in heterozygosity. Variants were distributed among 3 gene categories: PFIC genes, non-PFIC cholestasis genes, and other liver disease genes. Fourteen variants were found in 6 PFIC genes, with *ABCB4* having the highest frequency (n = 4). Two of them (c.217C>G in *ABCB4* and c.3962G>A in *MYO5B*), were found in more than one patient. Variants were detected in all patients with recurrent lithiasis, 42.9% of those with intrahepatic cholestasis, and 41.7% with PSC with unusual features. Sixty-eight variants were identified in 37 non-PFIC cholestasis genes. *PLEC* and *PKD1L1* had the highest variants number (n = 8 and n = 5, respectively). All patients carried at least one variant in this category. One hundred ninety-five variants were found in 113 other liver disease genes, with *DYNC2H1* and *PIEZO1* carrying the highest variants number (n = 8). All patients had at least one variant in this category. Overall, 26.7% of variants (74/277) were in 26 of the 58 genes (44.8%) included in the panel that encode proteins involved in ciliogenesis, primary cilia function, and ciliary intraflagellar transport and have been previously related to ciliopathies[21] (Figure 1). Further analysis using stringent filters identified 17 pathogenic variants unrelated to the liver phenotype, including *BRCA1* (c.626delC) and *MYBPC3* (c.26-2A>G), which confer increased risk for breast/ovarian cancer and hypertrophic cardiomyopathy, respectively.[22,23]

We conducted an exploratory analysis to compare the frequency of the detected variants in the patients' cohort with that of ethnically matched controls. Demographic and clinical features of the control cohort are listed in Supplementary Table 6. Among 294 variants analyzed, 18 were nominally more frequent in patients (unadjusted *P* values < .05), including variants in *ABCB4*, *ABCC2*, *PEX16*, and *PKHD1*. However, no significant differences were observed after FDR correction (Supplementary Figure 3; Supplementary Table 7).

Diagnostic Yield

A genetic diagnosis was established in 23.8% of patients (5/21) (Supplementary Figure 4). Diagnostic yield appeared to vary with clinical phenotype ($P = .048$), but not with other clinical variables including age at disease onset ($P = .999$) and family history of cholestatic disease ($P = .624$). However, the small sample size limits the strength and generalizability of these observations.

Genetic Diagnoses and Clinical Impact

WES confirmed *ABCB4* variants in both patients with recurrent biliary lithiasis, leading to a diagnosis of LPAC (#600803), a genetic condition associated with AD inheritance.[24] Ursodeoxycholic acid (UDCA) induced clinical remission and normalization of liver enzymes in both

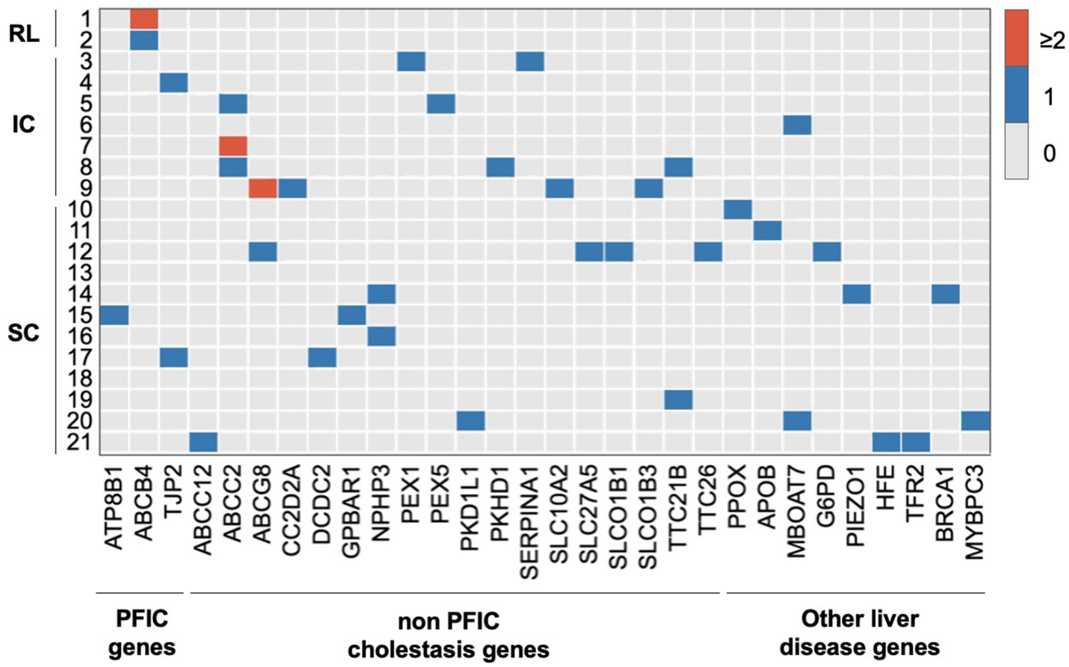

Figure 1. Heatmap-like distribution of pathogenic variants and rare/low frequency damaging VUS with a possible contribution to the phenotype in the study cohort. Bi-dimensional representation of mutated genes (columns) against individual patients (rows). Patients are arranged by distinct cholestatic phenotypes. Genes are organized by category, and each gene is color-coded based on its mutation frequency: *gray* for no variants, *blue* for one variant, and *orange* for two or more variants.

patients. Heterozygous carriers of *ABCB4* variants have an increased risk of cholangiocarcinoma.[25] Thus, a yearly clinical and radiological follow-up was established.

A genetic diagnosis was reached in 1 of 7 patients (14.3%) with intrahepatic cholestasis. The patient had long-standing episodic jaundice and adult-onset high GGT chronic cholestasis. Liver biopsy showed canalicular cholestasis and coarse granular brown pigments in the cytoplasm of centrilobular hepatocytes. WES identified 2 homozygous *ABCC2* variants, confirming Dubin Johnson syndrome (# 237500), an AR condition. In this patient, UDCA led to biochemical improvement, although not complete normalization.

Two patients with PSC with unusual features received genetic diagnoses. One patient harbored a heterozygous variant in *PPOX*, which led to the diagnosis of variegate porphyria (#176200). Variegate porphyria is a rare AD disorder caused by a deficient protoporphyrinogen oxidase that leads to the accumulation of porphyrins and their precursors with multisystemic sequelae.[26] Although it has been associated with liver enzyme abnormalities and a risk of cholelithiasis due to high levels of protoporphyrin in bile,[27] the association with sclerosing cholangitis has not been described yet and thus should be considered with caution. Of note, variegate porphyria may manifest with acute porphyric attack, and in the long term, is associated with an increased risk of hepatocarcinoma and cholangiocarcinoma even in the absence of liver fibrosis.[28] Following the genetic finding, the patient underwent clinical reassessment, and the porphyrin levels in urine and stool were found at the upper limit of normal, supporting the diagnosis. Therefore, annual surveillance and counseling on avoidance of porphyria-precipitating drugs were implemented. In a patient with PSC and hepatic steatosis, WES revealed the presence of a variant in *APOB*, leading to the diagnosis of familial hypo-betalipoproteinemia (#615558), a known cause of steatotic liver disease (SLD) with a high likelihood of progressing to advanced liver fibrosis and primary liver cancer.[29] Transient elastography (FibroScan) confirmed significant liver steatosis (controlled attenuation parameter [CAP], 351 dB/m with values ≥275 dB/m indicative of SLD), supported by abdominal ultrasound findings. Of note, SLD more likely presents with a biochemical hepatocellular pattern, but it may occasionally show a cholestatic or mixed pattern. The genetic diagnosis guided follow-up and cancer surveillance. Details of patients with a genetic diagnosis are shown in Table 3.

In 2 additional patients, WES identified clinically relevant findings in genes unrelated to liver disease. One patient with PSC carried a likely pathogenic variant in *BRCA1,* associated with breast and ovarian cancer and cholangiocarcinoma risk.[22,30] Another patient with PSC carried a pathogenic variant in *MYBPC3,* associated to cardiomyopathy risk.[23] These findings led to specialist referrals, counseling for the proband's relatives, and tailored follow-up.

Table 3. Demographics and Clinical Features of Patients With a Definite Genetic Diagnosis

ID	Age, *years*	Sex	Family history	Phenotype	Gene	Variant	Genotype	Associated disease (# OMIM)
1	37	M	Yes	Recurrent lithiasis	*ABCB4* *ABCB4*	c.754G>C (LP) c.2144C>T (VUS)	Het Het	LPAC (# 600803)
2	21	F	No	Recurrent lithiasis	*ABCB4*	c.526C>T (P)	Het	LPAC (# 600803)
7	38	M	No	Intrahepatic cholestasis	*ABCC2* *ABCC2*	c.468+1G>A (LP) c.842G>A (VUS)	Hom Hom	Dubin Johnson syndrome (# 237500)
10	32	M	No	SC with unusual features	*PPOX*	c.338+2dup (LP)	Het	Variegate porphyria (# 176200)
11	24	M	No	SC with unusual features and SLD	*APOB*	c.13480_13482del (LP)	Het	Hypobetalipoproteinemia (# 615558)

F, female; Het, heterozygous; Hom, homozygous; LP, likely pathogenic; LPAC, low phospholipid-associated cholelithiasis; M, male; OMIM, Online Mendelian Inheritance in Man database; P, pathogenic; SC, sclerosing cholangitis; SLD, steatotic liver disease; VUS, variant of uncertain significance.

Variants With a Possible Contribution to the Clinical Phenotype

Beside variants leading to a genetic diagnosis, we selected rare and low-frequency VUS with a high likelihood of disrupting protein function in genes known to be associated with the clinical phenotype, hypothesising that these variants could contribute to disease pathogenesis. A total of 25 heterozygous variants in 2 PFIC genes and in 18 non-PFIC cholestasis genes were selected in 14 of 21 patients (66.7%). Notably, 36.0% of these variants were in 7 ciliopathy-related genes[21] (Supplementary Table 5). Additional findings included rare VUS in *MBOAT7* (p.Leu76Val and p.Ala346Thr) in 2 patients with intrahepatic cholestasis or PSC and SLD, possibly contributing to hepatic steatotis.[31] Moreover, 1 patient with PSC with biochemical evidence of iron overload (ferritin up to 316 μg/L; transferrin saturation up to 47%), but no significant hepatic iron accumulation on magnetic resonance imaging (MRI), carried a heterozygous *HFE* variant (c.187C>G) and a rare VUS in *TFR2* (c.2377del). Of note, although the association between iron overload and PSC remains unclear, altered iron metabolism in other chronic liver diseases has been associated with fibrosis progression and increased cancer risk.[32–34]

Discussion

In this study, we explored the utility of WES in unexplained cholestatic liver disease, identifying inherited disorders in 23.8% of patients, with direct implications for clinical management, including tailored therapeutic strategies and cancer surveillance.

Adult-onset cholestatic liver disease is a group of rare disorders with highly heterogeneous clinical presentations, making diagnosis often challenging. There is little doubt that genetic analysis may identify Mendelian disorders behind unexplained or unusual cases. Nonetheless, environmental factors and the interplay between multiple genetic variants with an oligogenic or polygenic pattern of inheritance may significantly influence their phenotypic expression.[35] This complexity often hinders clear genotype-phenotype correlations in paediatric cases and is likely even more pronounced in adults. As a result, despite recommendations,[6] the possibility of a genetic etiology is still often overlooked in adults with unexplained cholestasis, as reflected by the nearly 10-year delay from disease onset to genetic testing observed in our cohort. Next-generation sequencing (NGS) technology provides the unprecedented possibility to identify genetic variants across the whole genome, representing a key step toward understanding the determinants of genotype-phenotype match in Mendelian disorders.[36]

The main study finding was that WES provided a genetic diagnosis in about one-quarter of cases and identified rare damaging variants with a possible contribution to the cholestatic phenotype in an additional two-thirds. Variants in cholestasis-associated genes were frequently detected across phenotypes, with PFIC genes accounting for 40% of genetic diagnoses. These results are in line with previous reports on unexplained cholestatic liver disease,[3,12,13] including a recent study that applied WES in a cohort of 17 adults with idiopathic cholestasis, which yielded 8 genetic diagnoses, 6 of which involved variants in PFIC-related genes.[37] Notably, in both studies, WES also uncovered diagnoses beyond classical genetic cholestatic disorders in a minority of patients, aiding interpretation of atypical or subtle phenotypes. However, most of the variants detected in our cohort would likely have been captured by current NGS cholestasis gene panels. Thus, although WES shows promise in expanding our understanding of genetic contributors to unexplained adult-onset liver disease,[36] its routine clinical use remains investigational and currently limited to research settings.

Although WES offers significant advantages, it also poses challenges, including the ethical and logistical complexities of managing incidental findings,[16,38] as well as the need to evaluate the potential clinical impact of VUS.[39] To address these issues, we employed a multidisciplinary review process, including hepatologists, geneticists, and molecular pathologists, as previously recommended.[40] This ensured rigorous phenotype-genotype correlation, particularly in patients with pathogenic/likely pathogenic (P/LP) or VUS variants in disease-relevant genes. When diagnostic criteria were met, genetic results enabled implementation of targeted surveillance strategies and familial cascade testing for an early diagnosis of affected family members. In cases where VUS were detected in relevant pathways, follow-up testing and family studies were proposed to clarify their contribution to disease.

We included 12 patients with PSC with unusual features. PSC is a chronic cholangiopathy with unknown pathogenesis and a highly heterogeneous clinical presentation, which often complicates a timely diagnosis. Adding to this complexity, there are genetic conditions that may mimic the sclerosing cholangitis phenotype,[25,41] making it difficult to distinguish between PSC and other liver disorders. This is the reason why genetic testing is recommended in PSC displaying unusual features,[6] but it is still not routinely performed, possibly leading to diagnostic misclassification. WES has been already used to investigate the contribution of rare variants to early-onset PSC in children.[42] This study supports the rationale of genetic testing in adult-onset PSC with unusual features, revealing a liver genetic condition mimicking the cholestatic phenotype in 2 patients. Although further studies are necessary, our preliminary findings suggest that these variants may help unravel the significant phenotypic heterogeneity that characterizes this disease and better classify those patients that presents with unusual features ensuring a tailored clinical management.

Our WES analysis identified several variants in ciliopathy genes, which were well-represented in the cholestasis and liver-disease gene panel. Ciliopathies are multisystem disorders caused by mutations in genes coding for the cilium-centrosome complex.[21,43] Variants in these genes have been linked to neonatal and PSC[41,44] and suggested to contribute to biliary atresia pathogenesis.[45] Interestingly, some ciliopathy gene variants act as disease modifiers,[46] influencing clinical phenotypes even in heterozygous states,[47] similar to what has been described for PFIC genes.[13] Consistent with a prior study,[48] we identified variants in ciliopathy genes in 26.7% of cases, including specific variants in *PKHD1* (c.11525G>T) and *PKD1* (c.8123C>T) that were more frequent in patients than controls. However, none of these findings remained significant after correcting for FDR, highlighting the need for large-scale validation studies.

The robustness of our findings is limited by the small sample size. Nonetheless, this study provides additional evidence on the utility of WES in unexplained adult-onset liver disease, by focusing specifically on a well-characterized cohort of adult cholestatic patients and expanding the spectrum of potentially relevant genetic variants. Although we performed proband-only WES, family-based sequencing would have strengthened variant interpretation and was offered when clinically indicated.

Many medical specialities have embraced genetic testing in clinical practice to advance personalized medicine.[38] In hepatology, polygenic risk scores based on genome-wide association studies (GWAS) can estimate risks for various liver diseases.[49–51] However, these common variants explain only a fraction of heritability in complex traits. Rare variants with significant effects, often overlooked by GWAS, can provide deeper insights into disease mechanisms.[52,53]

Our findings highlight the clinical and research potential of WES in adult-onset cholestatic liver disease and pave the way for further studies validating its application.

Supplementary Material

NOTE: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2025.07.031.

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Data Availability
The genetic data will be made available upon request.

Supplemental information

Diagnostic Yield of Whole Exome Sequencing in Adult-onset Cholestatic Liver Disease

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Supplementary Material

NOTE: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2025.07.031.

Supplementary Tables

Supplementary Table 1: List of analysis performed in the comprehensive diagnostic assessment of cholestatic liver disease.

Serological analysis
Hepatitis B, C, D, or E virus infections CMV, EBV, HIV, toxoplasmosis infections Lue, Borreliosis infections Fungal infections (Cryptosporidiosis, microsporidiosis) Parasitic infections (liver fluke, ascaris)
Autoimmunity
AMA, AMA M2 ANA, anti gp210, anti sp100 cANCA, pANCA IgG, IgA, IgM, IgG1, IgG4
Rare metabolic disease
Ferritin, transferrin saturation Ceruloplasmin, 24h urine copper ACEi
Imaging
Abdominal ultrasound MRCP
Liver biopsy

Abbreviations: ACE, angiotensin converting enzyme; MRCP, magnetic resonance cholangiopancreatography.

Supplementary Table 2: Gene panel of 494 cholestatic and liver-related genes: biological annotation, associated diseases and inheritance mode.

Genes	OMIM Phenotype number	OMIM phenotype	Inheritance	Classes	Subclasses
ATP8B1	243300	Cholestasis benign recurrent intrahepatic	AD and AR	PFIC	Canalicular transporter defects
	211600	Cholestasis progressive familial intrahepatic 1	AR		
	147480	Cholestasis intrahepatic of pregnancy 1	AD		
ABCB11	601847	Cholestasis progressive familial intrahepatic 2	AR	PFIC	Canalicular transporter defects
	605479	Cholestasis benign recurrent intrahepatic 2	AR		
ABCB4	614972	Cholestasis intrahepatic of pregnancy 3	AD, AR	PFIC	Canalicular transporter defects
	602347	Cholestasis progressive familial intrahepatic 3	AR		
	600803	Gallbladder disease 1	AD, AR		
TJP2	615878	Cholestasis progressive familial intrahepatic 4	AR	PFIC	Cytoskeletal and tight junction
NR1H4/FXR	617049	Cholestasis progressive familial intrahepatic 5	AR	PFIC	Canalicular transporter defects
SLC51A	619484	Cholestasis progressive familial intrahepatic 6	AR	PFIC	Basolateral transporter defects
USP53	619658	Cholestasis, progressive familial intrahepatic, 7, with or without hearing loss	AR	PFIC	Cytoskeletal and tight junction
KIF12	619662	Cholestasis, progressive familial intrahepatic, 8	AR	PFIC	Intracellular trafficking defects
ZFYVE19	619849	Cholestasis, progressive familial intrahepatic, 9	AR	PFIC	Ciliopathy
MYO5B	619868	Cholestasis, progressive familial intrahepatic, 10	AR	PFIC	Intracellular trafficking defects
SEMA7A	619874	Cholestasis, progressive familial intrahepatic, 11	AR	PFIC	Cytoskeletal and tight junction
LSR	NA	NA	NA	PFIC	Cytoskeletal and tight junction
ABCC2	237500	Dubin-Johnson syndrome	AR	non-PFIC	Canalicular transporter defects
ABCC12	NA	Bile duct paucity	Na	non-PFIC	Bile duct paucity
ABCD3	616278	Bile acid synthesis defect congenital 5	AR	non-PFIC	Bile acid metabolism
ABCG5	618666	Sitosterolemia 2	AR	non-PFIC	Sterol metabolism
ABCG8	210250	Sitosterolemia 1	AR	non-PFIC	Sterol metabolism
ACOX2	617308	Bile acid synthesis defect congenital 6	AR	non-PFIC	Bile acid metabolism
AKR1D1	235555	Bile acid synthesis defect congenital 2	AR	non-PFIC	Bile acid metabolism
ALDOB	229600	Fructose intolerance hereditary	AR	non-PFIC	Carbohydrate metabolism
AMACR	214950	Bile acid synthesis defect congenital 4	AR	non-PFIC	Bile acid metabolism
ANKS6	615382	Nephronophthisis 16	AR	non-PFIC	Ciliopathy
BAAT	619232	Bile acid conjugation defect 1	AR	non-PFIC	Bile acid metabolism
BLVRA/BVR	614156	Hyperbiliverdinemia	AD	non-PFIC	Bile acid metabolism
CC2D2A	612285	Joubert syndrome 9	AR	non-PFIC	Ciliopathy
CFTR	219700	Cystic fibrosis	AD and AR	non-PFIC	Cholangiocyte channelopathy
CLDN1	607626	Ichthyosis leukocyte vacuoles alopecia and sclerosing cholangitis	AR	non-PFIC	Cytoskeletal and tight junction

CYP27A1	213700	Cerebrotendinous xanthomatosis	AR	non-PFIC	Sterol metabolism
CYP7A1	NA	NA	NA	non-PFIC	Sterol metabolism
CYP7B1	613812	Bile acid synthesis defect congenital 3	AR	non-PFIC	Bile acid metabolism
CYP8B1	NA	Bile acids synthesis disorder	NA	non-PFIC	Bile acid metabolism
DCDC2	617394	Sclerosing cholangitis neonatal	AR	non-PFIC	Ciliopathy
DGUOK	617068	Portal hypertension noncirrhotic	AR	non-PFIC	Hepatocellular disease
	251880	Mitochondrial DNA depletion syndrome 3	AR	non-PFIC	
DHCR7	270400	Smith-Lemli-Opitz syndrome	AR	non-PFIC	Bile acid metabolism
EHHADH	615605	Fanconi renotubular syndrome 3	AD	non-PFIC	Bile acid metabolism
FAH	276700	Tyrosinemia type I	AR	non-PFIC	Amino acid metabolism
GPBAR1	NA	NA	NA	non-PFIC	Bile acid signaling
HNF1B	125853	Diabetes mellitus noninsulin-dependent	AD	non-PFIC	Ciliopathy
HSD17B4	233400	Perrault syndrome 1	AR	non-PFIC	Bile acid metabolism
HSD3B7	607765	Bile acid synthesis defect congenital 1	AR	non-PFIC	Bile acid metabolism
IFT172	615630	Short-rib thoracic dysplasia 1 with or without polydactyly	AR	non-PFIC	Ciliopathy
INVS	602088	Nephronophthisis 2 infantile	AR	non-PFIC	Ciliopathy
JAG1	118450	Alagille syndrome 1	AD	non-PFIC	Bile duct paucity
LIPA	278000	Cholesteryl ester storage disease	AR	non-PFIC	Sterol metabolism
MKS1	617121	Joubert syndrome 28	AR	non-PFIC	Ciliopathy
MPV17	256810	Mitochondrial DNA depletion syndrome 6	AR	non-PFIC	Hepatocellular disease
NEK8	613824	Nephronophthisis 9	AR	non-PFIC	Ciliopathy
NOTCH2	610205	Alagille syndrome 2	AD	non-PFIC	Bile duct paucity
NPC1	257220	Niemann-Pick disease type D	AR	non-PFIC	Sterol metabolism
NPC2	607625	Niemann-pick disease type C2	AR	non-PFIC	Sterol metabolism
NPHP1	256100	Nephronophthisis 1 juvenile	AR	non-PFIC	Ciliopathy
NPHP3	604387	Nephronophthisis 3	AR	non-PFIC	Ciliopathy
NPHP4	606966	Nephronophthisis 4	AR	non-PFIC	Ciliopathy
PEX1	601539	Peroxisome biogenesis disorder 1B	AR	non-PFIC	Bile acid metabolism
PEX10	614871	Peroxisome biogenesis disorder 6B	AR	non-PFIC	Bile acid metabolism
PEX11B	614920	Peroxisome biogenesis disorder 14B	AR	non-PFIC	Bile acid metabolism
PEX12	266510	Peroxisome biogenesis disorder 3B	AR	non-PFIC	Bile acid metabolism
PEX13	614883	Peroxisome biogenesis disorder 11A	AR	non-PFIC	Bile acid metabolism
PEX14	614887	Peroxisome biogenesis disorder 13A	AR	non-PFIC	Bile acid metabolism
PEX16	614876	Peroxisome biogenesis disorder 8A	AR	non-PFIC	Bile acid metabolism
PEX19	614886	Peroxisome biogenesis disorder 12A	AR	non-PFIC	Bile acid metabolism
PEX2	614866	Peroxisome biogenesis disorder 5A	AR	non-PFIC	Bile acid metabolism
PEX26	614873	Peroxisome biogenesis disorder 7B	AR	non-PFIC	Bile acid metabolism
PEX3	614882	Peroxisome biogenesis disorder 1A	AR	non-PFIC	Bile acid metabolism
PEX5	202370	Peroxisome biogenesis disorder 2B	AR	non-PFIC	Bile acid metabolism

PEX6	614863	Peroxisome biogenesis disorder 4B	AR	non-PFIC	Bile acid metabolism
PEX7	614879	Peroxisome biogenesis disorder 9B	AR	non-PFIC	Bile acid metabolism
PKD1L1	617205	Heterotaxy, visceral, 8, autosomal	AR	non-PFIC	Ciliopathy
PKHD1	263200	Polycystic kidney disease 4 with or without hepatic disease	AR	non-PFIC	Ciliopathy
PLEC	131950	Epidermolysis bullosa simplex 5A	AD	non-PFIC	Cytoskeletal and tight junction
POLG	613662	Mitochondrial DNA depletion syndrome 4B	AD and AR	non-PFIC	Hepatocellular disease
SCP2	613724	Leukoencephalopathy with dystonia and motor neuropathy	AR	non-PFIC	Sterol metabolism
SERPINA1	613490	Alpha-1-antitrypsin deficiency	AR	non-PFIC	Hepatocellular disease
SLC10A1	619256	Hypercholanemia, familial 2	AR	non-PFIC	Basolateral transporter defects
SLC10A2	613291	Bile acid malabsorption primary	AR	non-PFIC	Basolateral transporter defects
SLC25A13	603471	Citrullinemia adult-onset type II	AR	non-PFIC	Basolateral transporter defects
SLC27A5	NA	NA	NA	non-PFIC	Bile acid metabolism
SLC51B	619481	Bile acid malabsorption, primary, 2	AR	non-PFIC	Basolateral transporter defects
SLCO1B1	237450	Hyperbilirubinemia Rotor type digenic Digenic recessive	AR	non-PFIC	Basolateral transporter defects
SLCO1B3	237450	Hyperbilirubinemia Rotor type digenic Digenic recessive	AR	non-PFIC	Basolateral transporter defects
SMPD1	257200	Niemann-Pick disease type A	AR	non-PFIC	Sterol metabolism
TMEM67	610688	Joubert syndrome 6	AR	non-PFIC	Ciliopathy
TMEM216	608091	Joubert syndrome 2	AR	non-PFIC	Ciliopathy
TRMU	613070	Liver failure transient infantile	AR	non-PFIC	Hepatocellular disease
TTC21B	613820	Nephronophthisis 12	AD and AR	non-PFIC	Ciliopathy
TTC26/IFT56	619534	Biliary, renal, neurologic, and skeletal syndrome	AR	non-PFIC	Ciliopathy
UGT1A1	218800	Crigler-Najjar syndrome type I	AR	non-PFIC	Bilirubin metabolism
	606785	Crigler-Najjar syndrome type II	AR		
VIPAS39/VIPAR	613404	Arthrogryposis renal dysfunction and cholestasis 2	AR	non-PFIC	Intracellular trafficking defects
VPS33B	208085	Arthrogryposis renal dysfunction and cholestasis 1	AR	non-PFIC	Intracellular trafficking defects
VPS50	619685	Neurodevelopmental disorder with microcephaly, seizures, and neonatal cholestasis	AR	non-PFIC	Intracellular trafficking defects
ABCA1	205400	Tangier disease	AR	Other liver	Dyslipidemia
ABHD5	275630	Chanarin-Dorfman syndrome	AR	Other liver	Dyslipidemia
ACAD9	611126	Mitochondrial complex I deficiency nuclear type 2	AR	Other liver	Mitochondrial dysfunction
ACADM	201450	Acyl-CoA dehydrogenase medium chain deficiency of	AR	Other liver	Dyslipidemia
ACADVL	201475	VLCAD deficiency	AR	Other liver	Dyslipidemia
ACOX1	264470	Peroxisomal acyl-CoA oxidase deficiency	AR	Other liver	Liver-related disease
AGA	208400	Aspartylglucosaminuria	AR	Other liver	Disorders of glycoprotein synthesis
AGL	232400	Glycogen storage disease IIIb	AR	Other liver	Storage diseases
AGPAT2	608594	Lipodystrophy congenital generalized type 1	AR	Other liver	Dyslipidemia
AGXT	259900	Hyperoxaluria primary type 1	AR	Other liver	Liver-related disease

AHI1	608629	Joubert syndrome 3	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
AKT2	125853	Diabetes mellitus type II	AD	Other liver	Diabetes
ALAD	612740	Porphyria acute hepatic	AR	Other liver	Heme metabolism
ALAS2	300752	Protoporphyria erythropoietic X-linked	XLR	Other liver	Heme metabolism
ALDOA	611881	Glycogen storage disease XII	AR	Other liver	Storage diseases
ALG1	608540	Congenital disorder of glycosylation type Ik	AR	Other liver	Storage diseases
ALG12	607143	Congenital disorder of glycosylation type Ig	AR	Other liver	Storage diseases
ALG2	607906	Congenital disorder of glycosylation type Ii	AR	Other liver	Disorders of glycoprotein synthesis
ALG3	601110	Congenital disorder of glycosylation type Id	AR	Other liver	Storage diseases
ALG6	603147	Congenital disorder of glycosylation type Ic	AR	Other liver	Storage diseases
ALG8	608104	Congenital disorder of glycosylation type Ih	AD and AR	Other liver	Disorders of glycoprotein synthesis
	617874	Polycystic Liver Disease 3 with or without kidney cysts	AD and AR	Other liver	Congenital hepatic fibrosis_ciliopathy
ALG9	608776	Congenital disorder of glycosylation type Il	AR	Other liver	Storage diseases
ALMS1	203800	Alstrom syndrome	AR	Other liver	Hereditary Liver Disease_ciliopathy
ANK1	182900	Spherocytosis type 1	AD and AR	Other liver	Hemolytic anemia
APOA1	618463	Hypoalphalipoproteinemia primary 2 with or without corneal clouding	AD	Other liver	Dyslipidemia
APOA5	144650	Hyperchylomicronemia late-onset	AD	Other liver	Dyslipidemia
APOB	615558	Hypobetalipoproteinemia	AR	Other liver	Dyslipidemia
	144010	Hypercholesterolemia familial 2	AD	Other liver	Dyslipidemia
APOC2	207750	Hyperlipoproteinemia, type Ib	AR	Other liver	Dyslipidemia
APOE	617347	Hyperlipoproteinemia type III	AD and AR	Other liver	Dyslipidemia
ARHGAP31	100300	Adams-Oliver syndrome 1	AD	Other liver	Liver-related disease
ARSB	253200	Mucopolysaccharidosis type VI	AR	Other liver	Storage diseases
ASL	207900	Argininosuccinic aciduria	AR	Other liver	Disorders of glycoprotein synthesis
ASS1	215700	Citrullinemia	AR	Other liver	Liver-related disease
ATG7	619422	Spinocerebellar ataxia, autosomal recessive 31	AR	Other liver	Liver-diseases susceptibility
ATP5F1A/ ATP5A1	615228	Mitochondrial complex V deficiency nuclear type 4	AR	Other liver	Mitochondrial dysfunction
ATP5F1B/ ATP5B	620085	Hypermetabolism due to uncoupled mitochondrial oxidative phosphorylation 2	AD	Other liver	Mitochondrial dysfunction
ATP6AP1	300972	Immunodeficiency 47	XLR	Other liver	Immuno/vascular
ATP6AP2	301045	Congenital disorder of glycosylation type IIr	XLR	Other liver	Storage diseases
ATP7B	277900	Wilson disease	AR	Other liver	Hereditary Liver Disease
ATPAF2	604273	Mitochondrial complex V deficiency nuclear type 1	AR	Other liver	Mitochondrial dysfunction
B2M	241600	Immunodeficiency 43	AD and AR	Other liver	Immuno/vascular
B4GALT1	607091	Congenital disorder of glycosylation type IId	AR	Other liver	Storage diseases
B9D1	617120	Joubert syndrome 27	AR	Other liver	Congenital hepatic fibrosis_ciliopathy

B9D2	614175	Joubert syndrome 34	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
BBS1	209900	Bardet-Biedl syndrome 1	AR, DR	Other liver	Congenital hepatic fibrosis_ciliopathy
BCS1L	124000	Mitochondrial complex III deficiency nuclear type 1	AR	Other liver	Mitochondrial dysfunction
BMP6	NA	NA	NA	Other liver	Iron overload
BOLA3	614299	Multiple mitochondrial dysfunctions syndrome 2 with hyperglycinemia	AR	Other liver	Mitochondrial dysfunction
BSCL2	269700	Lipodystrophy congenital generalized type 2	AR	Other liver	Dyslipidemia
BTD	253260	Biotinidase deficiency	AR	Other liver	Liver-related disease
TWNK/ C10orf2	271245	Mitochondrial DNA depletion syndrome 7	AD and AR	Other liver	Mitochondrial dysfunction
CAV1	606721	Lipodystrophy familial partial type 7	AD and AR	Other liver	Dyslipidemia
CAVIN1	613327	Lipodystrophy congenital generalized type 4	AR	Other liver	Dyslipidemia
CBS	236200	Homocystinuria B6-responsive and nonresponsive types	AR	Other liver	Immuno/vascular
CCDC115	616828	Congenital disorder of glycosylation type IIo	AR	Other liver	Storage diseases
CD19	613493	Immunodeficiency common variable 3	AR	Other liver	Immuno/vascular
CD79A	613510	Agammaglobulinemia 3	AR	Other liver	Immuno/vascular
CD79B	612692	Agammaglobulinemia 6	AR	Other liver	Immuno/vascular
CD81	613496	Immunodeficiency common variable 6	AR	Other liver	Immuno/vascular
CDAN1	224120	Dyserythropoietic anemia congenital type Ia	AR	Other liver	Hemolytic anemia
CELA2A	618620	Abdominal obesity-metabolic syndrome 4	AD	Other liver	Dyslipidemia
CEP120	617761	Joubert syndrome 31	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
CEP164	614845	Nephronophthisis 15	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
CEP190	615730	Morbid obesity and spermatogenic failure	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
CEP290	610188	Joubert syndrome 5	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
CEP41	614464	Joubert syndrome 15	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
CEP83	615862	Nephronophthisis 18	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
CETP	143470	Hyperalphalipoproteinemia	AD	Other liver	Dyslipidemia
CIDEC	615238	Lipodystrophy familial partial type 5	AR	Other liver	Dyslipidemia
COA5	616500	Cardioencephalomyopathy fatal infantile due to cytochrome c oxidase deficiency 3	AR	Other liver	Mitochondrial dysfunction
COA6	616510	Cardioencephalomyopathy fatal infantile due to cytochrome c oxidase deficiency 4	AR	Other liver	Mitochondrial dysfunction
COA8	619061	Mitochondrial complex IV deficiency	AR	Other liver	Mitochondrial dysfunction
COG1	611290	Congenital disorder of glycosylation type IIg	AR	Other liver	Disorders of glycoprotein synthesis
COG2	617395	Congenital disorder of glycosylation type IIq	AR	Other liver	Mitochondrial dysfunction
COG4	613489	Congenital disorder of glycosylation type IIj	AD and AR	Other liver	Storage diseases
COG5	613612	Congenital disorder of glycosylation type IIi	AR	Other liver	Storage diseases
COG6	614576	Congenital disorder of glycosylation type III	AR	Other liver	Storage diseases

COG7	608779	Congenital disorder of glycosylation type IIe	AR	Other liver	Disorders of glycoprotein synthesis
COG8	611182	Congenital disorder of glycosylation type IIh	AR	Other liver	Storage diseases
COQ2	607426	Coenzyme Q1 deficiency primary 1	AD and AR	Other liver	Mitochondrial dysfunction
COX10	619046	Mitochondrial complex IV deficiency, nuclear type 3	AR	Other liver	Mitochondrial dysfunction
COX14	619053	Mitochondrial complex IV deficiency, nuclear type 10	AR	Other liver	Mitochondrial dysfunction
COX15	615119	Mitochondrial complex IV deficiency, nuclear type 6	AR	Other liver	Mitochondrial dysfunction
COX20	619054	Mitochondrial complex IV deficiency , nuclear type 11	AR	Other liver	Mitochondrial dysfunction
COX6B1	619051	Mitochondrial complex IV deficiency, nuclear type 7	AR	Other liver	Mitochondrial dysfunction
COX8A	619059	Mitochondrial complex IV deficiency, nuclear type 15	AR	Other liver	Mitochondrial dysfunction
CP	604290	Hypo/Aceruloplasminemia	AR	Other liver	Iron overload
CPOX	121300	Coproporphyria	AD and AR	Other liver	Heme metabolism
CPS1	237300	Carbamoylphosphate synthetase I deficiency	AR	Other liver	Liver-related disease
CPT1A	255120	CPT deficiency hepatic type IA	AR	Other liver	Disorders of glycoprotein synthesis
CPT2	255110	CPT II deficiency myopathic stress-induced	AD and AR	Other liver	Disorders of glycoprotein synthesis
CR2	614699	Immunodeficiency common variable 7	AR	Other liver	Immuno/vascular
CREB3L3	619324	Hypertriglyceridemia 2	AD	Other liver	Dyslipidemia
CSPP1	615636	Joubert syndrome 21	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
CTC1	612199	Cerebroretinal microangiopathy with calcifications and cysts	AR	Other liver	Immuno/vascular
CTLA4	601388	{Diabetes mellitus insulin-dependent 12}	AD	Other liver	Immuno/vascular
CTNS	219800	Cystinosis atypical nephropathic	AR	Other liver	Disorders of glycoprotein synthesis_ciliopath y
CYBA	233690	Chronic granulomatous disease autosomal due to deficiency of CYBA	AR	Other liver	Immuno/vascular
CYBB	306400	Chronic granulomatous disease X-linked	XLR	Other liver	Immuno/vascular
CYC1	615453	Mitochondrial complex III deficiency nuclear type 6	AR	Other liver	Mitochondrial dysfunction
DCLRE1C	624500	Severe combined immunodeficiency Athabascan type	AR	Other liver	Immuno/vascular
DDOST	614507	Congenital disorder of glycosylation type Ir	AR	Other liver	Storage diseases
DHCR24	602398	Desmosterolosis	AR	Other liver	Dyslipidemia
DLL4	616589	Adams-Oliver Syndrome 6	AD	Other liver	Liver-related disease
DNAJB11	618061	Polycystic kidney disease 6 with or without polycystic Liver?isease	AD	Other liver	Congenital hepatic fibrosis_ciliopathy
DOCK6	614219	Adams-Oliver Syndrome 2	AR	Other liver	Liver-related disease
DOLK	610768	Congenital disorder of glycosylation type Im	AR	Other liver	Storage diseases
DPAGT1	608093	Congenital disorder of glycosylation type Ij	AR	Other liver	Storage diseases
DPM1	608799	Congenital disorder of glycosylation type Ie	AR	Other liver	Disorders of glycoprotein synthesis

DPM3	612937	Muscular dystrophy-dystroglycanopathy type C 15	AR	Other liver	Liver-related disease
DYNC2H1	613091	Short-rib thoracic dysplasia 3 with or without polydactyly Digenic recessive	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
DZIP1L	617610	Polycystic kidney disease 5	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
EARS2	614924	Combined oxidative phosphorylation deficiency 12	AR	Other liver	Liver-related disease
ENG	187300	Telangiectasia hereditary hemorrhagic type 1	AD	Other liver	Immuno/vascular
ENO3	612932	Glycogen storage disease XIII	AR	Other liver	Storage diseases
EOGT	615297	Adams-Oliver Syndrome 4	AR	Other liver	Liver-related disease
EPHX1	607748	Hypercholanemia familial	AR	Other liver	Liver-related disease
ETFA	231680	Glutaric acidemia IIA	AR	Other liver	Liver-related disease
ETFB	231680	Glutaric acidemia IIB	AR	Other liver	Liver-related disease
ETFDH	231680	Glutaric acidemia IIC	AR	Other liver	Liver-related disease
F5	227400	Factor V deficiency	AR	Other liver	Immuno/vascular
FASTKD2	618855	Combined oxidative phosphorylation deficiency 44	AR	Other liver	Mitochondrial dysfunction
FBP1	229700	Fructose-16-bisphosphatase deficiency	AR	Other liver	Storage diseases
FBXL4	615471	Mitochondrial DNA depletion syndrome 13	AR	Other liver	Mitochondrial dysfunction
FCHSD1	NA	NA	AR	Other liver	Endothelial disfunction
FECH	177000	Protoporphyria erythropoietic 1	AR	Other liver	Heme metabolism
FGA	616004	Dysfibrinogenemia congenital	AD and AR	Other liver	Immuno/vascular
FGB	202400	Afibrinogenemia, congenital	AR	Other liver	Immuno/vascular
C4ORF54/ FOPV	NA	NA	AD	Other liver	Endothelial disfunction
FOXRED1	618241	Mitochondrial complex I deficiency nuclear type 19	AR	Other liver	Mitochondrial dysfunction
SLC40A1/ FPN1	606069	Hemochromatosis type 4	AD	Other liver	Iron overload
FTH1	615517	Hemochromatosis type 5	AD	Other liver	Iron overload
FTL	600886	Hyperferritinemia-cataract syndrome	AD	Other liver	Iron overload
FUCA1	203000	Fucosidosis	AR	Other liver	Liver-related disease
G6PC1	232200	Glycogen storage disease Ia	AR	Other liver	Storage diseases
G6PD	300908	Hemolytic anemia G6PD deficient	XLD	Other liver	Hemolytic anemia
GAA	232300	Glycogen storage disease II (Pompe disease)	AR	Other liver	Storage diseases
GALC	245200	Krabbe disease	AR	Other liver	Liver-related disease
GALE	230350	Galactose epimerase deficiency	AR	Other liver	Storage diseases
GALK1	230200	Galactokinase deficiency with cataracts	AR	Other liver	Storage diseases
GALM	618881	Galactosemia IV	AR	Other liver	Liver-related disease
GALNS	253000	Mucopolysaccharidosis IVA	AR	Other liver	Storage diseases
GALT	234000	Galactosemia	AR	Other liver	Carbohydrate metabolism
GANAB	600666	Polycystic kidney disease 3	AD	Other liver	Congenital hepatic fibrosis_ciliopathy
GBA	230800	Gaucher disease type I	AR	Other liver	Storage diseases
GBE1	232500	Glycogen storage disease IV	AR	Other liver	Storage diseases

GCK	125851	MODY type II	AD	Other liver	Diabetes
GCKR	613463	rare variants reported associated to Liver disease	NA	Other liver	Liver-diseases susceptibility
GDF2	615560	Telangiectasia hereditary hemorrhagic type 5	AD	Other liver	Immuno/vascular
GFM1	609060	Combined oxidative phosphorylation deficiency 1	AR	Other liver	Liver-related disease
GIMAP5	619463	Portal hypertension noncirrhotic 2	AR	Other liver	Endothelial disfunction
GK	307030	Glycerol kinase deficiency	XLR	Other liver	Liver-related disease
GLA	301500	Fabry disease	XL	Other liver	Liver-related disease
GLB1	253010	Mucopolysaccharidosis type IVB	AR	Other liver	Storage diseases
GLDC	605899	Glycine encephalopathy	AR	Other liver	Liver-related disease
GLIS3	610199	Diabetes mellitus neonatal with congenital hypothyroidism	AR	Other liver	Diabetes
GLRX5	616860	Anemia sideroblastic 3 pyridoxine-refractory	AR	Other liver	Hemolytic anemia
GLYCTK	220120	D-glyceric aciduria	AR	Other liver	Liver-related disease
GM2A	272750	GM2-gangliosidosis AB variant	AR	Other liver	Liver-related disease
GNMT	606664	Glycine N-methyltransferase deficiency	AR	Other liver	Liver-related disease
GNPTAB	252500	Mucolipidosis II alpha/beta	AR	Other liver	Storage diseases
GPD1	614480	Hypertriglyceridemia transient infantile	AR	Other liver	Dyslipidemia
GPIHBP1	615947	Hyperlipoproteinemia type 1D	AR	Other liver	Dyslipidemia
GUCY2D	601777	Cone-rod dystrophy 6	AD and AR	Other liver	Mitochondrial dysfunction
GUSB	253220	Mucopolysaccharidosis VII	AR	Other liver	Storage diseases
GYG1	613507	Glycogen storage disease XV	AR	Other liver	Storage diseases
GYS1	611556	Glycogen storage disease muscle	AR	Other liver	Storage diseases
GYS2	240600	Glycogen storage disease Liver	AR	Other liver	Storage diseases
HADH	609975	Hyperinsulinemic hypoglycemia familial 4	AR	Other liver	Diabetes
HADHA	609016	Fatty Liver acute of pregnancy	AR	Other liver	Liver-related disease
HADHB	609015	Trifunctional protein deficiency	AR	Other liver	Liver-related disease
HAMP	613313	Hemochromatosis type 2B	AR	Other liver	Iron overload
HEXB	268800	Sandhoff disease infantile juvenile and adult forms	AR	Other liver	Liver-related disease
HFE	235200	Hemochromatosis	AR	Other liver	Iron overload
HJV	602390	Hemochromatosis type 2A	AR	Other liver	Iron overload
HGSNAT	252930	Mucopolysaccharidosis type IIIC (Sanfilippo C)	AR	Other liver	Storage diseases
HMBS	176000	Porphyria acute intermittent	AD	Other liver	Heme metabolism
HMGCL	246450	HMG-CoA lyase deficiency	AR	Other liver	Liver-related disease
HMGCS2	605911	HMG-CoA synthase-2 deficiency	AR	Other liver	Liver-related disease
HNF4A	125850	MODY type I	AD	Other liver	Diabetes
HP	614081	[Hypohaptoglobinemia]	NA	Other liver	Liver-related disease
HPD	276710	Tyrosinemia type III	AD and AR	Other liver	Liver-related disease
HPS1	203300	Hermansky-Pudlak syndrome 1	AR	Other liver	Liver-related disease
HSD17B13	620116	{Fatty Liver?isease, protection from}	NA	Other liver	Liver-diseases susceptibility

HYAL1	601492	Mucopolysaccharidosis type IX	AR	Other liver	Storage diseases
IARS1	617093	Growth retardation, impaired intellectual development, hypotonia, and hepatopathy	AR	Other liver	Liver-related disease
ICOS	607594	Immunodeficiency common variable 1	AR	Other liver	Immuno/vascular
IDS	309900	Mucopolysaccharidosis II	XLR	Other liver	Storage diseases
IDUA	607015	Mucopolysaccharidosis Ih/s	AR	Other liver	Storage diseases
IFIH1	615846	Aicardi-Goutieres syndrome 7	AR	Other liver	Liver-related disease
IFT122	218330	Cranioectodermal dysplasia 1	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
IFT140	266920	Short-rib thoracic dysplasia 9 with or without polydactyly	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
IFT43	617866	Short-rib thoracic dysplasia 18 with polydactyly	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
IL21R	615207	Immunodeficiency 56	AD and AR	Other liver	Immuno/vascular
IL2RA	601942	{Diabetes mellitus insulin-dependent susceptibility to 1}	AR	Other liver	Immuno/vascular
IL7R	608971	Severe combined immunodeficiency T-cell negative B-cell/natural killer cell-positive type	AR	Other liver	Immuno/vascular
INPP5E	213300	Joubert syndrome 1	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
INSR	609968	Hyperinsulinemic hypoglycemia familial 5	AD and AR	Other liver	Congenital hepatic fibrosis_ciliopathy
IRF3	616532	{Encephalopathy acute infection-induced (herpes-specific) susceptibility to 7}	AD	Other liver	Liver-diseases susceptibility
ITCH	613385	Autoimmune disease multisystem with facial dysmorphism	AR	Other liver	Immuno/vascular
KCNN3	618658	Zimmermann-Laband syndrome 3	AD	Other liver	Endothelial disfunction
KHK	229800	?[Fructosuria essential]	AR	Other liver	Liver-related disease
KRT18	215600	Cirrhosis cryptogenic	AR	Other liver	Liver-diseases susceptibility
LARS1	615438	Infantile Liver Failure syndrome 1	AR	Other liver	Liver-related disease
LARS2	617021	Hydrops lactic acidosis and sideroblastic anemia	AR	Other liver	Liver-related disease
LCAT	245900	Norum disease	AR	Other liver	Dyslipidemia
LDHA	612933	Glycogen storage disease XI	AR	Other liver	Storage diseases
LDHB	614128	[Lactate dehydrogenase-B deficiency]	NA	Other liver	Liver-related disease
LDLR	143890	Hypercholesterolemia familial 1	AD, AR	Other liver	Dyslipidemia
LDLRAP1	603813	Hypercholesterolemia familial 4	AR	Other liver	Dyslipidemia
LIPC	614025	Hepatic lipase deficiency	AR	Other liver	Dyslipidemia
LIPE	615980	Lipodystrophy familial partial type 6	AR	Other liver	Dyslipidemia
LIPT1	616299	Lipoyltransferase 1 deficiency	AR	Other liver	Dyslipidemia
LMF1	246650	Lipase deficiency combined	AR	Other liver	Dyslipidemia
LMNA	151660	Lipodystrophy familial partial type 2	AD	Other liver	Dyslipidemia
LMNB2	608709	{Lipodystrophy partial acquired susceptibility to}	AD and AR	Other liver	Dyslipidemia
LOX	617168	Aortic aneurysm familial thoracic 10	AD	Other liver	Immuno/vascular
LPA	618807	[LPA deficiency, congenital] {Coronary artery disease, susceptibility to}	AD	Other liver	Dyslipidemia
LPL	144250	Combined hyperlipidemia familial	AD and AR	Other liver	Dyslipidemia

LRBA	614700	Immunodeficiency common variable 8 with autoimmunity	AR	Other liver	Immuno/vascular
LRP5	617875	Polycystic Liver?isease 4 with or without kidney cysts	AD and AR	Other liver	Congenital hepatic fibrosis_ciliopathy
LYRM4	615595	Combined oxidative phosphorylation deficiency 19	AR	Other liver	Mitochondrial dysfunction
LYRM7	615838	Mitochondrial complex III deficiency nuclear type 8	AR	Other liver	Mitochondrial dysfunction
MAN2B1	248500	Mannosidosis alpha- types I and II	AR	Other liver	Storage diseases
MANBA	248510	Mannosidosis beta	AR	Other liver	Liver-related disease
MARS1	615486	Interstitial lung and Liver disease	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
MBOAT7	617188	Mental retardation autosomal recessive 57	AR	Other liver	Liver-diseases susceptibility
MC4R	61846	Obesity	AR	Other liver	Dyslipidemia
MCCC1	210200	3-Methylcrotonyl-CoA carboxylase 1 deficiency	AR	Other liver	Liver-related disease
MCCC2	210210	3-Methylcrotonyl-CoA carboxylase 2 deficiency	AR	Other liver	Liver-related disease
MCOLN1	252650	Mucolipidosis IV	AR	Other liver	Liver-related disease
MEFV	249100	Familial Mediterranean fever	AD and AR	Other liver	Liver-related disease
MEGF8	614976	Carpenter syndrome 2	AR	Other liver	Liver-related disease
MICOS13	618329	Combined oxidative phosphorylation deficiency 37	AR	Other liver	Liver-related disease
MOGS	606056	Congenital disorder of glycosylation type IIb	AR	Other liver	Storage diseases
MPI	602579	Congenital disorder of glycosylation type Ib	AR	Other liver	Storage diseases
MRM2	618567	Mitochondrial DNA depletion syndrome 17	AR	Other liver	Mitochondrial dysfunction
MRPL12	618951	Combined oxidative phosphorylation deficiency 45	AR	Other liver	Mitochondrial dysfunction
MRPL3	614582	Combined oxidative phosphorylation deficiency 9	AR	Other liver	Mitochondrial dysfunction
MRPL44	615395	Combined oxidative phosphorylation deficiency 16	AR	Other liver	Mitochondrial dysfunction
MRPS16	614980	Combined oxidative phosphorylation deficiency 2	AR	Other liver	Mitochondrial dysfunction
MRPS23	618952	Combined oxidative phosphorylation deficiency 46	AR	Other liver	Mitochondrial dysfunction
MRPS28	618958	Combined oxidative phosphorylation deficiency 47	AR	Other liver	Mitochondrial dysfunction
MS4A1	613495	Immunodeficiency common variable 5	AR	Other liver	Immuno/vascular
MTHFD1	617780	Combined immunodeficiency and megaloblastic anemia with or without hyperhomocysteinemia	AR	Other liver	Immuno/vascular
MTM1	310400	Myotubular myopathy X-linked	XLR	Other liver	Immuno/vascular
MTTP	200100	Abetalipoproteinemia	AR	Other liver	Dyslipidemia
MMUT	251000	Methylmalonic aciduria mut type	AR	Other liver	Liver-related disease
MVK	610377	Mevalonic aciduria	AD and AR	Other liver	Storage diseases
NAGA	609242	Kanzaki disease	AR	Other liver	Disorders of glycoprotein synthesis
NAGLU	252920	Mucopolysaccharidosis type IIIB	AD and AR	Other liver	Storage diseases
NBAS	616483	Infantile Liver Failure syndrome 2	AR	Other liver	Liver-related disease
NDUFA1	301020	Mitochondrial complex I deficiency nuclear type 12	XLR	Other liver	Mitochondrial dysfunction
NDUFA10	618243	Mitochondrial complex I deficiency nuclear type 22	AR	Other liver	Mitochondrial dysfunction

NDUFA11	618236	Mitochondrial complex I deficiency nuclear type 14	AR	Other liver	Mitochondrial dysfunction
NDUFAF1	618234	Mitochondrial complex I deficiency nuclear type 11	AR	Other liver	Mitochondrial dysfunction
NDUFAF2	618233	Mitochondrial complex I deficiency nuclear type 1	AR	Other liver	Mitochondrial dysfunction
NDUFAF3	618240	Mitochondrial complex I deficiency nuclear type 18	AR	Other liver	Mitochondrial dysfunction
NDUFAF4	618237	Mitochondrial complex I deficiency nuclear type 15	AR	Other liver	Mitochondrial dysfunction
NDUFAF5	618238	Mitochondrial complex I deficiency nuclear type 16	AR	Other liver	Mitochondrial dysfunction
NDUFB3	618246	Mitochondrial complex I deficiency nuclear type 25	AR	Other liver	Mitochondrial dysfunction
NDUFB9	618245	?Mitochondrial complex I deficiency nuclear type 24	AR	Other liver	Mitochondrial dysfunction
NDUFS1	618226	Mitochondrial complex I deficiency nuclear type 5	AR	Other liver	Mitochondrial dysfunction
NDUFS2	618228	Mitochondrial complex I deficiency nuclear type 6	AR	Other liver	Mitochondrial dysfunction
NDUFS3	618230	Mitochondrial complex I deficiency nuclear type 8	AR	Other liver	Mitochondrial dysfunction
NDUFS4	252010	Mitochondrial complex I deficiency nuclear type 1	AR	Other liver	Mitochondrial dysfunction
NDUFS6	618232	Mitochondrial complex I deficiency nuclear type 9	AR	Other liver	Mitochondrial dysfunction
NDUFV1	618225	Mitochondrial complex I deficiency nuclear type 4	AR	Other liver	Mitochondrial dysfunction
NDUFV2	618229	Mitochondrial complex I deficiency nuclear type 7	AR	Other liver	Mitochondrial dysfunction
NEK1	263520	Short-rib thoracic dysplasia 6 with or without polydactyly Digenic recessive	AD and AR	Other liver	Congenital hepatic fibrosis_ciliopathy
NFKB1	616576	Immunodeficiency common variable 12	AD	Other liver	Immuno/vascular
NFKB2	615577	Immunodeficiency common variable 1	AD	Other liver	Immuno/vascular
NFS1	619386	Combined oxidative phosphorylation deficiency 52	AR	Other liver	Liver-related disease
NGLY1	615273	Congenital disorder of deglycosylation	AR	Other liver	Liver-related disease
NMBR	NA	NA	NA	Other liver	Iron overload
NME8	610852	Ciliary dyskinesia primary 6	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
NOTCH1	616028	Adams-Oliver Syndrome 5	AD	Other liver	Liver-related disease
NUBPL	618242	Mitochondrial complex I deficiency nuclear type 21	AR	Other liver	Mitochondrial dysfunction
OFD1	311200	Orofaciodigital syndrome I	XLR	Other liver	Congenital hepatic fibrosis_ciliopathy
OTC	311250	Ornithine transcarbamylase deficiency	XLR	Other liver	Disorders of glycoprotein synthesis
PC	266150	Pyruvate carboxylase deficiency	AR	Other liver	Liver-related disease
PCK1	261680	Phosphoenolpyruvate carboxykinase deficiency cytosolic	AR	Other liver	Liver-related disease
PCK2	261650	PEPCK deficiency mitochondrial	AR	Other liver	Liver-related disease
PCSK7	NA	NA	NA	Other liver	Iron overload/Dyslipidemia
PCSK9	603776	Hypercholesterolemia familial 3	AD	Other liver	Dyslipidemia
PEPD	170100	Prolidase deficiency	AR	Other liver	Liver-related disease
PET100	619055	Mitochondrial complex IV deficiency, nuclear type 12	AR	Other liver	Mitochondrial dysfunction
PFKM	232800	Glycogen storage disease VII	AR	Other liver	Storage diseases
PGAM2	261670	Glycogen storage disease X	AR	Other liver	Storage diseases

PGK1	300653	Phosphoglycerate kinase 1 deficiency	XLR	Other liver	Liver-related disease
PGM1	614921	Congenital disorder of glycosylation type It	AR	Other liver	Storage diseases
PHKA1	300559	Muscle glycogenosis	XLR	Other liver	Storage diseases
PHKA2	306000	Glycogen storage disease type IXa2	XLR	Other liver	Storage diseases
PHKB	261750	Phosphorylase kinase deficiency of Liver?nd muscle	AR	Other liver	Storage diseases
PHKG2	613027	Glycogen storage disease IXc	AR	Other liver	Storage diseases
PHYH	266500	Refsum disease	AR	Other liver	Liver-related disease
PIEZO1	194380	Dehydrated hereditary stomatocytosis with or without pseudohyperkalemia and/or perinatal edema	AD and AR	Other liver	Hemolytic anemia
PIGA	301072	Neurodevelopmental disorder with epilepsy and hemochromatosis	XLR	Other liver	Iron overload
PIGM	610293	Glycosylphosphatidylinositol deficiency	AR	Other liver	Liver-related disease
PIK3R1	616005	Immunodeficiency 36	AD and AR	Other liver	Immuno/vascular
PKD1	173900	Polycystic kidney disease 1	AD	Other liver	Congenital hepatic fibrosis_ciliopathy
PKD2	613095	Polycystic kidney disease 2	AD	Other liver	Congenital hepatic fibrosis_ciliopathy
PKLR	266200	Pyruvate kinase deficiency	AD and AR	Other liver	Liver-related disease
PLIN1	613877	Lipodystrophy familial partial type 4	AD	Other liver	Dyslipidemia
PMM2	212065	Congenital disorder of glycosylation type Ia	AR	Other liver	Disorders of glycoprotein synthesis
PNPLA2	610717	Neutral lipid storage disease with myopathy	AR	Other liver	Dyslipidemia
PNPLA3	613282	{Fatty Liver Disease nonalcoholic susceptibility to 1}	Mu	Other liver	Liver-diseases susceptibility
PNPT1	614932	Combined oxidative phosphorylation deficiency 13	AR	Other liver	Liver-related disease
POLD1	615381	Mandibular hypoplasia deafness progeroid features and lipodystrophy syndrome	AD	Other liver	Dyslipidemia
POLG2	618528	Mitochondrial DNA depletion syndrome 16	AD and AR	Other liver	Mitochondrial dysfunction
POMC	609734	Obesity adrenal insufficiency and red hair due to POMC deficiency	AR	Other liver	Liver-related disease
PPARG	604367	Lipodystrophy familial partial type 3	AD	Other liver	Dyslipidemia
PPOX	176200	Porphyria variegata	AD	Other liver	Heme metabolism
PRF1	603553	Hemophagocytic lymphohistiocytosis familial 2	AR	Other liver	Immuno/vascular
PRKAG2	261740	Glycogen storage disease of heart lethal congenital	AD	Other liver	Storage diseases
PRKCD	615559	Autoimmune lymphoproliferative syndrome type III	AR	Other liver	Immuno/vascular
PRKCSH	174050	Polycystic Liver disease 1	AD	Other liver	Congenital hepatic fibrosis_ciliopathy
PSAP	610539	Gaucher disease atypical	AR	Other liver	Liver-related disease
PSMB4	617591	Proteasome-associated autoinflammatory syndrome 3 and digenic forms	AR	Other liver	Immuno/vascular
PSMB8	256040	Proteasome-associated autoinflammatory syndrome 1 and digenic forms	AR	Other liver	Immuno/vascular
PTPRC	608971	Severe combined immunodeficiency T cell-	AR	Other liver	Immuno/vascular

		negative B-cell/natural killer-cell positive			
PUS1	600462	Myopathy lactic acidosis and sideroblastic anemia 1	AR	Other liver	Liver-related disease
PYGL	232700	Glycogen storage disease VI	AR	Other liver	Storage diseases
PYGM	232600	McArdle disease	AR	Other liver	Storage diseases
QRSL1	618835	Combined oxidative phosphorylation deficiency 40	AR	Other liver	Liver-related disease
RBPJ	614814	Adams-Oliver syndrome 3	AD	Other liver	Liver-related disease
RFT1	612015	Congenital disorder of glycosylation type In	AR	Other liver	Disorders of glycoprotein synthesis
RFX5	615710	Mitchell-Riley syndrome	AR	Other liver	Liver-related disease
RFXANK	209920	MHC class II deficiency complementation group B	AR	Other liver	Immuno/vascular
RFXAP	209920	Bare lymphocyte syndrome type II complementation group D	AR	Other liver	Immuno/vascular
RHAG	185000	Overhydrated hereditary stomatocytosis	AD	Other liver	Hemolytic anemia
RINT1	618641	Infantile Liver?ailure syndrome 3	AR	Other liver	Liver-related disease
RMND1	614922	Combined oxidative phosphorylation deficiency 11	AR	Other liver	Liver-related disease
RPGRIP1L	611560	Joubert syndrome 7	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
RPL11	612562	Diamond-Blackfan anemia 7	AD	Other liver	Hemolytic anemia
RPS7	612563	Diamond-Blackfan anemia 8	AD	Other liver	Hemolytic anemia
RRM2B	612075	Mitochondrial DNA depletion syndrome 8A	AD and AR	Other liver	Mitochondrial dysfunction
RTEL1	616373	Pulmonary fibrosis and/or bone marrow failure, telomere-related, 3	AD	Other liver	Congenital hepatic fibrosis_ciliopathy
SC5D	607330	Lathosterolosis	AR	Other liver	Dyslipidemia
SCARB1	601762	[High density lipoprotein cholesterol level QTL6]	NA	Other liver	Dyslipidemia
SCO1	619048	Mitochondrial complex IV deficiency, nuclear type 4	AR	Other liver	Mitochondrial dysfunction
SCO2	604377	Mitochondrial complex IV deficiency, nuclear type 2	AD and AR	Other liver	Mitochondrial dysfunction
SEC63	617004	Polycystic Liver?isease 2	AD	Other liver	Congenital hepatic fibrosis_ciliopathy
SERAC1	614739	3-methylglutaconic aciduria with deafness encephalopathy and Leigh-like syndrome	AR	Other liver	Mitochondrial dysfunction
SERPINC1	613118	Thrombophilia 7 due to antithrombin III deficiency	AD AR	Other liver	Immuno/vascular
SGSH	252900	Mucopolysaccharidosis type IIIA	AR	Other liver	Storage diseases
SH2D1A	382400	Lymphoproliferative syndrome X-linked 1	XLR	Other liver	Immuno/vascular
SLC11A2	206100	Anemia hypochromic microcytic with iron overload 1	AR	Other liver	Iron overload
SLC17A5	206992	Sialic acid storage disorder infantile	AR	Other liver	Liver-related disease
SLC22A5	212140	Carnitine deficiency systemic primary	AR	Other liver	Disorders of glycoprotein synthesis
SLC25A15	238970	Hyperornithinemia-hyperammonemia-homocitrullinemia syndrome	AR	Other liver	Liver-related disease
SLC25A20	212138	Carnitine-acylcarnitine translocase deficiency	AR	Other liver	Disorders of glycoprotein synthesis
SLC25A4	615418	Mitochondrial DNA depletion syndrome 12B AR	AD and AR	Other liver	Mitochondrial dysfunction
SLC2A2	227810	Fanconi-Bickel syndrome	AR	Other liver	Storage diseases

SLC30A10	601328	Hypermanganesemia with dystonia 1	AR	Other liver	Liver-related disease
SLC37A4	232220	Glycogen storage disease Ib	AR	Other liver	Storage diseases
SLC39A8	616721	Congenital disorder of glycosylation type IIn	AR	Other liver	Storage diseases
SLC7A7	222700	Lysinuric protein intolerance	AR	Other liver	Liver-related disease
SLX4	613951	Fanconi anemia complementation group P	AR	Other liver	Liver-related disease
SP110	235550	Hepatic venoocclusive disease with immunodeficiency	AR	Other liver	Immuno/vascular
SQOR	619221	Sulfide:quinone oxidoreductase deficiency	AR	Other liver	Liver-related disease
SRD5A3	612379	Congenital disorder of glycosylation type Iq	AR	Other liver	Disorders of glycoprotein synthesis
STAT1	614162	Immunodeficiency 31C	AD and AR	Other liver	Immuno/vascular
STAT2	616636	Immunodeficiency 44	AR	Other liver	Immuno/vascular
STN1	617341	Cerebroretinal microangiopathy with calcifications and cysts 2	AR	Other liver	Liver-related disease
STT3B	615597	Congenital disorder of glycosylation type Ix	AR	Other liver	Disorders of glycoprotein synthesis
SUMF1	272200	Multiple sulfatase deficiency	AR	Other liver	Liver-related disease
SYK	619381	Immunodeficiency 82 with systemic inflammation	AD	Other liver	Immuno/vascular
TACO1	220110	Mitochondrial complex IV deficiency, nuclear type 1	AR	Other liver	Mitochondrial dysfunction
TALDO1	606003	Transaldolase deficiency	AR	Other liver	Hepatocellular disease
TARS2	615918	Combined oxidative phosphorylation deficiency 21	AR	Other liver	Liver-related disease
TCTN2	616654	Joubert syndrome 24	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
TERC	614743	Pulmonary fibrosis idiopathic susceptibility to	AD	Other liver	Liver-related disease
TERT	614742	{Pulmonary fibrosis and/or bone marrow failure telomere-related 1}	AD	Other liver	Liver-related disease
TF	209300	Atransferrinemia	AR	Other liver	Iron overload
TFAM	617156	Mitochondrial DNA depletion syndrome 15 (hepatocerebral type)	AR	Other liver	Mitochondrial dysfunction
TFR2	604250	Hemochromatosis type 3	AR	Other liver	Iron overload
TKFC	618805	Triokinase and FMN cyclase deficiency syndrome	AR	Other liver	Liver-related disease
TM6SF2	NA	NA	NA	Other liver	Liver-diseases susceptibility
TMC4	NA	NA	NA	Other liver	Liver-diseases susceptibility
TMEM126B	618250	Mitochondrial complex I deficiency nuclear type 29	AR	Other liver	Mitochondrial dysfunction
TMEM138	614465	Joubert syndrome 16	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
TMEM165	614727	Congenital disorder of glycosylation type IIk	AR	Other liver	Disorders of glycoprotein synthesis
TMEM199	616829	Congenital disorder of glycosylation type IIp	AR	Other liver	Disorders of glycoprotein synthesis
TMEM231	614970	Joubert syndrome 2	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
TMEM237	614424	Joubert syndrome 14	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
TNFAIP3	616744	Autoinflammatory syndrome familial Behcet-like 1	AD	Other liver	Immuno/vascular
TNFRSF13B	240500	Immunodeficiency common variable 2	AR	Other liver	Immuno/vascular

TREX1	192315	Vasculopathy retinal with cerebral leukodystrophy	AD and AR	Other liver	Immuno/vascular
TRMT5	616539	Peripheral neuropathy with variable spasticity, exercise intolerance, and developmental delay	AR	Other liver	Endothelial disfunction
TRMT10C	616974	Combined oxidative phosphorylation deficiency 3	AR	Other liver	Liver-related disease
UBE2T	616435	Fanconi anemia complementation group T	AR	Other liver	Immuno/vascular
UNC13D	608898	Hemophagocytic lymphohistiocytosis familial 3	AR	Other liver	Immuno/vascular
UQCC2	615824	Mitochondrial complex III deficiency nuclear type 7	AR	Other liver	Mitochondrial dysfunction
UQCRB	615158	Mitochondrial complex III deficiency nuclear type 3	AR	Other liver	Mitochondrial dysfunction
UQCRC2	615160	Mitochondrial complex III deficiency nuclear type 5	AR	Other liver	Mitochondrial dysfunction
UQCRQ	615159	Mitochondrial complex III deficiency nuclear type 4	AR	Other liver	Mitochondrial dysfunction
UROD	176100	Porphyria hepatoerythropoietic	AD	Other liver	Heme metabolism
WDR19	614377	Nephronophthisis 13	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
WDR34/ DYNC2I2	615633	Short-rib thoracic dysplasia 11 with or without polydactyly	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
WDR35	614091	Short-rib thoracic dysplasia 7 with or without polydactyly	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
WDR60/ DYNC2I1	615503	Short-rib thoracic dysplasia 8 with or without polydactyly	AR	Other liver	Congenital hepatic fibrosis_ciliopathy
XIAP	300635	Lymphoproliferative syndrome X-linked 2	XLR	Other liver	Immuno/vascular
XPNPEP3	613159	Nephronophthisis-like nephropathy 1	AR	Other liver	Congenital hepatic fibrosis_ciliopathy

Supplementary Table 3: Clinical details of patients with primary sclerosing cholangitis with unusual features.

	PSC with unusual features (n=12)
Type, n (%) Large duct Small duct	 10 (83.3%) 2 (16.7%)
Age at disease onset (years), mean (SD)	32.6 (11.5)
Age at genetic test (years), mean (SD)	41.0 (12.1)
Time from disease onset to genetic test (years), mean (SD)	8.4 (4.5)
Sex, male (%)	7 (58.3%)
Cholestatic liver disease in first degree relatives, n (%)	4 (33.3%)
Pruritus, n (%)	1 (8.3%)
Liver biopsy, n (%)	9 (75.0%)
Inflammatory bowel disease, n (%)	0 (0.0%)
ALP (IU/L), mean (SD)	246 (175)
GGT (IU/L), mean (SD)	191 (148)
TBIL (mg/dL), mean (SD)	1.0 (0.7)

Abbreviations: PSC, primary sclerosing cholangitis. SD, standard deviation. ALP, alkaline phosphatase. GGT, gamma-glutamyltrasferase. TBIL, total bilirubin.

Supplementary Table 4: Histological features of patients who underwent liver biopsy.

ID	Liver biopsy	Inflammatory bile duct injury	Ductular reaction	Periductular fibrosis	Biliary metaplasia	Steatosis	Iron deposition	Staging (Ishak)
1	no							
2	n/a							
3	yes	1	0	1	n/a	yes, 5%	no	1
4	yes	1	1	1	n/a	no	no	1
5	yes	1	1	0	n/a	no	no	0
6	yes	1	2	2	1	yes, 5%	no	1
7	yes	0	0	0	1	no	no	0
8	yes	0	1	1	2	no	no	1
9	yes	1	2	2	1	no	yes, mild	2
10	n/a							
11	n/a							
12	yes	1	0	0	n/a	no	no	0
13	yes	0	0	0	n/a	no	no	0
14	no	1	0	2	1	no	yes, mild	1
15	n/a							
16	no							
17	yes	1	1	0	1	no	no	0
18	yes	1	1	2	1	no	no	2
19	no							
20	yes	1	1	0	n/a	yes, 10%	no	0
21	yes	0	0	0	1	no	yes, mild	0

Inflammatory bile duct injury: absent, 0; focal (<10% portal tracts (PT)), 1; multifocal (10-50% PT) 2; diffuse (>50% PT), 3.
Ductular reaction: absent, 0; focal (<10% PT), 1; multifocal (10-50% PT), 2; diffuse (>50% PT), 3.
Periductular fibrosis: absent 0; focal (<10% PT), 1; multifocal (10-50% PT), 2; diffuse (>50% PT), 3.
Biliary metaplasia: absent, 0; focal (<10% PT), 1; multifocal (10-50% PT), 2; diffuse (>50% PT), 3.

Supplementary Table 5: Demographics, clinical and genetic information of each patient.

Pt	Phenotype	Age diagnosis	Age test	Sex	Ethnicity	Family history	Gene	Classes	transcript	dbSNP	Nucleotide change	Protein change	zygosity	gnomAD NFE	CADD	ACMG	Genetic diagnosis	Associated disease	OMIM	inheritance
1	RL	37	39	M	caucasian	yes	*ABCB4*	PFIC	NM_000443	NA	c.754G>C	p.Ala252Pro	Het	NA	33	LP	Definite	Low phospholipid-associated cholelithiasis	#600803	AD
							ABCB4	PFIC	NM_000443	rs138773456	c.2144C>T	p.Thr715Ile	Het	0.0009	16	VUS	Possible contribution	Low phospholipid-associated cholelithiasis	#600803	AD
							*PKD1L1**	non-PFIC	NM_138295	rs372058157	c.3310G>A	p.Glu1104Lys	Het	0.00003	12	VUS				
							MYO5B	PFIC	NM_001080467	rs1942418	c.3962G>A	p.Gly1321Glu	Het	0.04781	24	B				
							*AHI1**	other liver	NM_001134830	rs200816459	c.2672G>A	p.Arg891Gln	Het	0.0001	34	VUS				
							CFTR	non-PFIC	NM_000492	rs1800076	c.224G>A	p.Arg75Gln	Het	0.02851	27	LB				
							PEX16	non-PFIC	NM_057174	rs11553094	c.307G>A	p.Val103Met	Het	0.02	23	LB				
							*PKD1L1**	non-PFIC	NM_138295	rs199719516	c.5770-7G>A	//	Het	0.0001763	NA	LB				
							*PKD1L1**	non-PFIC	NM_138295	rs201106567	c.399-6A>G	//	Het	0.002165	NA	B				
							PLEC	non-PFIC	NM_201380	rs138924815	c.1298G>A	p.Arg433Gln	Het	0.02	25	B				
							*TMEM67**	non-PFIC	NM_153704	rs35765535	c.1309C>G	p.Leu437Val	Het	0.003054	14	LB				
							ANK1	other liver	NM_001142446	rs2304877	c.1955G>A	p.Arg652His	Het	0.04	23	B				
							COG2	other liver	NM_001145036	rs143526339	c.1532C>G	p.Thr511Ser	Het	0.004221	7	LB				
							*DYNC2H1**	other liver	NM_001377	rs61898615	c.2860G>A	p.Glu954Lys	Het	0.02	24	B				
							EARS2	other liver	NM_001083614	rs201941745	c.209G>T	p.Ser70Ile	Het	0.0006179	23	LB				
							FBXL4	other liver	NM_001278716	NA	c.513-5G>T	//	Het	NA	NA	VUS				
							LRBA	other liver	NM_006726	rs1313934523	c.149T>C	p.Val50Ala	Het	0.000008	26	VUS				
							PIEZO1	other liver	NM_001142864	rs372188504	c.635-4G>A	//	Het	0.000652	NA	LB				
							*PKD1**	other liver	NM_001009944	rs147350387	c.8123C>T	p.Thr2708Met	Het	0.01744	26	LB				
							UROD	other liver	NM_000374	rs36033115	c.758T>A	p.Leu253Gln	Het	0.007086	22	B				
2	RL	21	38	F	caucasian	no	*ABCB4*	PFIC	NM_000443	rs754287486	c.526C>T	p.Arg176Trp	Het	0.00001	26	P	Definite	Low phospholipid-associated cholelithiasis	#600803	AD
							ABCB4	PFIC	NM_000443	rs8187788	c.217C>G	p.Leu73Val	Het	0.001	18	VUS				
							ABCC12	non-PFIC	NM_033226	NA	c.3071G>A	p.Trp1024Ter	Het	0.02	42	VUS				

							NOTCH2	non-PFIC	NM_024408	rs782566552	c.665A>G	p.Tyr222Cys	Het	0.039	24	VUS				
							PLEC	non-PFIC	NM_201384	rs782134950	c.1270C>T	p.Arg424Trp	Het	0.000018	30	VUS				
							*NPHP1**	non-PFIC	NM_001128178	rs765568261	c.426G>T	p.Glu142Asp	Het	0.000032	14	LB				
							*NPHP3**	non-PFIC	NM_153240	rs34391943	c.3550G>A	p.Ala1184Thr	Het	0.008	25	B				
							PEX12	non-PFIC	NM_000286	rs147530802	c.102A>T	p.Arg34Ser	Het	0.005	25	LB				
							DOCK6	other liver	NM_020812	rs375012919	c.3532C>T	p.Arg1178Trp	Het	0.0008	26	VUS				
							NBAS	other liver	NM_015909	rs200344246	c.256A>C	p.Lys86Gln	Het	0.0006	23	VUS				
							OFD1	other liver	NM_003611	rs759835018	c.2884A>G	p.Met962Val	Het	0.0001	24	VUS				
							SLC11A2	other liver	NM_000617	rs115874705	c.625G>A	p.Ala209Thr	Het	0.0015	32	VUS				
							TMC4	other liver	NM_144686	rs368252966	c.271A>G	p.Met91Val	Het	0.0012	22	VUS				
							ACOX1	other liver	NM_004035	rs145082938	c.80C>T	p.Pro27Leu	Het	0.0035	23	LB				
							ATP7B	other liver	NM_000053	rs60986317	c.4301C>T	p.Thr1434Met	Het	0.002	22	LB				
							COQ2	other liver	NM_015697	rs112033303	c.64A>T	p.Arg22*	Het	0.018	26	LB				
							*DYNC2H1**	other liver	NM_001377	rs112718117	c.195+7T>C	//	Het	0.01	4	LB				
							*DYNC2H1**	other liver	NM_001377	rs78309870	c.9353+7G>A	//	Het	0.009	1	LB				
							G6PD	other liver	NM_001360016	rs1557230573	c.448G>A	p.Val150Ile	Het	0.000005	24	LP				
							GALM	other liver	NM_138801	rs200292259	c.566T>C	p.Ile189Thr	Het	0.0012	25	LB				
							*PKD1**	other liver	NM_001009944	NA	c.8659C>G	p.His2887Asp	Het	0	5	LB				
							PRKCD	other liver	NM_006254	rs150331740	c.1213G>A	p.Ala405Thr	Het	0.0004	16	LB				
							INPP5K	other	NM_016532	rs750781027	c.67G>A	p.Val23Met	Het	0.0007	24	LP				
3	IC	40	43	F	caucasian	no	*SERPINA1*	non-PFIC	NM_000295	rs28931570	c.187C>T	p.Arg63Cys	Het	0.002	26	P	Possible contribution	Alpha-1-antitrypsin deficiency	# 613490	AR
							PEX1	non-PFIC	NM_000466	rs182452430	c.3503A>G	p.Asp1168Gly	Het	0.0004	23	VUS	Possible contribution			
							SLC10A2	non-PFIC	NM_000452	rs56398830	c.868C>T	p.Pro290Ser	Het	0.013	28	B				
							CFTR	non-PFIC	NM_000492	rs1800100	c.2002C>T	p.Arg668Cys	Het	0.009573	33	B				
							*IFT172**	non-PFIC	NM_015662	rs61747073	c.2723G>A	p.Arg908Gln	Het	0.01947	21	B				
							*CEP120**	other liver	NM_001375405	na	c.2195A>G	p.Glu732Gly	Het	NA	25	VUS				
							*PKD2**	other liver	NM_000297	rs775470869	c.2428G>A	p.Asp810Asn	Het	0.00005	27	VUS				
							MVK	other liver	NM_001114185	rs28934897	c.1129G>A	p.Val377Ile	Het	0.002	20	LP				
							APOB	other liver	NM_000384	rs12713844	c.3337G>C	p.Asp1113His	Het	0.01	24	LB				
							NBAS	other	NM_015909	rs116210837	c.3392G>A	p.Arg1131His	Het	0.03	25	B				

								liver												
							DCT	other	NM_001129889	rs937496254	c.448A>T	p.Lys150Ter	Het	NA	34	LP				
4	IC	42	57	F	caucasian	no	*TJP2*	PFIC	NM_001170416	rs138241615	c.278C>T	p.Thr93Met	Het	0.002	27	VUS	Possible contribution	Heterozygous cholestasis, progressive familial intrahepatic 4	# 615878	AR
							DHCR7	non-PFIC	NM_001360	rs139724817	c.988G>A	p.Val330Met	Het	0.0004955	27	VUS				
							PLEC	non-PFIC	NM_201380	rs145977158	c.8362C>T	p.Arg2788Trp	Het	0.0002	29	B				
							PLEC	non-PFIC	NM_201380	rs35723243	c.8461C>T	p.Arg2821Trp	Het	0.03	24	B				
							*DYNC2H1**	other liver	NM_001377	rs201043335	c.3419G>T	p.Gly1140Val	Het	0.0006	20	VUS				
							IFIH1	other liver	NM_022168	rs145520044	c.1121G>A	p.Arg374His	Het	0.0007	11	VUS				
							IFIH1	other liver	NM_022168	rs35732034	c.2807+1G>A	//	Het	0.009	27	VUS				
							NFKB1	other liver	NM_003998	rs368017285	c.2273A>G	p.Asp758Gly	Het	0.00004	29	VUS				
							*ALMS1**	other liver	NM_001378454	rs28730854	c.6299C>T	p.Ser2100Leu	Het	0.04	23	B				
							BTD	other liver	NM_000060	rs13078881	c.1330G>C	p.Asp444His	Het	0.04	21	P				
							CBS	other liver	NM_000071	rs201372812	c.133C>T	p.Arg45Trp	Het	0.0001947	29	LB				
							CR2	other liver	NM_001006658	rs201760344	c.640C>T	p.Arg214Cys	Het	0.00005	24	LB				
							HFE	other liver	NM_000410	rs1799945	c.187C>G	p.His63Asp	Het	0.15	21	LP				
							HNF4A	other liver	NM_178849	rs1800961	c.416C>T	p.Thr139Ile	Het	0.03222	25	LB				
							HPS1	other liver	NM_000195	rs58548334	c.11T>C	p.Val4Ala	Het	0.02607	25	LB				
							NOTCH1	other liver	NM_017617	rs750169914	c.3694G>A	p.Val1232Met	Het	0.00003	14	LB				
							PNPLA2	other liver	NM_020376	rs140201358	c.756C>G	p.Asn252Lys	Het	0.01381	24	LB				
							UNC13D	other liver	NM_199242	rs758000434	c.2581G>A	p.Gly861Ser	Het	0.00001	30	VUS				
5	IC	22	38	F	caucasian	yes	*ABCC2*	non-PFIC	NM_000392	rs201874841	c.2714G>T	p.Arg905Ile	Het	0.00003	24	VUS	Possible contribution	Dubin-Johnson syndrome	# 237500	AR
							PEX5	non-PFIC	NM_001351132	rs373763823	c.966+3G>A	//	Het	0.00006	6	VUS	Possible contribution			
							SERPINA1	non-PFIC	NM_000295	rs17580	c.863A>T	p.Glu288Val	Het	0.03	25	LP				
							ABCD3	non-PFIC	NM_002858	rs142075958	c.155G>T	p.Gly52Val	Het	0.006	22	LB				
							PEX6	non-PFIC	NM_000287	rs61752141	c.235G>C	p.Ala79Pro	Het	0.02	22	LB				
							*IFT172**	non-PFIC	NM_015662	rs148624326	c.3401G>T	p.Arg1134Leu	Het	0.005	30	LB				
							POLG2	other liver	NM_007215	NA	c.1111-1G>C	//	Het	0	34	P				
							ACADVL	other liver	NM_000018	rs146379816	c.1591C>T	p.Arg531Trp	Het	0.0004	25	VUS				
							DYNC2I1-	other liver	NM_018051	rs754130259	c.2052G>T	p.Trp684Cys	Het	0.00008	27	VUS				

							WDR60*													
							ANK1	other liver	NM_000037	rs749236684	c.2276C>A	p.Ser759Tyr	Het	0.00003	25	VUS				
							GLIS3	other liver	NM_001042413	rs200694226	c.2339G>A	p.Arg780Gln	Het	0.00007	21	VUS				
							AGL	other liver	NM_000642	rs149210307	c.2390A>G	p.Asn797Ser	Het	0.0017	23	LB				
							APOB	other liver	NM_000384	rs533617	c.5768A>G	p.His1923Arg	Het	0.03	25	LB				
							ATP7B	other liver	NM_000053	rs74567941	c.3580A>G	p.Ile1194Val	Het	0.00004	15	LB				
							F5	other liver	NM_000130	rs9332701	c.6443T>C	p.Met2148Thr	Het	0.03	25	LB				
							IFT140*	other liver	NM_014714	rs150903791	c.1541T>A	p.Leu514His	Het	0.004	24	LB				
							NBAS	other liver	NM_015909	rs76459791	c.1093G>C	p.Asp365His	Het	0.008	27	LB				
							NOTCH1	other liver	NM_017617	rs61751543	c.3836G>A	p.Arg1279His	Het	0.015	23	B				
							PKD1*	other liver	NM_001009944	rs146507511	c.10351G>A	p.Asp3451Asn	Het	0.0002	24	LB				
							TF	other liver	NM_001063	rs185023567	c.1688-4C>A	//	Het	0.003	//	LB				
							TYR	other	NM_000372	rs151206295	c.1064C>T	p.Ala355Val	Het	0.0001	24.2	P				
6	IC and SLD	33	55	F	caucasian	no	MBOAT7	other liver	NM_024298	rs766158021	c.226C>G	p.Leu76Val	Het	0.00001	24	VUS	Possible contribution	SLD	//	//
							PKHD1*	non-PFIC	NM_138694	rs76572975	c.11525G>T	p.Arg3842Leu	Het	0.02	23	B				
							CFTR	non-PFIC	NM_000492	rs1800076	c.224G>A	p.Arg75Gln	Het	0.02851	27	B				
							ALMS1*	other liver	NM_001378454	rs759735286	c.12293G>A	p.Arg4098Lys	Het	0.00008	11	VUS				
							CPT2	other liver	NM_000098	rs144658100	c.1025T>C	p.Met342Thr	Het	0.00149	23	VUS				
							SLX4	other liver	NM_032444	rs137976282	c.421G>T	p.Gly141Trp	Het	0.001169	24	VUS				
							TFR2	other liver	NM_003227	rs41303495	c.1127C>A	p.Ala376Asp	Het	0.004	26	VUS				
							CTC1	other liver	NM_025099	rs62624978	c.1241G>C	p.Gly414Ala	Het	0.01842	22	B				
							ALMS1*	other liver	NM_001378454	rs28730854	c.6299C>T	p.Ser2100Leu	Het	0.04	23	B				
							NMBR	other liver	NM_002511	rs138994608	c.443C>A	p.Pro148His	Het	0.03185	28	B				
7	IC	38	46	M	caucasian	no	ABCC2	non-PFIC	NM_000392	rs1472214411	c.468+1G>A	//	Hom	0.00008	25	LP	Definite	Dubin-Johnson syndrome	#237500	AR
							ABCC2	non-PFIC	NM_000392	rs56131651	c.842G>A	p.Ser281Asn	Hom	0.007	24	VUS		Dubin-Johnson syndrome	#237500	AR
							SLC10A2	non-PFIC	NM_000452	rs143297386	c.230G>A	p.Gly77Glu	Het	0.0002	30	VUS				
							MYO5B	PFIC	NM_001080467	rs61737448	c.2343G>C	p.Lys781Asn	Het	0.002041	22	B				
							JAG1	non-PFIC	NM_000214	rs149366993	c.1439C>T	p.Ala480Val	Het	0.0004	23	B				
							PEX16	non-PFIC	NM_057174	rs11553094	c.307G>A	p.Val103Met	Het	0.02	23	B				

							PEX19	non-PFIC	NM_000433	rs141133579	c.771+3A>G	//	Het	0.006234	NA	B				
							PEX26	non-PFIC	NM_018671	rs2234338	c.*855-7C>T	//	Het	0.01902	NA	B				
							PLEC	non-PFIC	NM_201380	rs78461695	c.12131C>T	p.Thr4044Met	Het	0.01	26	B				
							ALG1	other liver	NM_001193644	rs145474820	c.191C>A	p.Thr64Asn	Het	0.003835	25	LB				
							ANK1	other liver	NM_000452	rs77646170	c.-207C>G	//	Hom	NA	NA	B				
							LMF1	other liver	NM_022773	rs35168378	c.1091G>A	p.Arg364Gln	Het	0.02932	27	B				
							NCF2	other liver	NM_000392	rs35012521	c.1256A>T	p.Asn419Ile	Het	0.006749	28	LB				
							PIEZO1	other liver	NM_001142864	rs139051768	c.5195C>T	p.Thr1732Met	Het	0.01	26	B				
							DCAF17	other	NM_025000	rs172325465	c.906G>A	p.Trp302Ter	Het	0.00001761	40	P				
							SURF1	other	NM_001280787	rs136221678	c.240+1G>T	//	Het	0.00004	24.2	P				
							TMEM70	other	NM_001040613	rs74893388	c.317-2A>G	//	Het	0.00009	24.7	P				
							UPB1	other	NM_016327	rs24919586	c.917-1G>A	//	Het	0.002699	23.9	P				
8	IC	52	56	F	caucasian	no	*ABCC2*	non-PFIC	NM_000392	rs56131651	c.842G>A	p.Ser281Asn	Het	0.007	24	VUS	Possible contribution	Dubin-Johnson syndrome	#237500	AR
							*PKHD1**	non-PFIC	NM_138694	rs150838488	c.5768A>T	p.Gln1923Leu	Het	0.002	19	VUS	Possible contribution			
							SERPINA1	non-PFIC	NM_000295	rs17580	c.863A>T	p.Glu288Val	Het	0.03	25	LP				
							*TTC21B**	non-PFIC	NM_024753	rs572065013	c.-17C>T	//	Het	0.004	na	VUS	Possible contribution			
							ABCB11	PFIC	NM_003742	rs138642043	c.2093G>A	p.Arg698His	Het	0.003	26	LB				
							ABCB11	PFIC	NM_003742	rs11568363	c.389+8G>A	//	Het	0.01	NA	LB				
							*ZFYVE19**	PFIC	NM_001077268	rs116166434	c.214C>G	p.Leu72Val	Het	0.002173	0,8	B				
							*ALMS1**	other liver	NM_001378454	rs28730854	c.6299C>T	p.Ser2100Leu	Het	0.04	23	B				
							BSCL2	other liver	NM_001122955	rs145649423	c.1280T>C	p.Leu427Pro	Het	0.004977	17	B				
							*DYNC2I1-WDR60**	other liver	NM_018051	rs759916390	c.2959A>G	p.Ser987Gly	Het	0.00003	23	VUS				
							EOGT	other liver	NM_173654	rs376499113	c.301G>A	p.Asp101Asn	Het	0.001055	25	VUS				
							HNF4A	other liver	NM_178849	rs1800961	c.416C>T	p.Thr139Ile	Het	0.03222	25	LB				
							LRBA	other liver	NM_006726	NA	c.4894G>A	p.Ala1632Thr	Het	NA	19	VUS				
							NCF2	other liver	NM_000433	rs35012521	c.1256A>T	p.Asn419Ile	Het	0.006749	28	LB				
							NFS1	other liver	NM_021100	rs112446981	c.437A>G	p.Lys146Arg	Het	0.007501	20	B				
							POLG2	other liver	NM_007215	rs17850455	c.1247G>C	p.Gly416Ala	Het	0.01	25	B				
							PYGM	other liver	NM_005609	rs113806080	c.2009C>T	p.Ala670Val	Het	0.005162	34	LB				
							UNC13D	other liver	NM_199242	rs9904366	c.175G>A	p.Ala59Thr	Het	0.0156	22	B				

9	IC	23	35	M	caucasian	yes	*ABCG8*	non-PFIC	NM_022437	rs137852991	c.1234C>T	p.Arg412Ter	Het	0.0001	43	P	Possible contribution	Sitosterolemia 1	#210250	AR
							ABCG8	non-PFIC	NM_022437	rs376362072	c.578C>T	p.Ala193Val	Het	0.00009	34	VUS	Possible contribution	Sitosterolemia 1	#210250	AR
							SLC10A2	non-PFIC	NM_000452	rs56398830	c.868C>T	p.Pro290Ser	Het	0.01	28	VUS	Possible contribution			
							SLCO1B3	non-PFIC	NM_019844	rs558592800	c.205_209dup	p.Asp70GlufsTer13	Het	0.003	28	VUS	Possible contribution			
							*CC2D2A**	non-PFIC	NM_001378615	rs370014549	c.298A>C	p.Met100Leu	Het	0.00009	18	VUS	Possible contribution			
							*PKHD1**	non-PFIC	NM_138694	rs76572975	c.11525G>T	p.Arg3842Leu	Het	0.02	23	B				
							SLC10A2	non-PFIC	NM_000452	rs2301157	c.*120T>C	//	Het	NA	NA	B				
							ACADVL	other liver	NM_001270447	rs113994167	c.917T>C	p.Val306Ala	Het	0.002	26	P				
							ANK1	other liver	NM_001142446	rs557897612	c.4550G>T	p.Arg1517Leu	Het	0.00001	32	VUS				
							ATG7	other liver	NM_006395	rs36117895	c.1412T>C	p.Val471Ala	Het	0.03	25	LP				
							MEFV	other liver	NM_000243	rs104895157	c.1016C>T	p.Ser339Phe	Het	0.002883	23	VUS				
							TRMU	other liver	NM_018006	rs138150773	c.1126G>A	p.Glu376Lys	Het	0.0008	31	VUS				
							*CEP120**	other liver	NM_001375405	rs2303720	c.2840G>A	p.Arg947His	Het	0.03		B				
							HFE	other liver	NM_000410	rs1800562	c.845G>A	p.Cys282Tyr	Het	0.07	27	P				
							NOTCH1	other liver	NM_017617	rs61751543	c.3836G>A	p.Arg1279His	Het	0.015	23	B				
							PHKB	other liver	NM_000293	rs16945474	c.2309A>G	p.Tyr770Cys	Het	0.0412	25	B				
							SGSH	other liver	NM_000199	rs62620232	c.1159G>A	p.Val387Met	Het	0.0114	25	B				
							PADI3	other	NM_016233	rs142129409	c.335T>A	p.Leu112His	Het	0.007072	28.3	P				
10	PSC	32	41	M	caucasian	no	*PPOX*	other liver	NM_001122764	NA	c.338+2dup	//	Het	NA	NA	LP	Definite	Variegate porphyria	#176200	AD
							ABCB4	PFIC	NM_000443	rs8187788	c.217C>G	p.Leu73Val	Het	0.001	18	VUS				
							*ZFYVE19**	PFIC	NM_001077268	rs78819718	c.-77C>G	//	Het	NA	NA	B				
							*PKHD1**	non-PFIC	NM_138694	rs116124750	c.1234-5C>T	//	Het	0.003212	NA	B				
							SLC27A5	non-PFIC	NM_012254	rs142672241	c.1160G>A	p.Arg387Gln	Het	0.004	34	LB				
							AGL	other liver	NM_000028	rs150441555	c.2522C>T	p.Ser841Phe	Het	0.003065	25	B				
							*AHI1**	other liver	NM_001134830	rs1316545198	c.1468A>G	p.Ile490Val	Het	NA	9	VUS				
							PIEZO1	other liver	NM_001142864	rs561397138	c.4997C>T	p.Ala1666Val	Het	0.001	13	VUS				
							ASS1	other liver	NM_054012	rs183276875	c.919C>T	p.Arg307Cys	Het	0.0008	24	LP				
							SLX4	other liver	NM_032444	rs376112909	c.4198G>A	p.Asp1400Asn	Het	0.00009	24	VUS				
							*CEP120**	other liver	NM_001375405	rs114280473	c.2134C>T	p.Leu712Phe	Het	0.004	31	B				

							CPS1	other liver	NM_001122633	rs1405780 09	c.4144G>A	p.Gly1382Ser	Het	0.01412	23	B				
							DOCK6	other liver	NM_020812	rs199838752	c.2104G>A	p.Gly702Ser	Het	0.001421	24	B				
							IFIH1	other liver	NM_022168	rs74162090	c.2962G>T	p.Val988Leu	Het	0.0004	32	LB				
							MANBA	other liver	NM_005908	rs75826658	c.2482G>A	p.Val828Ile	Het	0.01759	29	LB				
							PYGL	other liver	NM_002863	rs34313873	c.2416A>T	p.Ile806Leu	Het	0.01669	25	B				
							UNC13D	other liver	NM_199242	rs9904366	c.175G>A	p.Ala59Thr	Het	0.0156	22	B				
11	PSC and SLD	49	59	F	caucasian	no	*APOB*	other liver	NM_000384	rs562574661	c.13480_13482del	p.Gln4494del	Het	0.0007	NA	LP	Definite	Hypercholesterolemia, familial, 2	#144010	AD
							*PKD1L1**	non-PFIC	NM_138295	rs148011149	c.2399T>C	p.Ile800Thr	Het	0.0003	23	VUS				
							ABCD3	non-PFIC	NM_002858	rs760083671	c.673A>G	p.Ile225Val	Het	0.00009	16	VUS				
							*CC2D2A**	non-PFIC	NM_001378615	rs144439937	c.1519A>G	p.Lys507Glu	Het	0.01049	27	B				
							*DCDC2**	non-PFIC	NM_001195610	rs33914824	c.454C>G	p.Pro152Ala	Het	0.04	26	B				
							PEX16	non-PFIC	NM_057174	rs11553094	c.307G>A	p.Val103Met	Het	0.02	23	B				
							*PKHD1**	non-PFIC	NM_138694	rs76572975	c.11525G>T	p.Arg3842Leu	Het	0.02	23	B				
							ACOX1	other liver	NM_004035	rs145082938	c.80C>T	p.Pro27Leu	Het	0.001247	23	B				
							APOB	other liver	NM_000384	rs200824333	c.8725G>A	p.Glu2909Lys	Het	0.0008	13	VUS				
							BTD	other liver	NM_000060	rs13078881	c.1330G>C	p.Asp444His	Het	0.04	21	P				
							*WDR19**	other liver	NM_025132	NA	c.1624T>A	p.Cys542Ser	Het	NA	15	VUS				
							*WDR19**	other liver	NM_025132	rs199812132	c.814C>T	p.Arg272Cys	Het	0.00004	23	VUS				
							*DNAJB11**	other liver	NM_016306	rs139260755	c.226-3C>T	//	Het	0.0001584	NA	B				
							LPA	other liver	NM_005577	rs41259144	c.2969G>A	p.Arg990Gln	Het	0.01084	27	B				
							TFR2	other liver	NM_003227	rs41295942	c.2255G>A	p.Arg752His	Het	0.03	33	LB				
							TSHR	other	NM_000369	rs121908863	c.484C>G	p.Pro162Ala	Het	0.0002639	19	P				
12	PSC	24	25	M	caucasian	yes	*SLC27A5*	non-PFIC	NM_012254	rs748955596	c.668G>A	p.Arg223Gln	Het	0.000005	12	VUS	Possible contribution	Bile acid metabolism	NA	NA
							ABCG8	non-PFIC	NM_022437	rs377340438	c.322+5C>T	//	Het	0.00005	NA	VUS	Possible contribution			
							SLCO1B1	non-PFIC	NM_006446	rs71581985	c.*46T>G	//	Het	0.005601	NA	VUS	Possible contribution			
							*TTC26**	non-PFIC	NM_001287513	rs766788483	c.*7G>A	//	Het	0.00002	NA	VUS	Possible contribution			
							*DCDC2**	non-PFIC	NM_001195610	rs9460973	c.1368A>T	p.Lys456Asn	Het	0.03	25	B				
							AGL	other liver	NM_000028	rs2230307	c.3343G>A	p.Gly1115Arg	Het	0.04888	34	B				

							BCS1L	other liver	NM_001079866	rs747956412	c.269G>A	p.Arg90His	Het	0	17	LP				
							*CEP120**	other liver	NM_001375405	rs372774629	c.1873G>A	p.Val625Ile	Het	0.00002	6	VUS				
							DPAGT1	other liver	NM_001382	rs896612042	c.1208G>A	p.Arg403Gln	Het	0.00002	27	VUS				
							*DYNC2H1**	other liver	NM_001377	rs201860217	c.5473A>G	p.Ile1825Val	Het	0.0003	26	VUS				
							*DYNC2H1**	other liver	NM_001377	rs375988913	c.6697T>C	p.Ser2233Pro	Het	0.00006	5	VUS				
							G6PD	other liver	NM_001360016	rs137852318	c.934G>C	p.Asp312His	Het	0.001	26	P	Definite	Hemolytic anemia G6PD deficient	#300908	XLD
							LPA	other liver	NM_005577	rs41267807	c.6068A>G	p.Tyr2023Cys	Het	0.01552	24	B				
							MRPL12	other liver	NM_002949	rs764594902	c.580A>G	p.Thr194Ala	Het	0.0030049	24	VUS				
							PHKB	other liver	NM_00293	rs117218785	c.574A>G	p.Ile192Val	Het	0.002282	15	B				
							PHKB	other liver	NM_00293	rs56257827	c.555G>T	p.Met185Ile	Het	0.01391	29	B				
							PIEZO1	other liver	NM_001142864	rs185326407	c.3667G>A	p.Val1223Ile	Het	0.004	25	LB				
							*PKD1**	other liver	NM_001009944	rs755942659	c.7516G>A	p.Ala2506Thr	Het	0.00007	13	VUS				
							SLC37A4	other liver	NM_001164278	rs34203644	c.593A>T	p.Asn198Ile	Het	0.005493	24	B				
13	PSC	43	46	M	caucasian	no	*PKHD1**	non-PFIC	NM_138694	rs76572975	c.11525G>T	p.Arg3842Leu	Het	0.02451	23	B	Negative			
							*DYNC2H1**	other liver	NM_001377	rs189806840	c.3682C>A	p.Leu1228Ile	Het	0.003	24	VUS				
							AGPAT2	other liver	NM_006412	rs761378691	c.179T>A	p.Met60Lys	Het	0.00003	23	VUS				
							CDAN1	other liver	NM_138477	rs201079951	c.1705G>C	p.Gly569Arg	Het	0.001111	26	VUS				
							CDAN1	other liver	NM_138477	rs201599639	c.1649T>C	p.Met550Thr	Het	0.001128	18	VUS				
							*CEP164**	other liver	NM_014956	rs143659874	c.380C>A	P.Pro127His	Het	0.005	24	VUS				
							*AHI1**	other liver	NM_001134830	rs13312995	c.2488C>T	p.Arg830Trp	Het	0.03	27	LB				
							CIDEC	other liver	NM_001199551	rs61742367	c.146C>T	p.Thr49Met	Het	0.03685	23	B				
							COG1	other liver	NM_018714	rs375609831	c.87G>C	p.Glu29Asp	Het	0.00008	26	LB				
							GLDC	other liver	NM_000170	rs147275962	c.2113G>A	p.Val705Met	Het	0.003359	27	B				
							PCK2	other liver	NM_004563	rs749499634	c.350G>A	p.Arg117Gln	Het	0.00003	24	LB				
							PYGL	other liver	NM_002863	rs34313873	c.2416A>T	p.Ile806Leu	Het	0.01669	25	B				
							SERAC1	other liver	NM_032861	rs112780453	c.139T>A	p.Phe47Ile	Het	0.02227	28	B				
							KIAA1033	other	NM_015275	rs201428088	c.1508A>G	p.His503Arg	Het	0.0004681	14	P				
14	PSC	27	34	M	caucasian	yes	*NPHP3**	non-PFIC	NM_153240	NA	c.1996A>G	p.Thr666Ala	Het	NA	26	VUS	Possible contribution	Nephronophthisis 3	#604387	AR
							ABCC12	non-PFIC	NM_033226	rs141807269	c.490G>T	p.Gly164Ter	Het	0.003	27	B				
							NOTCH2	non-PFIC	NM_024408	rs61752484	c.3980A>G	p.Asp1327Gly	Het	0.007	23	B				

							PEX16	non-PFIC	NM_057174	rs11553094	c.307G>A	p.Val103Met	Het	0.02	23	B				
							SLC25A13	non-PFIC	NM_014251	rs148962110	c.1910T>C	p.Val637Ala	Het	0	23	LB				
							*CEP290**	other liver	NM_025114	rs761907569	c.3894dup	p.Lys1299Ter	Het	0	32	P				
							PIEZO1	other liver	NM_001142864	rs201442593	c.5773C>T	p.Arg1925Trp	Het	0.001	17	LP	Definite	Dehydrated hereditary stomatocytosis 1	#194380	AD
							NEK1	other liver	NM_001199397	rs200161705	c.782G>A	p.Arg261His	Het	0.004	31	VUS				
							PCK2	other liver	NM_004563	NA	c.383G>C	p.Arg128Pro	Het	NA	22	VUS				
							PHKB	other liver	NM_000293	rs965005343	c.5C>T	p.Ala2Val	Het	NA	23	VUS				
							PIEZO1	other liver	NM_001142864	rs200291894	c.7219G>C	p.Glu2407Gln	Het	0	12	VUS				
							*PKD1**	other liver	NM_001009944	rs138575342	c.2081C>T	p.Pro694Leu	Het	0.021	24	VUS				
							CSPP1	other liver	NM_001382391	rs16933182	c.2630G>A	p.Arg877His	Het	0.034	23	B				
							EARS2	other liver	NM_001083614	rs187662524	c.1045G>A	p.Glu349Lys	Het	0.002	24	LB				
							GAA	other liver	NM_000152	rs1800299	c.271G>A	p.Asp91Asn	Het	0.033	25	B				
							HFE	other liver	NM_000410	rs1799945	c.187C>G	p.His63Asp	Het	0.15	21	LP				
							LRBA	other liver	NM_001364905	rs35879351	c.5989C>T	p.Arg1997Cys	Het	0.035	32	B				
							MEGF8	other liver	NM_001271938	rs151116615	c.2450A>G	p.His817Arg	Het	0.001	19	LB				
							BRCA1	other	NM_007294	rs886040920	c.626delC	p.Pro209Leufs*25	Het	NA	23	LP	Definite	Susceptibility to breast-ovarian cancer	#604370	AD, Mu
15	PSC	39	45	M	caucasian	no	*ATP8B1*	PFIC	NM_001374385	rs150860808	c.913T>A	p.Phe305Ile	Het	0.002	6	VUS	Possible contribution	Heterozygous cholestasis, progressive familial intrahepatic 2	#601847	AR
							GPBAR1	non-PFIC	NM_170699	rs201881617	c.442C>T	p.His148Tyr	Het	0.0003	23	VUS	Possible contribution			
							IFIH1	other liver	NM_022168	rs35732034	c.2807+1G>A	//	Het	0.009	27	VUS				
							CYP7A1	non-PFIC	NM_000780	rs142708991	c.1192C>G	p.Pro398Ala	Het	0.004334	23	B				
							*IFT172**	non-PFIC	NM_015662	rs148624326	c.3401G>T	p.Arg1134Leu	Het	0.005725	35	B				
							ATG7	other liver	NM_006395	rs36117895	c.1412T>C	p.Val471Ala	Het	0.03	25	LP				
							*CEP164**	other liver	NM_014956	NA	c.2556C>A	p.Asp852Glu	Het	NA	19	VUS				
							*CEP164**	other liver	NM_014956	rs200103555	c.3216+20_3216+33del	//	Het	0.02497	NA	B				
							GLDC	other liver	NM_000170	rs535143891	c.52G>T	p.Gly18Cys	Het	0.01539	26	B				
							MRPS23	other liver	NM_016070	rs760880323	c.337G>T	p.Asp113Tyr	Het	0.00005	32	LB				
							NOTCH1	other liver	NM_017617	rs61751543	c.3836G>A	p.Arg1279His	Het	0.015	23	B				
							SERAC1	other liver	NM_032861	rs112780453	c.139T>A	p.Phe47Ile	Het	0.02227	28	B				

16	PSC	38	48	F	caucasian	no	*NPHP3**	non-PFIC	NM_153240	rs780267481	c.*2219T>C	//	Het	0.0009	6	VUS	Possible contribution	Nephronophthisis 3	#604387	AR
							SLC10A2	non-PFIC	NM_000452	rs55971546	c.292G>A	p.Val98Ile	Het	0.04	21	B				
							APOB	other liver	NM_000384	rs6752026	c.433C>T	p.Pro145Ser	Het	0.0004	25	VUS				
							*DYNC2H1**	other liver	NM_001377	rs144717489	c.12865G>C	p.Gly4289Arg	Het	0.01	25	VUS				
							*DYNC2I1-WDR60**	other liver	NM_018051	rs374477653	c.49G>A	p.Asp17Asn	Het	0.00005	24	VUS				
							LDLR	other liver	NM_000527	rs148698650	c.829G>A	p.Glu277Lys	Het	0.0003	23	VUS				
							SLC44A1	other liver	NM_080546	rs1230776546	c.166G>C	p.Ala56Pro	Het	0	24	VUS				
							BTD	other liver	NM_000060	rs13078881	c.1330G>C	p.Asp444His	Het	0.04	21	P				
							CTSD	other liver	NM_001909	rs147278302	c.844G>A	p.Gly282Arg	Het	0.006852	23	LB				
							GLDC	other liver	NM_000170	rs148540696	c.2863G>A	p.Val955Ile	Het	0	17	LB				
							HFE	other liver	NM_000410	rs143175221	c.884T>C	p.Val295Ala	Het	0.003441	0,08	LB				
							HPS1	other liver	NM_000195	rs58548334	c.11T>C	p.Val4Ala	Het	0.02607	24	LB				
							TSHR	other	NM_000369	rs121908863	c.484C>G	p.Pro162Ala	Het	0.002639	19	P				
							VPS13B	other	NM_017890	rs1057516331	c.6374G>A	p.Trp2125Ter	Het	NA	46	P				
17	PSC	34	41	M	caucasian	no	*DCDC2**	non-PFIC	NM_016356	rs9460973	c.1368A>T	p.Lys456Asn	Het	0.03	25	VUS	Possible contribution	Sclerosing cholangitis neonatal	#617394	AR
							TJP2	PFIC	NM_001170416	rs200415824	c.154-6A>T	//	Het	0.002084	NA	B				
							NOTCH2	non-PFIC	NM_024408	rs141935585	c.1396C>A	p.Gln466Lys	Het	0.000503	20	B				
							*ALMS1**	other liver	NM_001378454	rs28730854	c.6299C>T	p.Ser2100Leu	Het	0.04	23	B				
							ANK1	other liver	NM_001142446	rs61735313	c.753C>A	p.Asn251Lys	Het	0.02	30	VUS				
							*CEP290**	other liver	NM_025114	rs200211587	c.1298A>G	p.Asp433Gly	Het	0.001	26	VUS				
							*DYNC2H1**	other liver	NM_001377	rs144717489	c.12865G>C	p.Gly4289Arg	Het	0.01	25	VUS				
							PRF1	other liver	NM_005041	rs35947132	c.272C>T	p.Ala91Val	Het	0.04662	26	VUS				
							HFE	other liver	NM_000410	rs1799945	c.187C>G	p.His63Asp	Hom	0.15	21	LP				
							LIPE	other liver	NM_005357	rs145456377	c.280G>A	p.Ala94Thr	Het	0.001776	20	LB				
							CTC1	other liver	NM_025099	rs78870822	c.248G>C	p.Ser83Thr	Het	0.01007	25	B				
							LPA	other liver	NM_005577	rs41267807	c.6068A>G	p.Tyr2023Cys	Het	0.01552	24	B				
							*RPGRIP1L**	other liver	NM_015272	rs2302677	c.2231G>A	p.Arg744Gln	Het	0.03	31	LB				
							SGSH	other liver	NM_000199	rs62620232	c.1159G>A	p.Val387Met	Het	0.0114	25	B				
							COL18A1	other	NM_030582	NA	c.3712G>T	p.Glu1238Ter	Het	0	40	P				
18	PSC	33	42	F	caucasian	no	*MYO5B*	PFIC	NM_001080467	rs1942418	c.3962G>A	p.Gly1321Glu	Het	0.04781	24	B	Negative			
							PEX16	non-	NM_057174	rs11553094	c.307G>A	p.Val103Met	Het	0.02	23	B				

								PFIC												
							*PKHD1**	non-PFIC	NM_138694	rs76572975	c.11525G>T	p.Arg3842Leu	Het	0.02	23	B				
							*PKHD1**	non-PFIC	NM_138694	rs368339881	c.8107+8T>G	//	Het	0.002466	NA	LB				
							PLEC	non-PFIC	NM_201380	rs3135103	c.2117G>A	p.Arg706Gln	Het	0.02	26	B				
							*TTC26**	non-PFIC	NM_001287513	rs13225917	c.928G>A	p.Asp310Asn	Het	0.002028	26	LB				
							*ALMS1**	other liver	NM_001378454	rs201028172	c.11408G>A	p.Arg3803Lys	Het	0.0002	26	VUS				
							*CEP290**	other liver	NM_025114	rs147371999	c.1558T>C	p.Phe520Leu	Het	0.0001	25	VUS				
							GYS1	other liver	NM_002103	rs747911098	c.1559C>T	p.Thr520Met	Het	0.00003	34	VUS				
							MEGF8	other liver	NM_001271938	rs753199102	c.3359G>C	p.Trp1120Ser	Het	0.00009	13	VUS				
							PHKG2	other liver	NM_000294	rs146181866	c.495G>T	p.Met165Ile	Het	0.00003	17	VUS				
							*PKD2**	other liver	NM_000297	rs748914485	c.865G>A	p.Asp289Asn	Het	0	17	VUS				
							CETP	other liver	NM_000078	rs767437395	c.472C>T	p.Pro158Ser	Het	0	0.027	LB				
							CTSD	other liver	NM_001909	rs147278302	c.844G>A	p.Gly282Arg	Het	0.006852	23	LB				
							GANAB	other liver	NM_198335	rs199956781	c.2239G>A	p.Val747Ile	Het	0.004314	18	B				
							GBA	other liver	NM_001005742	rs75548401	c.1223C>T	p.Thr408Met	Het	0.009176	22	B				
							NBAS	other liver	NM_015909	rs147322367	c.3217C>T	p.Arg1073Cys	Het	0.005	31	LB				
							NBAS	other liver	NM_015909	rs116210837	c.3392G>A	p.Arg1131His	Het	0.03	25	B				
							PIEZO1	other liver	NM_001142864	rs185326407	c.3667G>A	p.Val1223Ile	Het	0.004	25	LB				
							TRMT5	other liver	NM_020810	rs76079086	c.535C>A	p.His179Asn	Het	0.001055	9	B				
19	PSC	11	18	F	caucasian	yes	*TTC21B**	non-PFIC	NM_024753	rs748659179	c.571C>T	p.Arg191Cys	Het	0.00007	25	VUS	Possible contribution	Nephronophthisis 12	#613820	AD/AR
							PEX26	non-PFIC	NM_001127649	rs12484657	c.457C>G	p.Leu153Val	Het	0.017	23	B				
							*ALMS1**	other liver	NM_001378454	rs28730854	c.6299C>T	p.Thr2100Ile	Het	0.037	20	B				
							*CEP164**	other liver	NM_014956	rs143802594	c.3416G>T	p.Arg1139Leu	Het	0	17	VUS				
							*CEP290**	other liver	NM_025114	NA	c.6533A>G	p.Glu2178Gly	Het	NA	29	VUS				
							COG6	other liver	NM_020751	rs200410517	c.1459G>A	p.Val487Ile	Het	0	21	VUS				
							HEXB	other liver	NM_000521	rs28942073	c.1250C>T	p.Pro417Leu	Het	0.0008	15	LP				
							*IFT122**	other liver	NM_052989	rs150550701	c.1103G>A	p.Ser368Asn	Het	0.002	17	B				
							RAD50	other	NM_005732	rs397507177	c.2821C>T	p.Gln941Ter	Het	0.00001		P				
20	PSC and SLD	45	59	F	caucasian	yes	*PKD1L1**	non-PFIC	NM_138295	rs759416849	c.5722G>T	p.Val1908Leu	Het	0.00009	26	VUS	Possible contribution	Heterotaxy, visceral, 8, autosomal	#617205	AR

							MBOAT7	other liver	NM_024298	rs372242233	c.1036G>A	p.Ala346Thr	Het	0.00007	32	VUS	Possible contribution	SLD	//	//
							PLEC	non-PFIC	NM_201380	rs138924815	c.1298G>A	p.Arg433Gln	Het	0.02	25	B				
							*CEP120**	other liver	NM_001375405	rs150132498	c.1831C>G	p.Arg611Gly	Het	0.000003	24	VUS				
							*PKD1**	other liver	NM_001009944	rs368575965	c.6875C>T	p.Thr2292Met	Het	0.00002	29	VUS				
							GLB1	other liver	NM_000404	rs369627064	c.75+3A>G	//	Het	0.00007	NA	VUS				
							*PKD2**	other liver	NM_000297	rs75762896	c.1445T>G	p.Phe482Cys	Het	0.002	28	B				
							*CEP41**	other liver	NM_018718	rs11765434	c.208-5A>G	//	Het	0.006033	NA	B				
							ABCD1	other liver	NM_000033	rs782693577	c.50G>A	p.Arg17His	Het	0.000217	25	B				
							CP	other liver	NM_000096	rs61733458	c.1652C>T	p.Thr551Ile	Het	0.0307	30	LB				
							GAA	other liver	NM_000152	rs1800299	c.271G>A	p.Asp91Asn	Het	0.03265	25	B				
							HFE	other liver	NM_000410	rs1799945	c.187C>G	p.His63Asp	Het	0.15	21	LP				
							IFIH1	other liver	NM_022168	rs35732034	c.2807+1G>A	//	Het	0.009	27	B				
							POLG2	other liver	NM_007215	rs17850455	c.1247G>C	p.Gly416Ala	Het	0.01	25	LB				
							ADSL	other	NM_000026	rs372895468	c.1349C>G	p.Thr450Ser	Het	0.000006	24	P				
							MYBPC3	other	NM_000256	rs376395543	c.26-2A>G	//	Het	0.000005	24	P	Definite	Suscepti biity to hypertrophic cardiomyopathy	# 115197	AD, AR
21	PSC and iron overload	16	34	M	caucasian	no	*HFE*	other liver	NM_000410	rs1799945	c.187C>G	p.His63Asp	Het	0.15	21	LP	Possible contribution	Hemochromatosis type 1	# 235200	AR
							TFR2	other liver	NM_003227	rs41303501	c.1364G>A	p.Arg455Gln	Het	0.003	24	VUS	Possible contribution	Hemochromatosis type 3	# 604250	AR
							TFR2	other liver	NM_003227	NA	c.2377del	p.Asp793MetfsTer	Het	NA	NA	VUS	Possible contribution	Hemochromatosis type 3	# 604250	AR
							ABCC12	non-PFIC	NM_033226	rs36102575	c.3071G>A	p.Trp1024Ter	Het	0.02	42	VUS	Possible contribution	Bile duct paucity	//	//
							MYO5B	PFIC	NM_001080467	rs145598498	c.4145C>T	p.Thr1382Met	Het	0.003655	23	LB				
							PEX16	non-PFIC	NM_057174	rs11553094	c.307G>A	p.Val103Met	Het	0.02	23	B				
							PLEC	non-PFIC	NM_201380	rs35723243	c.8461C>T	p.Arg2821Trp	Het	0.03	24	B				
							LRBA	other liver	NM_006726	rs148699393	c.5941C>T	p.Arg1981Cys	Het	0.00006	33	VUS				
							MEGF8	other liver	NM_001271938	rs554274233	c.1057C>T	p.Arg353Cys	Het	0.00008	25	VUS				
							PEPD	other liver	NM_000285	rs371934154	c.1331G>A	p.Arg444His	Het	0.00008	33	VUS				
							AGPAT2	other liver	NM_006412	rs142993240	c.475C>T	p.Arg159Cys	Het	0.006237	25	B				
							*AHI1**	other liver	NM_001134830	rs35433555	c.1643G>A	p.Arg548His	Het	0.02	24	B				
							*AHI1**	other liver	NM_001134830	rs13312995	c.2488C>T	p.Arg830Trp	Het	0.03	34	B				
							HNF4A	other	NM_178849	rs1800961	c.416C>T	p.Thr139Ile	Het	0.03222	25	LB				

	liver								
NOTCH1	other liver	NM_017617	rs61751543	c.3836G>A	p.Arg1279His	Het	0.015	23	B
PC	other liver	NM_001040716	rs147945506	c.616G>T	p.Val206Leu	Het	0.002063	25	LB
PCSK7	other liver	NM_004716	rs763046297	c.595C>T	p.Pro199Ser	Het	0.00002	21	LB
PIEZO1	other liver	NM_001142864	rs188337046	c.4385G>A	p.Arg1462Gln	Het	0.005	21	B
*PKD1**	other liver	NM_001009944	rs756979518	c.2371C>T	p.Arg791Trp	Het	0.00004	23	LB
*RPGRIP1L**	other liver	NM_015272	rs2302677	c.2231G>A	p.Arg744Gln	Het	0.03	31	LB
SERAC1	other liver	NM_032861	rs112780453	c.139T>A	p.Phe47Ile	Het	0.02227	28	B
SLC12A3	other	NM_001126108	rs780299444	c.237_238dup	p.Arg80ProfsTer35	Het	0.00002	NA	P

*ciliopathy genes

Supplementary Table 6: Demographic and clinical features of the control cohort.

	Control cohort (n=266)
Age at genetic test (years), median [IQR]	42 [31-52]
Sex, male (%)	153 (58%)
ALT (IU/L)*, median [IQR]	18 [14-22]
GGT (IU/L)*, median [IQR]	13 [10-18]
PLT (10^3/uL)*, median [IQR]	232 [196-267]
Advanced chronic liver disease, yes (%)	0 (0%)

*Available for 261 individuals. Abbreviations: IQR, interquartile range; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; PLT, platelets.

Supplementary Table 7: Frequency of variants in patients and controls.

Class	Gene	dbSNP	protein change	AC CTRLs	AC CASEs	AF ctrl	AF case	pval chi	OR chi	CI chi 95	FDR
PFIC	ABCB4	rs8187788	p.Leu73Val	2	2	0,004	0,048	**2,00E-02**	13,10	2.2-77.83	0,139
	ABCB4		p.Ala252Pro	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	ABCB4	rs754287486	p.Arg176Trp	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	ATP8B1	rs150860808	p.Phe305Ile	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	TJP2	rs200415824		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	ABCB11	rs138642043	p.Arg698His	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
	ABCB4	rs138773456	p.Thr715Ile	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
	TJP2	rs138241615	p.Thr93Met	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
	ZFYVE19*	rs116166434	p.Leu72Val	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
	ZFYVE19*	rs78819718		15	2	0,028	0,048	8,09E-01	2,06	0.52-8.14	0,428
	MYO5B	rs145598498	p.Thr1382Met	4	1	0,008	0,024	8,17E-01	4,24	0.65-27.67	0,393
	MYO5B	rs61737448	p.Lys781Asn	4	1	0,008	0,024	8,17E-01	4,24	0.65-27.67	0,393
	MYO5B	rs1942418	p.Gly1321Glu	34	2	0,064	0,048	9,29E-01	0,89	0.24-3.35	1,000
	ABCB11	rs11568363		20	1	0,038	0,024	9,75E-01	0,90	0.17-4.89	1,000
non-PFIC	ABCC2			0	2	0,000	0,048	**2,31E-04**	65,74	3.1-1392.56	0,139
	PEX16	rs11553094	p.Val103Met	19	6	0,036	0,143	**3,94E-03**	4,69	1.82-12.11	0,139
	PKHD1*	rs76572975	p.Arg3842Leu	15	5	0,028	0,119	**7,95E-03**	4,90	1.75-13.68	0,139
	ABCC2	rs56131651	p.Ser281Asn	5	3	0,009	0,071	**8,85E-03**	8,50	2.14-33.73	0,139
	ABCC12	rs141807269	p.Gly164*	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	ABCC2	rs201874841	p.Arg905Ile	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	ABCD3	rs760083671	p.Ile225Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	ABCG8	rs377340438		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	ABCG8	rs376362072	p.Ala193Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139

ABCG8	rs137852991	p.Arg412Ter	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CC2D2A*	rs370014549	p.Met100Leu	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CYP7A1	rs142708991	p.Pro398Ala	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
GPBAR1	rs201881617	p.His148Tyr	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
JAG1	rs149366993	p.Ala480Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
NOTCH2	rs141935585	p.Gln466Lys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
NOTCH2	rs782566552	p.Tyr222Cys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
NPHP1*	rs765568261	p.Glu142Asp	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
NPHP3*		p.Thr666Ala	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
NPHP3*	rs780267481		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PEX1	rs182452430	p.Asp1168Gly	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PEX5	rs373763823		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD1L1*	rs199719516		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD1L1*	rs759416849	p.Val1908Leu	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD1L1*	rs372058157	p.Glu1104Lys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD1L1*	rs148011149	p.Ile800Thr	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKHD1*	rs368339881		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKHD1*	rs150838488	p.Gln1923Leu	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PLEC	rs782134950	p.Arg561Trp	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
SLC10A2	rs143297386	p.Gly77Glu	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
SLC25A13	rs148962110	p.Val637Ala	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
SLC27A5	rs748955596	p.Arg223Gln	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
SLCO1B3	rs558592800	p.Asp70GlufsTer13	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
TMEM67*	rs35765535	p.Leu437Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
TTC21B*	rs748659179	p.Arg191Cys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
TTC26*	rs766788483		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PEX26	rs2234338		11	3	0,021	0,071	1,25E-01	4,02	1.16-13.88	0,142
CFTR*	rs1800076	p.Arg75Gln	5	2	0,009	0,048	1,49E-01	5,92	1.28-27.31	0,162
IFT172*	rs148624326	p.Arg1134Leu	7	2	0,013	0,048	2,78E-01	4,33	1-18.75	0,220
DHCR7	rs139724817	p.Val330Met	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
PKD1L1*	rs201106567		1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
PKHD1*	rs116124750		1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
SLC27A5	rs142672241	p.Arg387Gln	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
PLEC	rs35723243	p.Arg2821Trp	18	3	0,034	0,071	4,11E-01	2,46	0.75-8.08	0,291
ABCD3	rs142075958	p.Gly52Val	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
PEX19	rs141133579		2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
TTC21B*	rs572065013		2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
TTC26*	rs13225917	p.Asp310Asn	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
SLC10A2	rs2301157		255	18	0,479	0,429	6,36E-01	0,82	0.44-1.54	0,690

	SERPINA1	rs17580	p.Glu288Val	13	2	0,024	0,048	6,86E-01	2,38	0.59-9.51	0,391
	CC2D2A*	rs144439937	p.Lys507Glu	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
	IFT172*	rs61747073	p.Arg908Gln	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
	PLEC	rs145977158	p.Arg2788Trp	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
	SLCO1B1	rs71581985		3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
	DCDC2*	rs33914824	p.Pro152Ala	26	1	0,049	0,024	7,19E-01	0,69	0.13-3.69	0,764
	DCDC2*	rs9460973	p.Lys456Asn	14	2	0,026	0,048	7,49E-01	2,21	0.56-8.77	0,404
	ABCC12	rs36102575	p.Trp1024Ter	15	2	0,028	0,048	8,09E-01	2,06	0.52-8.14	0,428
	SLC10A2	rs56398830	p.Pro290Ser	15	2	0,028	0,048	8,09E-01	2,06	0.52-8.14	0,428
	NPHP3*	rs34391943	p.Ala1184Thr	4	1	0,008	0,024	8,17E-01	4,24	0.65-27.67	0,393
	PLEC	rs78461695	p.Thr4044Met	4	1	0,008	0,024	8,17E-01	4,24	0.65-27.67	0,393
	PLEC	rs3135103	p.Arg706Gln	4	1	0,008	0,024	8,17E-01	4,24	0.65-27.67	0,393
	SERPINA1	rs28931570	p.Arg63Cys	4	1	0,008	0,024	8,17E-01	4,24	0.65-27.67	0,393
	PLEC	rs138924815	p.Arg433Gln	16	2	0,030	0,048	8,66E-01	1,93	0.49-7.59	0,446
	CFTR*	rs1800100	p.Arg668Cys	5	1	0,009	0,024	9,23E-01	3,47	0.55-21.67	0,428
	PEX12	rs147530802	p.Arg34Ser	5	1	0,009	0,024	9,23E-01	3,47	0.55-21.67	0,428
	PEX26	rs12484657	p.Leu153Val	7	1	0,013	0,024	1,00E+00	2,53	0.43-15.04	0,517
	SLC10A2	rs55971546	p.Val98Ile	15	1	0,028	0,024	1,00E+00	1,21	0.22-6.64	1,000
	NOTCH2	rs61752484	p.Asp1327Gly	10	1	0,019	0,024	1,00E+00	1,80	0.32-10.25	0,626
	PEX6	rs61752141	p.Ala79Pro	8	1	0,015	0,024	1,00E+00	2,23	0.38-13.02	0,557
other liver	PIEZO1	rs185326407	p.Val1223Ile	1	3	0,002	0,071	**2,11E-05**	31,40	4.51-218.46	0,139
	TF	rs185023567		0	2	0,000	0,048	**2,31E-04**	65,74	3.1-1392.56	0,139
	HNF4A	rs1800961	p.Thr139Ile	7	4	0,013	0,095	**1,63E-03**	8,19	2.43-27.56	0,139
	ACOX1	rs145082938	p.Pro27Leu	1	2	0,002	0,048	**4,42E-03**	21,87	2.82-169.79	0,139
	G6PD	rs137852318	p.Asp312His	1	2	0,002	0,048	**4,42E-03**	21,87	2.82-169.79	0,139
	IFIH1	rs35732034		5	3	0,009	0,071	**8,85E-03**	8,50	2.14-33.73	0,139
	FBXL4			6	3	0,011	0,071	**1,75E-02**	7,18	1.88-27.39	0,139
	LPA	rs41267807	p.Tyr2023Cys	2	2	0,004	0,048	**2,00E-02**	13,10	2.2-77.83	0,139
	SERAC1	rs112780453	p.Phe47Ile	7	3	0,013	0,071	**3,03E-02**	6,21	1.68-22.99	0,139
	PKD1*	rs147350387	p.Thr2708Met	3	2	0,006	0,048	**5,04E-02**	9,34	1.79-48.83	0,139
	POLG2	rs17850455	p.Gly416Ala	3	2	0,006	0,048	**5,04E-02**	9,34	1.79-48.83	0,139
	SGSH	rs62620232	p.Val387Met	3	2	0,006	0,048	**5,04E-02**	9,34	1.79-48.83	0,139
	NOTCH1	rs61751543	p.Arg1279His	16	4	0,030	0,095	7,51E-02	3,66	1.23-10.91	0,139
	ABCD1	rs782693577	p.Arg17His	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	ACADVL	rs113994167	p.Val306Ala	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	ACADVL	rs146379816	p.Arg554Trp	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	AGPAT2	rs761378691	p.Met60Lys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139

AHI1*	rs200816459	p.Arg891Gln	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
AHI1*		p.Ile490Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
ALMS1*	rs201028172	p.Arg3803Thr	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
ALMS1*	rs759735286	p.Arg4098Lys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
ANK1	rs557897612	p.Arg1517His	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
ANK1	rs749236684	p.Ser792Tyr	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
APOB	rs562574661	p.Gln4494del	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
APOB	rs200824333	p.Glu2909Lys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
ASS1	rs183276875	p.Arg307Cys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
ATP7B	rs745679410	p.Ile1194Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
BCS1L	rs747956412	p.Arg90His	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CBS	rs201372812	p.Arg45Trp	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CEP120*		p.Glu732Gly	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CEP120*	rs372774629	p.Val625Ile	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CEP120*	rs150132498	p.Arg611Gly	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CEP164*		p.Asp852Glu	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CEP164*	rs143802594	p.Arg1139Leu	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CEP290*		p.Glu2178Gly	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CEP290*	rs761907569	p.Lys1299Ter	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CEP290*	rs147371999	p.Phe520Leu	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CEP290*	rs200211587	p.Asp433Gly	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CETP	rs767437395	p.Pro158Ser	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
COG1	rs375609831	p.Glu29Asp	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
CR2	rs201760344	p.Arg214Cys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
DNAJB11*	rs139260755		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
DOCK6	rs375012919	p.Arg1178Trp	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
DPAGT1	rs896612042	p.Arg403Gln	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
DYNC2H1*	rs201043335	p.Gly1140Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
DYNC2H1*	rs189806840	p.Leu1228Ile	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
DYNC2H1*	rs201860217	p.Ile1825Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
DYNC2H1*	rs375988913	p.Ser2233Pro	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
DYNC2H1*	rs78309870		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
EOGT	rs376499113	p.Asp101Asn	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
G6PD		p.Val180Ile	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
GANAB	rs199956781	p.Val747Ile	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
GLB1	rs369627064		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
GLDC	rs148540696	p.Val955Ile	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
GLIS3	rs200694226	p.Arg780Gln	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
HEXB	rs28942073	p.Pro417Leu	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
HFE	rs143175221	p.Val295Ala	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139

IFIH1	rs74162090	p.Val988Leu	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
IFIH1	rs145520044	p.Arg374His	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
LDLR	rs148698650	p.Glu277Lys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
LRBA	rs148699393	p.Arg1981Cys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
LRBA		p.Ala1632Thr	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
LRBA		p.Val50Ala	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
MBOAT7	rs372242233	p.Ala346Thr	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
MBOAT7	rs766158021	p.Leu76Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
MEFV	rs104895157	p.Ser339Phe	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
MEGF8	rs554274233	p.Arg353Cys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
MEGF8	rs151116615	p.His817Arg	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
MEGF8	rs753199102	p.Trp1120Ser	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
MRPL12	rs764594902	p.Thr194Ala	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
MRPS23	rs760880323	p.Asp113Tyr	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
NBAS	rs200344246	p.Lys86Gln	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
NOTCH1	rs750169914	p.Val1232Met	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
OFD1	rs759835018	p.Met962Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PCK2	rs749499634	p.Arg117Gln	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PCK2		p.Arg128Pro	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PCSK7	rs763046297	p.Pro199Ser	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PEPD	rs371934154	p.Arg444His	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PHKB	rs965005343	p.Ala2Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PHKG2	rs146181866	p.Met165Ile	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PIEZO1	rs201442593	p.Arg1925Trp	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PIEZO1	rs561397138	p.Ala1666Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD1*	rs146507511	p.Asp3451Asn	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD1*		p.His2887Asp	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD1*	rs755942659	p.Ala2506Thr	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD1*	rs368575965	p.Thr2292Met	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD1*	rs756979518	p.Arg791Trp	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD1*	rs138575342	p.Pro694Leu	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD2*	rs748914485	p.Asp289Asn	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PKD2*	rs775470869	p.Asp810Asn	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
POLG2			0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PPOX			0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
PRKCD	rs150331740	p.Ala405Thr	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
SLC11A2	rs115874705	p.Ala238Thr	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
SLC44A1		p.Ala56Pro	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
SLX4	rs376112909	p.Asp1400Asn	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139

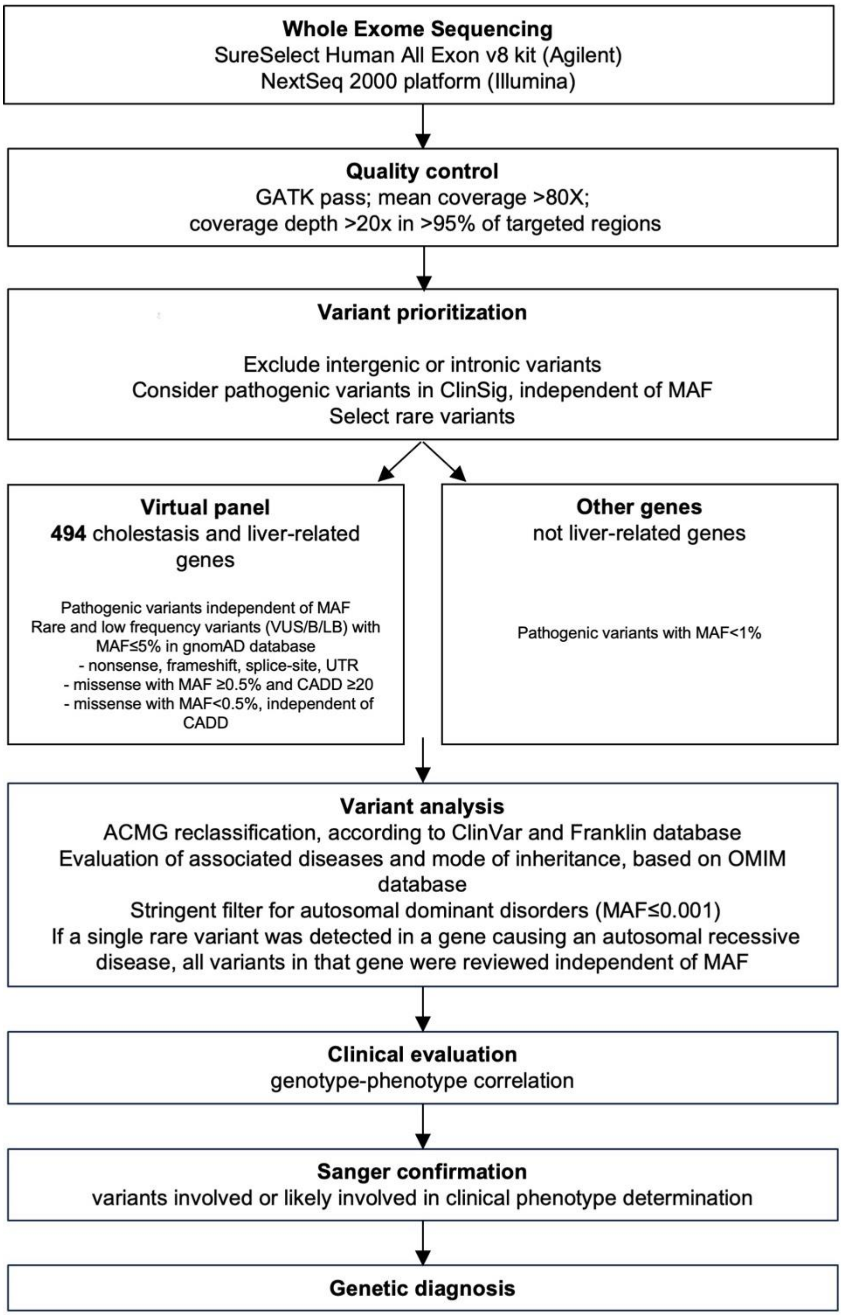
TFR2		p.Asp793MetfsTer31	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
TFR2	rs41303501	p.Arg455Gln	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
TRMT5	rs76079086	p.His179Asn	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
TRMU	rs138150773	p.Glu376Lys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
UNC13D	rs758000434	p.Gly861Ser	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
WDR19*	rs199812132	p.Arg272Cys	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
WDR19*		p.Cys542Ser	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
DYNC2I1-WDR60*	rs374477653	p.Asp17Asn	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
DYNC2I1-WDR60*	rs759916390	p.Ser987Gly	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
NBAS	rs116210837	p.Arg1131His	5	2	0,009	0,048	1,49E-01	5,92	1.28-27.31	0,162
CSPP1	rs16933182	p.Arg877His	32	1	0,060	0,000	1,98E-01	0,18	0.01-3.01	0,244
CTSD	rs147278302	p.Gly282Arg	6	2	0,011	0,048	2,11E-01	5,00	1.12-22.26	0,206
F5	rs9332701	p.Met2148Thr	7	2	0,013	0,048	2,78E-01	4,33	1-18.75	0,220
NCF2	rs35012521	p.Asn419Ile	7	2	0,013	0,048	2,78E-01	4,33	1-18.75	0,220
ANK1	rs77646170		61	2	0,115	0,048	2,79E-01	0,47	0.13-1.74	0,391
ALG1	rs145474820	p.Thr64Asn	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
APOB	rs6752026	p.Pro145Ser	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
CDAN1	rs201079951	p.Gly569Arg	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
CDAN1	rs201599639	p.Met550Thr	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
CEP164*	rs143659874	p.Pro127His	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
CPT2	rs144658100	p.Met342Thr	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
EARS2	rs201941745	p.Ser70Ile	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
GALM	rs200292259	p.Ile189Thr	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
GYS1	rs747911098	p.Thr520Met	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
IFT122*	rs150550701	p.Ser419Asn	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
MVK	rs28934897	p.Val377Ile	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
NFKB1	rs368017285	p.Asp758Gly	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
PIEZO1	rs200291894	p.Glu2407Gln	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
PIEZO1	rs188337046	p.Arg1462Gln	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
PIEZO1	rs372188504		1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
PYGM	rs113806080	p.Ala670Val	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
TMC4	rs368252966	p.Met97Val	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
DYNC2I1-WDR60*	rs754130259	p.Trp684Cys	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
CTC1	rs62624978	p.Gly414Ala	8	2	0,015	0,048	3,47E-01	3,81	0.9-16.17	0,250
DYNC2H1*	rs144717489	p.Gly4296Arg	9	2	0,017	0,048	4,16E-01	3,40	0.81-14.21	0,291
CEP120*	rs114280473	p.Leu712Phe	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291

COG6	rs200410517	p.Val487Ile	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
DOCK6	rs199838752	p.Gly702Ser	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
GLDC	rs535143891	p.Gly18Cys	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
NFS1	rs112446981	p.Lys146Arg	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
PC	rs147945506	p.Val206Leu	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
PHKB	rs117218785	p.Ile192Val	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
UROD	rs36033115	p.Leu253Gln	2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
DYNC2H1*	rs112718117		12	2	0,023	0,048	6,21E-01	2,57	0.64-10.37	0,360
AGL	rs2230307	p.Gly1115Arg	28	1	0,053	0,024	6,49E-01	0,64	0.12-3.41	0,764
GAA	rs1800299	p.Asp91Asn	13	2	0,024	0,048	6,86E-01	2,38	0.59-9.51	0,391
PYGL	rs34313873	p.Ile806Leu	13	2	0,024	0,048	6,86E-01	2,38	0.59-9.51	0,391
AGL	rs149210307	p.Asn797Ser	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
COG2	rs143526339	p.Thr511Ser	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
GBA	rs75548401	p.Thr408Met	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
IFT140*	rs150903791	p.Leu514His	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
NBAS	rs147322367	p.Arg1073Cys	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
NBAS	rs76459791	p.Asp365His	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
NEK1	rs200161705	p.Arg261His	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
PNPLA2	rs140201358	p.Asn252Lys	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
SLX4	rs137976282	p.Gly141Trp	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
TFR2	rs41303495	p.Ala376Asp	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348
RPGRIP1L*	rs2302677	p.Arg744Gln	40	2	0,075	0,048	7,24E-01	0,75	0.2-2.8	0,810
ANK1	rs2304877	p.Arg652His	15	2	0,028	0,048	8,09E-01	2,06	0.52-8.14	0,428
APOB	rs12713844	p.Asp1113His	4	1	0,008	0,024	8,17E-01	4,24	0.65-27.67	0,393
ATP7B	rs60986317	p.Thr1434Met	4	1	0,008	0,024	8,17E-01	4,24	0.65-27.67	0,393
CEP41*	rs11765434		4	1	0,008	0,024	8,17E-01	4,24	0.65-27.67	0,393
CTC1	rs78870822	p.Ser83Thr	4	1	0,008	0,024	8,17E-01	4,24	0.65-27.67	0,393
PKD2*	rs75762896	p.Phe482Cys	4	1	0,008	0,024	8,17E-01	4,24	0.65-27.67	0,393
BTD	rs13078881	p.Asp444His	27	3	0,051	0,071	8,26E-01	1,63	0.51-5.19	0,535
AGL	rs150441555	p.Ser841Phe	5	1	0,009	0,024	9,23E-01	3,47	0.55-21.67	0,428
GLDC	rs147275962	p.Val705Met	5	1	0,009	0,024	9,23E-01	3,47	0.55-21.67	0,428
LIPE	rs145456377	p.Ala94Thr	5	1	0,009	0,024	9,23E-01	3,47	0.55-21.67	0,428
LPA	rs41259144	p.Arg990Gln	5	1	0,009	0,024	9,23E-01	3,47	0.55-21.67	0,428
MANBA	rs75826658	p.Val828Ile	5	1	0,009	0,024	9,23E-01	3,47	0.55-21.67	0,428
PHKB	rs56257827	p.Met185Ile	5	1	0,009	0,024	9,23E-01	3,47	0.55-21.67	0,428
TFR2	rs41295942	p.Arg752His	5	1	0,009	0,024	9,23E-01	3,47	0.55-21.67	0,428
ALMS1*	rs28730854	p.Ser2100Leu	42	4	0,079	0,095	9,37E-01	1,35	0.48-3.76	0,814
LRBA	rs35879351	p.Arg1997Cys	18	2	0,034	0,048	9,74E-01	1,72	0.44-6.68	0,708
EARS2	rs187662524	p.Glu349Lys	7	1	0,013	0,024	1,00E+00	2,53	0.43-15.04	0,517

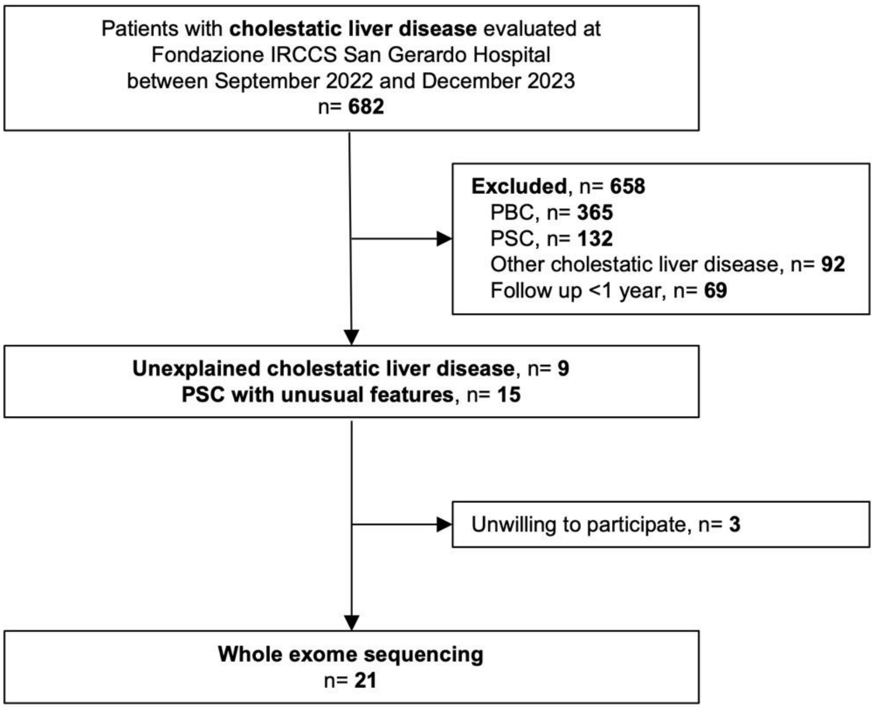
	CEP164*	rs200103555		15	1	0,028	0,024	1,00E+00	1,21	0.22-6.64	1,000
	LMF1	rs35168378	p.Arg364Gln	15	1	0,028	0,024	1,00E+00	1,21	0.22-6.64	1,000
	AHI1*	rs35433555	p.Arg548His	9	1	0,017	0,024	1,00E+00	1,99	0.35-11.47	0,591
	HFE	rs1800562	p.Cys282Tyr	9	1	0,017	0,024	1,00E+00	1,99	0.35-11.47	0,591
	APOB	rs533617	p.His1923Arg	18	1	0,034	0,024	1,00E+00	1,01	0.18-5.47	1,000
	CEP120*	rs2303720	p.Arg947His	18	1	0,034	0,024	1,00E+00	1,01	0.18-5.47	1,000
	CPS1	rs140578009	p.Gly1382Ser	18	1	0,034	0,024	1,00E+00	1,01	0.18-5.47	1,000
	HPS1	rs58548334	p.Val4Ala	20	2	0,038	0,048	1,00E+00	1,54	0.4-5.96	0,728
	AGPAT2	rs142993240	p.Arg159Cys	6	1	0,011	0,024	1,00E+00	2,93	0.48-17.77	0,471
	BSCL2	rs145649423	p.Leu427Pro	6	1	0,011	0,024	1,00E+00	2,93	0.48-17.77	0,471
	DYNC2H1*	rs61898615	p.Glu954Lys	6	1	0,011	0,024	1,00E+00	2,93	0.48-17.77	0,471
	NMBR	rs138994608	p.Pro148His	6	1	0,011	0,024	1,00E+00	2,93	0.48-17.77	0,471
	SLC37A4	rs34203644	p.Asn198Ile	6	1	0,011	0,024	1,00E+00	2,93	0.48-17.77	0,471
	HFE	rs1799945	p.His63Asp	77	6	0,145	0,143	1,00E+00	1,05	0.44-2.49	1,000
	ANK1	rs61735313	p.Asn251Lys	14	1	0,026	0,024	1,00E+00	1,29	0.23-7.15	1,000
	COQ2	rs112033303	p.Arg22Ter	14	1	0,026	0,024	1,00E+00	1,29	0.23-7.15	1,000
	ATG7	rs36117895	p.Val471Ala	21	2	0,039	0,048	1,00E+00	1,47	0.38-5.65	0,737
	AHI1*	rs13312995	p.Arg830Trp	24	2	0,045	0,048	1,00E+00	1,28	0.34-4.89	1,000
	PHKB	rs16945474	p.Tyr770Cys	24	2	0,045	0,048	1,00E+00	1,28	0.34-4.89	1,000
	CP	rs61733458	p.Thr551Ile	16	1	0,030	0,024	1,00E+00	1,13	0.21-6.2	1,000
	CIDEC	rs61742367	p.Thr49Met	26	2	0,049	0,048	1,00E+00	1,18	0.31-4.49	1,000
	PIEZO1	rs139051768	p.Thr1732Met	8	1	0,015	0,024	1,00E+00	2,23	0.38-13.02	0,557
	PRF1	rs35947132	p.Ala91Val	31	2	0,058	0,048	1,00E+00	0,98	0.26-3.7	1,000
	UNC13D	rs9904366	p.Ala59Thr	23	2	0,043	0,048	1,00E+00	1,34	0.35-5.12	0,758
other	TSHR	rs121908863	p.Pro162Ala	1	2	0,002	0,048	**4,42E-03**	21,87	2.82-169.79	0,139
	DCAF17	rs761229686	p.Trp302Ter	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
	DCT	rs937496254	p.Lys150Ter	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139

SLC12A3	rs780299444	p.Arg80ProfsTer35	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
TMEM70	rs183973249		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
VPS13B	rs1057516331	p.Trp2125Ter	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
COL18A1		p.Glu1238Ter	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
BRCA1	rs886040920	p.Pro209Leufs*25	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
KIAA1033	rs201428088	p.His503Arg	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
RAD50			0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
TYR	rs151206295	p.Ala355Val	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
INPP5K	rs750781027	p.Val23Met	0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
SURF1	rs781948238		0	1	0,000	0,024	1,01E-01	38,49	1.54-959.79	0,139
MYBPC3	rs376395543		1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
ADSL	rs372895468	p.Thr450Ser	1	1	0,002	0,024	3,36E-01	12,81	1.3-125.86	0,220
UPB1	rs143493067		2	1	0,004	0,024	5,33E-01	7,67	0.99-59.51	0,291
PADI3	rs142129409	p.Leu112His	3	1	0,006	0,024	6,90E-01	5,47	0.79-38	0,348

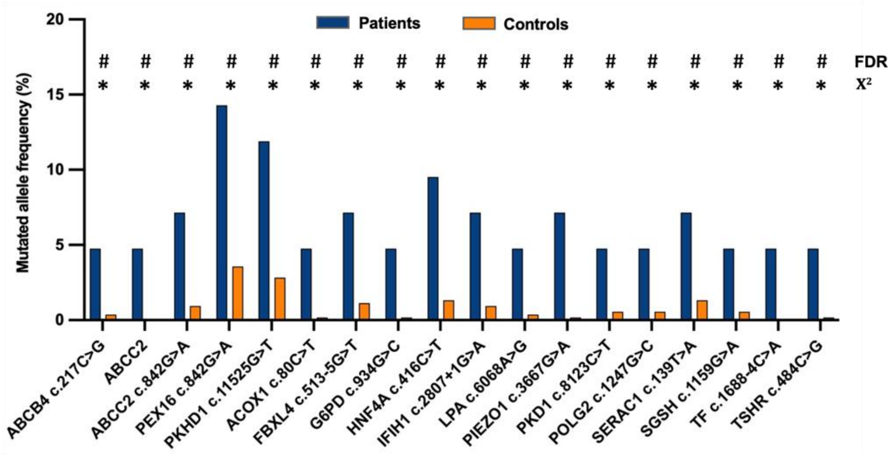
P value, OR and CI were calculated using Chi-squared test. *ciliopathy genes. In bold the nominally significant p-value. Abbreviations: OR: odds ratio; CI: confidence interval 95%



Supplementary Figure 1: Diagnostic flow chart of variant filtering strategy. Abbreviations: MAF, minor allele frequency; CADD, Combined Annotation Dependent Depletion; OMIM, Online Mendelian Inheritance in Man database; gnomAD, Genome Aggregation Database; ACMG, American College of Medical Genetics.

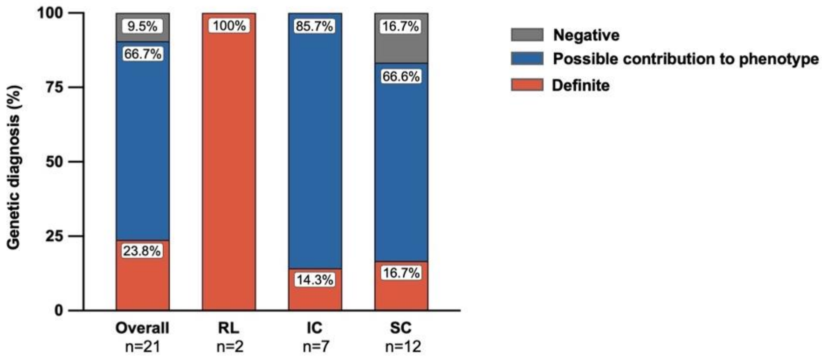


Supplementary Figure 2: Flowchart of patients' recruitment. Abbrevations: PBC, primary biliary cholangitis; PSC primary sclerosing cholangitis.



Supplementary Figure 3: Mutated allele frequency of selected variants in patients and controls.

Differences between frequencies were evaluated by chi-squared test with and without false discovery correction. Abbreviations: FDR, false discovery rate; $X2$, chi squared test. #p>0.05, *p<0.0001.



Supplementary Figure 4: Diagnostic yield of WES in the overall cohort and in different phenotypes. Overall, n=21; RL, n=2; IC, n=7; SC, n=12. Abbreviations: WES, whole exome sequencing; RL, recurrent lithiasis; IC, intrahepatic cholestasis; SC, sclerosing cholangitis with unusual features.