Supplementary Table 1 Classifications for various histopathological parameters

Grade of Liver Fibrosis	Score
Absent	0
Portal/Portoseptal Fibrosis	1
Portoportal Bridging Fibrosis (< 50% of portal tracts)	2
Portoportal Bridging Fibrosis (> 50% of portal tracts)	3
Portocentral Bridging Fibrosis with Cirrhotic Nodule Formation	4
Ductular reaction (evaluated in CK7 stain)	
None (< 5/portal)	0
Mild (5-9/portal)	1
Moderate (≥ 10/portal)	2
Marked (≥ 10/portal with elongated, angulated ductules)	3
Ductular metaplasia (evaluated by CK7 stain)	
None to occasional periportal hepatocytes expressing aberrant membrano-cytoplasmic CK7	0
More than occasional periportal and/or perivenular hepatocytes expressing aberrant membrano-cytoplasmic CK7	1
Hepatocytes till mid-acinus expressing aberrant membrano-cytoplasmic CK7	2
Numerous hepatocytes in panacinar distribution expressing aberrant membrano-cytoplasmic CK7	3
Giant cell transformation	
0% involvement	0
5% involvement	1
6%-50% involvement	2
> 50% involvement	3
Lobular inflammation	
< 2/10X	1
2-4/10X	2
> 4/10X	3

Supplementary Table 2 Definitions of histopathological parameters

Parameter	Definition
Cholestasis: Hepatocellular/intracanalicular	Presence of bilirubin pigment within the ductule, canaliculus, hepatocyte, or Kupffer cell usually as a bilirubin plug
Feathery degeneration	Hepatocyte cytoplasmic change due to the retention of bile acids characterized by a pale wispy reticular cytoplasm
Ductular cholestasis	Presence of bilirubin plugs within the ductules
Cholangio-cytopathy	Various nucleocytoplasmic changes of the cholangiocytes of the interlobular bile ducts signifying an ongoing damage including nucleomegaly, anisochromia, nucleolar prominence, cytoplasmic vacuolization, nuclear disarray, single cell necrosis/ apoptosis, lymphocytic cholangitis *etc.*
Perisinusoidal fibrosis	The presence of fibrosis around the sinusoids highlighted by Masson trichrome and/ or reticulin
Ductopenia	Inadequate number of interlobular bile ducts in the portal tracts highlighted by interlobular bile duct: portal tract ratio < 0.5
Extra-medullary hematopoiesis	Presence of any hematopoietic lineage element in the postnatal liver biopsy

Supplementary Table 3 Next-generation sequencing methodology

Genomic sequencing
Genomic DNA was extracted from peripheral blood samples (3ml EDTA). Targeted gene capture was performed using a custom capture kit, and sequencing libraries were prepared and processed on the Illumina platform, achieving a mean coverage of >80– 100X
Sequencing data were analyzed following the GATK Best Practices framework, utilizing Sentieon (v201808.07) for variant identification
Reads were aligned to the human reference genome (GRCh38.p13) using the Sentieon aligner, with subsequent removal of duplicate reads and recalibration of indels
Variants were identified using Sentieon Haplotype Caller and annotated using the Variant Effect Predictor (VEP) based on the Ensembl release 99 human gene model

Copy number variants (CNVs) were detected using ExomeDepth (v1.1.10), which compares read depths of the test sample with an aggregated reference dataset

The sensitivity of this assay to detect large deletions/duplications of more than 10 bp or CNV is 70%-75%

Clinically relevant mutations in both coding and non-coding regions are annotated using published variants in literature and a set of diseases databases: ClinVar, OMIM, HGMD, LOVD, DECIPHER (population CNV) and SwissVar

Common variants are filtered based on allele frequency in 1000Genome Phase 3, gnomAD (v3.1 and 2.1.1), dbSNP (GCF_000001405.38), 1000 Japanese Genome, TOPMed (Freeze_8), Genome Asia, and our internal Indian population database (MedVarDb v3.0)

Non-synonymous variants effect is calculated using multiple algorithms such as PolyPhen-2, SIFT, MutationTaster2 and LRT. Clinically significant variants are used for interpretation and reporting

Supplementary Table 4 Comparison of Histopathological parameters between bi-allelic and monoallelic *ABCB4* mutations

Histopathological Parameters	**Homozygous/compound heterozygous mutation (*n* = 16)**	**Heterozygous mutation (*n* = 10)**	**Significance**
Portal Fibrosis			
Absent	0%	10%	0.48
Portal/Portoseptal Fibrosis	0%	10%	
Portoportal bridging fibrosis (< 50% of portal tract)	6.7%	10%	
Portoportal bridging fibrosis (> 50% of portal tract)	26.7%	30%	
Portocentral bridging fibrosis with cirrhotic nodule formation	66.7%	40%	
Portal Inflammation			
None	13.3%	20%	0.33

Mild	80%	50%	
Moderate	6.7%	30%	
Cholangio-cytopathy	26.7%	0%	0.12
Ductular reaction			
None	0%	10%	0.36
Mild (5-9/portal tract)	33.3%	50%	
Moderate (>/= 10/portal tract)	26.7%	30%	
Marked (>/= 10/portal tract, with elongated angulated ductule)	40%	10%	
Ductular cholestasis	26.7%	0	0.12