Supplementary material

Supporting TABLE S1. Genetic Profile and Corresponding Genotype Severity Allocation of the 130 Included Patients

	First Allele	Second Allele	n
FIC1-A	c.923G>T; p.Gly308Val	c.923G>T; p.Gly308Val	18
	c.1660G>A; p.Asp554Asn	c.1660G>A; p.Asp554Asn	8
	c.1367C>T; p.Thr456Met	c.1367C>T; p.Thr456Met	4
	c.1799G>A; p.Arg600Gln	c.1799G>A; p.Arg600Gln	3
	c.625A>C; p.Pro209Thr	c.625A>C; p.Pro209Thr	2
	c.625A>C; p.Pro209Thr	c.2081T>A; p.Ile694Asn	2
	c.1587_1589delCTT; p.Phe529del	c.1587_1589delCTT; p.Phe529del	2
	c.2081T>A; p.Ile694Asn	c.2081T>A; p.Ile694Asn	2
	c.886C>T ; p.Arg296Cys	c.2081T>A; p.Ile694Asn	2
	c.1208C>T; p.Ser403Phe	c.1208C>T; p.Ser403Phe	1
	c.1264G>C; p.Asp422His	c.2734G>A; p.Gly912Arg	1
	c.1697G>A; p.Gly566Asp	c.1697G>A; p.Gly566Asp	1
	c.1798C>T; p.Arg600Trp	c.1367C>G; p.Thr456Arg	1
	c.1798C>T; p.Arg600Trp	c.2966A>T; p.Asn989Ile	1
	c.1798C>T; p.Arg600Trp	c.1798C>T; p.Arg600Trp	1
	c.1982T>C; p.Ile661Thr	c.2103G>C; p.Gly702Arg	1
	c.1982T>C; p.Ile661Thr +c.923G>T; p.Gly308Val	c.1220G>A; p.Ser407Asn	1
	c.2081T>A; p.Ile694Asn	c.2663C>A; p.Thr888Lys	1
	c.2081T>A; p.Ile694Asn	c.2236T>C; p.Cys746Arg	1
	c.2199A>C; p.Asp734Ala	c.2199A>C; p.Asp734Ala	1
	c.2450C>A; p.Thr717Asn	c.2450C>A; p.Thr717Asn	1
	c.2558T>C; p.Phe853Ser	c.2558T>C; p.Phe853Ser	1
	c.2663C>T; p.Thr888Met	c.2081T>A; p.Ile694Asn	1

	c.2674G>A; p.Gly892Arg	c.1982T>C; p.Ile661Thr	1
	c.2989G>A; p.Val997Met	c.2699T>C; p.Met900Thr	1
	c.2989G>A; p.Val997Met +c.2699T>C; p.Met900Thr	c.913T>A; p.Phe305Ile	1
	c.319T>C; p.Cys107Arg)	c.319T>C; p.Cys107Arg	1
	c.625C>A; p.Pro209Thr	c.632A>C; p.Asp211Ala	1
	c.644T>G; p.Leu215Arg	c.644T>G; p.Leu215Arg	1
	c.697G>A; p.Gly233Arg	c.697G>A; p.Gly233Arg	1
	c.863T>C; p.Leu288Ser	c.863T>C; p.Leu288Ser	1
	c.886C>T; pArg296Cys	c.886C>T; p.Arg296Cys	1
	c.940G>C; p.Gly314Arg	c.1798C>T; p.Arg600Trp	1
FIC1-B	c.1367C>T; p.Thr456Met	**c.1804C>T; p.Arg602Ter**	2
	c.625A>C; p.Pro209Thr	**c.2854C>T; p.Arg952Ter**	1
	c.2374_2375insT; p.Pro792fsTer808	c.2989G>A; p.Val997Met	1
	c.1367C>T; p.Thr456Met	**c.1804C>T; p.TerArg602Ter**	1
	c.1194del; p.Met399TrpfsTer12	c.2237G>A; p.Cys746Tyr	1
	c.1232dupT; p.Arg412SerfsTer18	c.1798C>T; p.Arg600Trp	1
	c.1336G>A; p.Gly446Arg	**c.2271T>A; p.Tyr757Ter**	1
	c.1336G>A; p.Gly446Arg	**c.782-1G>A; p.(?)**	1
	c.1336G>A; p.Gly446Arg	**c.1587_1589delCTT; p.Phe527Ter**	1
	c.1367C>A; p.Thr456Lys	**c.3292delG; p.Val1098Ter**	1
	c.1660G>A; p.Asp554Asn	**c.3602delG; p.Gly1201AlafsTer88**	1
	c.1660G>A; p.Asp554Asn	**c.2097+2T>C; p.(?)**	1
	c.1753G>T; p.Glu585Ter	c.2246T>C; p.Leu749Pro	1
	c.1982T>C; p.Ile661Thr	**c.1804C>T; p.Arg602Ter**	1
	c.1982T>C; p.Ile661Thr	**c.2097+2T>C; p.(?)**	1

	c.1982T>C; p.Ile661Thr	**c.279G>A; p.(?)**	1
	c.2081T>A; p.Ile694Asn	**c.279G>A; p.(?)**	1
	c.2081T>A; p.Ile694Asn	**c.2788C>T; p.Arg930Ter**	1
	c.2097+2T>C; p.(Ile645-Ile699del)	c.2982C>A; p.Ser994Arg	1
	c.2150C>A; p.Thr717Asn	**c.2854C>T; p.Arg952Ter**	1
	c.2741A>T; p.Glu914Val	**c.3399+2G>A; p.(?)**	1
	c.279G>A; p.(?)	c.1660G>A; p.Asp555Asn	1
	c.2821C>T; p.TerArg941Ter	c.2081T>A; p.Ile694Asn	1
	c.2854C>T; p.TerArg952Ter	c.1982T>C; p.Ile661Thr	1
	c.2877dup; p.Ala960CysfsTer50	c.2558T>C; p.Phe853Ser	1
	c.571T>A; p.Trp191Arg	**c.884T>G; p.Leu295Ter**	1
	c.749T>A; p.Leu250His	**c.811C>T; p.TerArg271Ter**	1
	c.886C>T; p.Arg296Cys	**c.1675_1689delGTAAACGCTGCCAGG; p.Val559_Arg563del**	1
FIC1-C	**c.2932-3C>A; p.(?)**	**c.2932-3C>A; p.(?)**	6
	c.2097+2T>C; p.(Ile645-Ile699del)	**c.2097+2T>C; p.(Ile645-Ile699del)**	3
	c.1030-1G>A; p.(?)	**c.2014_2015delAA; p.Lys672ValfsTer17**	2
	c.2742_2743delAGinsT; p.Gly914AspfsTer32	**c.2742_2743delAGinsT; p.Gly914AspfsTer32**	2
	c.763C>T; p.Arg255Ter	**c.1587_1589del; p.Phe529del**	2
	c.1429+1G>A; p.(?)	**c.1429+1G>A; p.(?)**	1
	c.1602C>A; p.Cys534Ter	**c.2844delC; p.Cys948Ter**	1
	c.1631-?_1932+?del; p.(?)	**c.1631-?_1932+?del; p.(?)**	1
	c.1993G>T; p.Glu665Ter	**c.3617_3623dupGCTCGGC; p.Tyr1209LeufsTer29**	1
	c.208G>A; p.Asp70Asn (VOUS) **+c.811C>T; p.Arg271Ter**	c.208G>A; p.Asp70Asn (VOUS) **+c.811C>T; p.Arg271Ter**	1

	c.2418+5G>A; p.(?)	**c.2418+5G>A; p.(?)**	1
	c.2737C>T; p.Gln913Ter	**c.2737C>T; p.Gln913Ter**	1
	c.2821C>T; p.Arg941Ter	**c.2821C>T; p.Arg941Ter**	1
	c.3040C>T; p.Arg1014Ter	**c.2097+2T>C; p.(?)**	1
	c.3127delA; p.Thr1043HisfsTer3	**c.3127delA; p.Thr1043HisfsTer3**	1
	c.3410C>G; p.Ser1137Ter	**c.3410C>G; p.Ser1137Ter**	1
	c.3531+1G>A; p.(?)	**c.3531+1G>A; p.(?)**	1
	c.3554T>A; p.Leu1185Ter	**c.2707+4A>G; p.(?)**	1
	c.3622_3628delGCCTACG; p.(?)	**c.3622_3628delGCCTACG; p.(?)**	1
	c.589_592delinsCTCCA; p.Gly197LeufsTer10	**c.589_592delinsCTCCA; p.Gly197LeufsTer10**	1
	c.607insA; p.Asn205LysfsTer2	**c.2532delT; p.Lys845ArgfsTer36**	1
	c781+1G>A; p.(?)	**c.2097+2T>C; p.(?)**	1
	c.958-967del; p.Met320ValfsTer13	**c.958-967del; p.Met320ValfsTer13**	1
	g.24774-42062del	**g.24774-42062del**	1

Genetic profile includes mutations in *ATP8B1* on first and second allele.

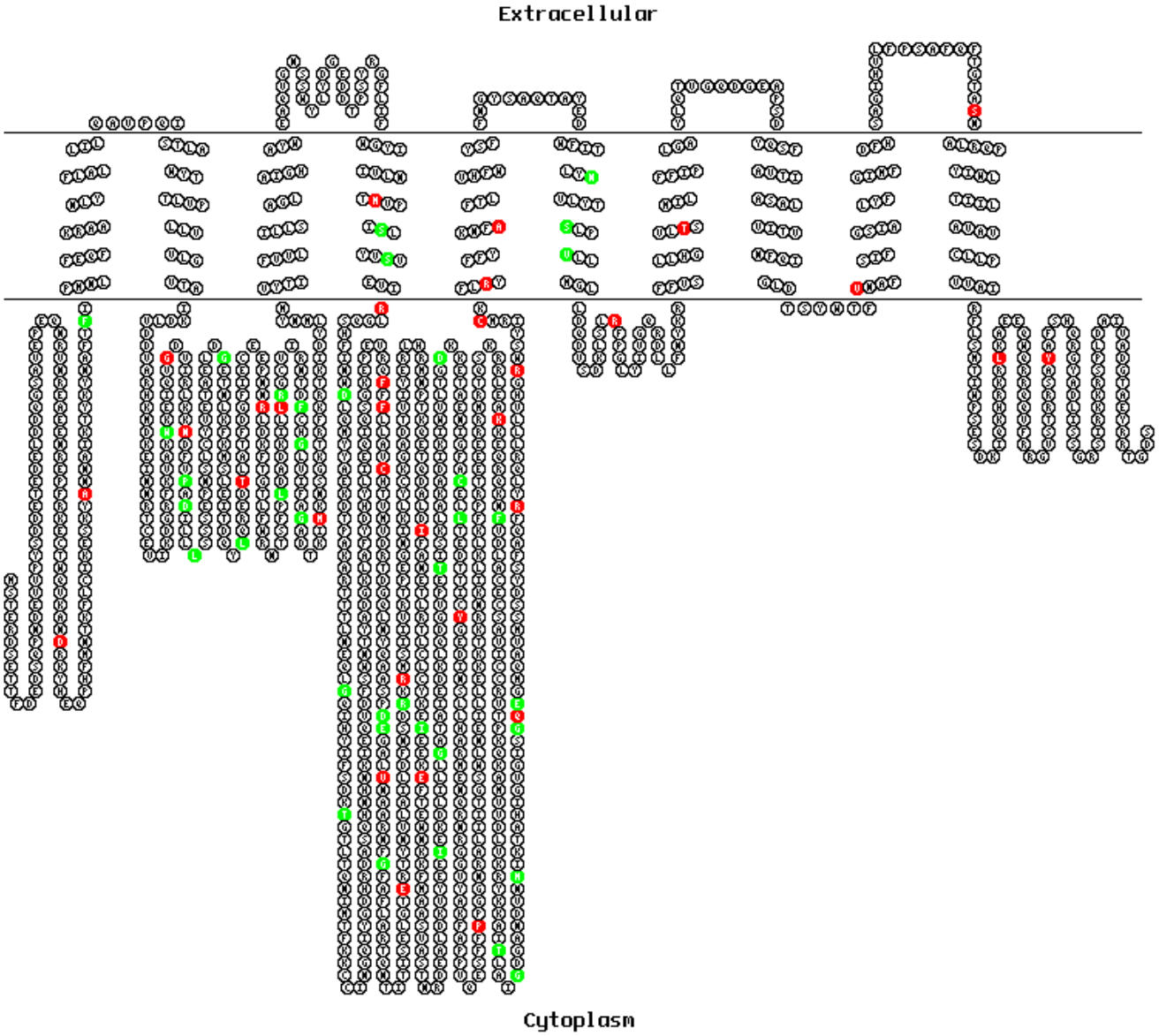
Bold indicates PPTM.

Abbreviations: *ATP8B1*, adenosine triphosphate (ATP)ase phospholipid transporting 8B1; FIC1, familial intrahepatic cholestasis type 1; FIC1-A, no PPTM; FIC1-B, 1 PPTM; FIC1-C, 2 PPTMs; PPTM, predicted protein truncating mutation; VOUS, variant of unknown significance.

Supporting TABLE S2. Follow-Up Characteristics of All Included FIC1 Deficiency Patients

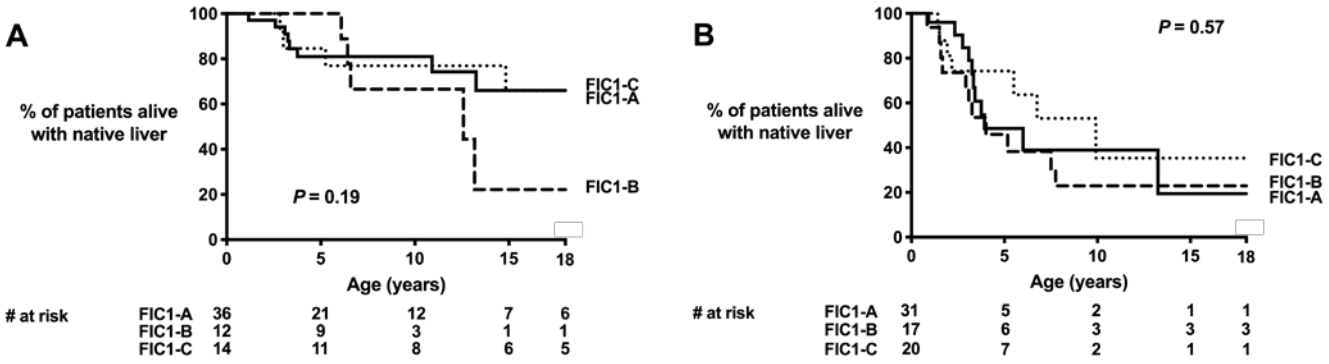
Parameter	Outcome
SBD	**n = 62**
PEBD, n (%)	49 (79)
GCD, n (%)	6 (10)
IE, n (%)	4 (5)
TBD, n (%)	1 (2)
Cholecystojejunostomy, n (%)	1 (2)
Unknown, n (%)	1 (2)
Indication for SBD	
Pruritus, n (%)	21 (32)
Cholestasis, n (%)	1 (2)
Unknown, n (%)	41 (65)
LT	**n = 38**
Indication for LT	
Pruritus, n (%)	19 (50)
ESLD, n (%)	9 (23)
Unknown, n (%)	10 (28)
Mortality (pre-LT)	8 (6)
Causes of death	
Related to liver disease, n (%)	6 (75)
Unrelated to liver disease, n (%)	2 (25)
HCC, n (%)	0 (0)

Abbreviations: ESLD, end-stage liver disease; GCD, gallbladder-colic diversion; HCC, hepatocellular carcinoma; IE, ileal exclusion; LT, liver transplantation; PEBD, partial external biliary diversion; SBD, surgical biliary diversion; TBD, total biliary diversion.

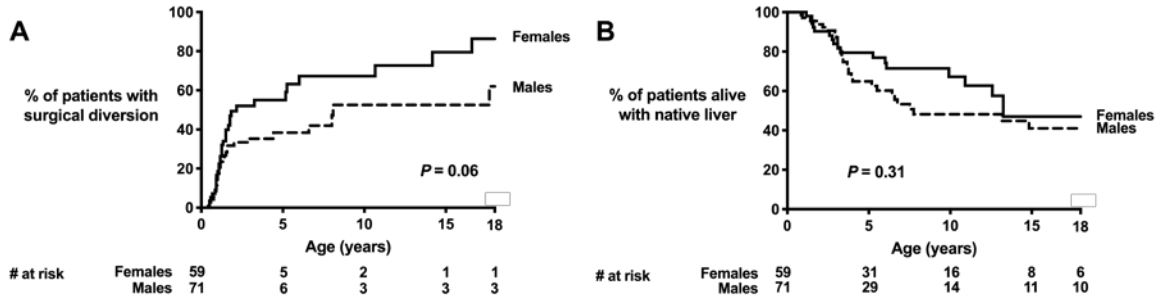


Supporting FIG. S1. Locations of observed mutations in *ATP8B1*. TOPO2 software model of FIC1 protein based on sequence and transmembrane regions by UniProt. Red: PPTM. Green: non-PPTM. The first affected position is marked for frameshift variants.

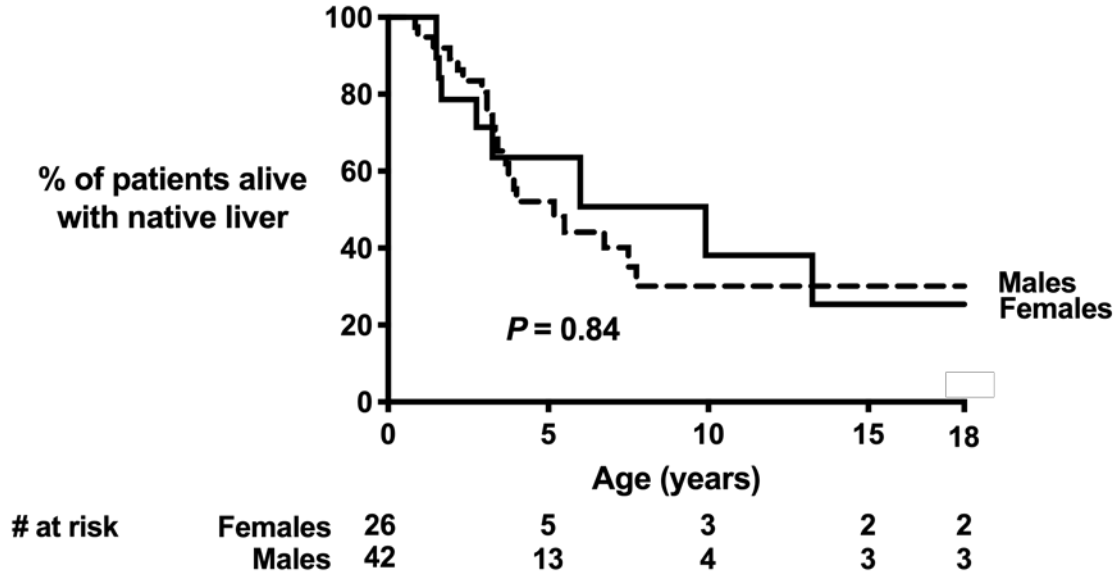
Abbreviations: ATP8B1, adenosine triphosphate (ATP)ase phospholipid transporting 8B1; FIC1, familial intrahepatic cholestasis type 1; PPTM, predicted protein truncating mutation.



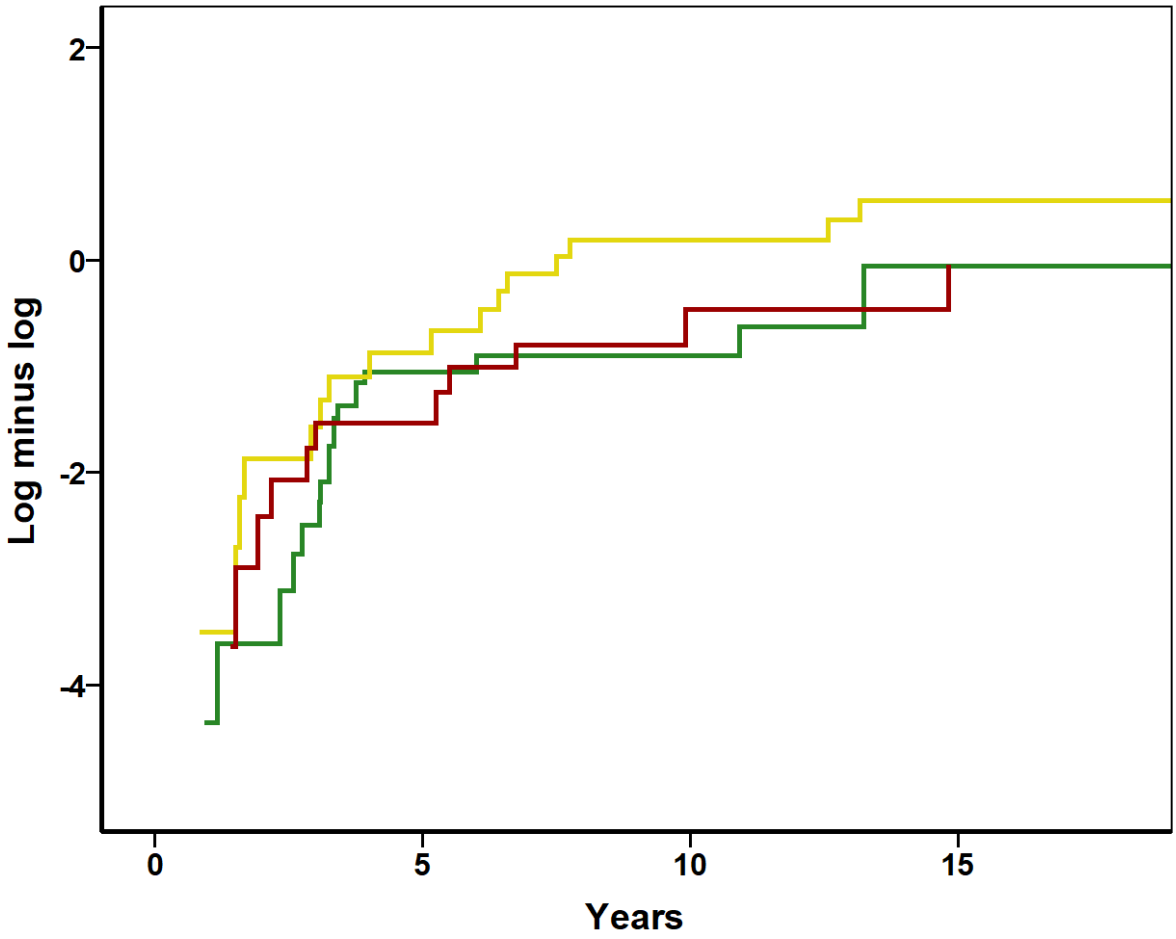
Supporting FIG. S2. NLS in (A) patients who had undergone SBD during follow-up and (B) patients who had not undergone SBD during follow-up. Abbreviations: FIC1-A, no PPTM; FIC1-B, 1 PPTM; FIC1-C, 2 PPTMs; NLS, native liver survival; SBD, surgical biliary diversion.



Supporting FIG. S3. (A) Proportion of patients with an SBD over time in male and female patients. (B) Proportion of patients alive with native liver over time in male and female patients.



Supporting FIG. S4. Proportion of patients alive with native liver over time in male and female patients who had not undergone surgical diversion during follow-up.



Supporting FIG. S5. Log minus log plot to assess the assumption of proportional hazard for time-dependent Cox regression (Fig. 5) in patients with an FIC1-A (green line), FIC1-B (orange line), and FIC1-C (red line) genotype. This graph shows that in FIC1-B patients, the risk for an event (i.e., LT or death) increases to a greater extent than in FIC1-A or FIC1-C patients. Abbreviation: LT, liver transplantation.