Supplemented material:

Literature on the identified genetic variants.

After identifying the respective genetic variants in our patients with intrahepatic cholestasis using next-generation sequencing, we compared our findings with relevant publications from other research groups. The references abbreviated as Ref1 - Ref11 in Figure 1B are listed here with their corresponding literature citations.

1. Kruk, B., et al. (2022). "A common variant in the hepatobiliary phospholipid transporter ABCB4 modulates liver injury in PBC but not in PSC: prospective analysis in 867 patients." Orphanet J Rare Dis **17**(1): 419.
2. Jungst, C., et al. (2022). "Common ABCB4 and ABCB11 Genotypes Are Associated with Idiopathic Chronic Cholestasis in Adults." Dig Dis **40**(4): 489-496.
3. Cheng, F., et al. (2022). "Tacrolimus Concentration Is Effectively Predicted Using Combined Clinical and Genetic Factors in the Perioperative Period of Kidney Transplantation and Associated with Acute Rejection." J Immunol Res **2022**: 3129389.
4. Sissung, T. M., et al. (2019). "Severe Hepatotoxicity of Mithramycin Therapy Caused by Altered Expression of Hepatocellular Bile Transporters." Mol Pharmacol **96**(2): 158-167.
5. Schreiner, P., et al. (2019). "A rare cause of a cholestatic jaundice in a North African teenager." Liver Int **39**(11): 2036-2041.
6. Zhan, L., et al. (2016). "Prevalence of ABCB4 polymorphisms in gallstone disease in han-Chinese population." Am J Transl Res **8**(2): 1218-1227.
7. Chen, R. R., et al. (2014). "The association between bile salt export pump single-nucleotide polymorphisms and primary biliary cirrhosis susceptibility and ursodeoxycholic acid response." Dis Markers **2014**: 350690.
8. Blackmore, L., et al. (2013). "Polymorphisms in ABCB11 and ATP8B1 Associated with Development of Severe Intrahepatic Cholestasis in Hodgkin's Lymphoma." J Clin Exp Hepatol **3**(2): 159-161.

9. Janssen, M. J., et al. (2012). "Loss of heterozygosity is present in SEC63 germline carriers with polycystic liver disease." PLoS One **7**(11): e50324.
10. Acalovschi, M., et al. (2009). "Common variants of ABCB4 and ABCB11 and plasma lipid levels: a study in sib pairs with gallstones, and controls." Lipids **44**(6): 521-526.
11. van IJzendoorn, Sven C D et al. "Unequal Effects of Myosin 5B Mutations in Liver and Intestine Determine the Clinical Presentation of Low-Gamma-Glutamyltransferase Cholestasis." Hepatology (Baltimore, Md.) vol. **72,4** (2020

Supplementary Table 1 The different variants have been linked to previously published references

Genes	Variants		Proteins	MAF	ClinVar	References	Phenotypes	Patient 1	Patient 2
ABCB4	rs2302387	c.175C > T	p.L59 L	0,25	benign	Ref4	DILI		heterozygous
ABCB4	rs1202283	c.504C > T	p.N168N	0,35	benign	Ref2,Ref6	Cholestasis, gall stones	homozygous	
ABCB4	rs2109505	c.711A > T	p.I237I	0,26	benign	Ref1,Ref2	Idiopathic cholestasis, PBC	homozygous	heterozygous
ABCB4	rs31668	c.2211 + 16C > T		0,13	benign	Ref5	DILI	homozygous	homozygous
ABCB4	rs31653	c.3508-16T > C		0,12	benign	Ref10	Low HDL cholesterol	heterozygous	homozygous
ABCB11	rs2287618	c.909-15A > G		0,23	benign	Ref5,Ref7	DILI, protective in PBC	homozygous	
ABCB11	rs373048820	c.1092C > T	p.L364 L	< 0,01	likely benign			heterozygous	
ABCB11	rs2287622	c.1331C > T	p.A444V	0,41	benign	Ref2	Idiopathic cholestasis	homozygous	homozygous

ATP8B1	rs319438	c.696T > C	p.D232D	0,01	benign	Ref5,Ref8	DILI, severe cholestasis	homozygous	homozygous
ATP8B1	rs319443	c.811A > C	p.R271R	0,01	benign	Ref5	DILI	homozygous	homozygous
ATP8B1	rs665278	c.2098-8C > A		0,15	likely benign			heterozygous	heterozygous
ATP8B1		c.2098-4C > A			n/a			heterozygous	heterozygous
ATP8B1	rs222581	c.3454G > A	p.A1152T	< 0,01	n/a	Ref5,Ref8	DILI, severe cholestasis	homozygous	homozygous
ATP8B1	rs34027711	c.3531 + 8G > T		0,09	benign				heterozygous
MYO5B	rs1815930	c.376A > G	p.T126A	0,03	benign			homozygous	homozygous
MYO5B	rs17715416	c.1545 + 11T > C		0,32	benign			homozygous	heterozygous
MYO5B		c.2004-12C > A			n/a			heterozygous	

MYO5B	rs200559863	c.2076T > C	p.A692A	0,02	likely benign			heterozygous	
MYO5B	rs200219597	c.3163_3165dup	p.L1056dup	< 0,01	n/a	Ref11	Low gGT Cholestasis	heterozygous	heterozygous
MYO5B	rs2276176	c.3276 + 11T > C		0,29	benign			heterozygous	heterozygous
MYO5B	rs75971548	c.3396 + 9T > C		0,21	n/a				heterozygous
MYO5B	rs3826579	c.3591C > T	p.Y1197Y	0,3	benign			heterozygous	heterozygous
MYO5B	rs1942418	c.3962G > A	p.G1321E	0,42	benign			heterozygous	
MYO5B	rs488890	c.4315 + 5G > C		0,35	n/a				heterozygous
MYO5B	rs2276170	c.4464G > A	p.L1488L	0,42	benign			heterozygous	
SEC63	rs675117	c.564C > T	p.N188N	0,14	benign	Ref9	Polycystic liver disease	homozygous	heterozygous

NR1H4	rs561638	c.-1G > T	benign	heterozygous