Genetic testing in adults with unexplained cholestasis

Clinical Aid

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Section 1 : Technology

Next-generation sequencing (NGS) has transformed diagnostic yield in adults with suspected genetic cholestasis, including cases previously labeled idiopathic or cryptogenic.

Three approaches are used in practice:

Approach	What it covers	Where it helps and when it is used
Targeted gene panel	A curated set of known cholestasis-associated genes (see Section 2)	First-line where a genetic cause is suspected on clinical grounds; scope limited to curated, well-characterized genes, which narrows the number of variants requiring interpretation; allows faster turnaround.
Whole-exome sequencing (WES)	All protein-coding regions genome-wide	When panel testing is negative but suspicion remains high, or the phenotype is atypical/ syndromic. In some countries, WES is available as the first-line NGS approach.
Whole-genome sequencing (WGS)	Coding and non-coding regions	Currently reserved for research settings or when WES is uninformative but clinical features strongly suggest a genetic cause (e.g., a positive family history); can detect deep intronic/regulatory variants that panels and WES miss.



Sample requirements: For DNA extraction, peripheral blood (EDTA) is standard; saliva or buccal swab is acceptable where phlebotomy is impractical. Liver tissue is not required for germline testing.

Interpretation caveats:

- **Variants of uncertain significance (VUS)** are commonly detected and do not confirm or exclude a diagnosis. They require phenotype correlation, segregation analysis in family members where possible, and periodic reclassification as evidence accumulates.
- **Genotype must be interpreted against phenotype,** not read in isolation: biochemical pattern, age of onset, family history, and imaging/histology all inform whether a variant is disease-causing.
- **A negative panel does not exclude genetic cholestasis;** consider reanalysis using WES and/or genes not yet on standard liver/cholestasis panels or not clearly related to cholestasis (see Section 2). EASL guidelines also recommend reanalyzing the data **at least every 3 years** in patients who remain undiagnosed after the first round of genetic testing, to check for newly discovered variants.
- **Genetic counseling** should accompany result disclosure, particularly for reproductive-age patients and relatives eligible for cascade testing, and to address follow-up requirements.

Section 2 : Key genes for an NGS panel

The genetic architecture of adult cholestatic liver disease is heterogeneous and continues to expand. The genes listed below represent established causes of inherited cholestasis and related disorders that may present or be recognized for the first time in adulthood.

Disease expression ranges from mild recurrent cholestasis and pregnancy-associated disease to progressive fibrosis, cirrhosis, and multisystem syndromes. Genetic findings should always be interpreted in the context of clinical phenotype, biochemical profile, imaging, and family history.

Gene	Protein/mechanism	Principal disease association(s)
ABCB4	MDR3, biliary phospholipid transporter	*ABCB4*-related cholestatic disease spectrum, including LPAC syndrome, ICP susceptibility, and progressive cholangiopathy
ABCB11	BSEP, bile salt export pump	*ABCB11* deficiency and recurrent or intermittent cholestatic liver disease; DILI susceptibility
ATP8B1	FIC1, aminophospholipid flippase	*ATP8B1* deficiency with hepatic and extrahepatic manifestations
JAG1	Notch ligand	Alagille syndrome
NOTCH2	Notch receptor	Alagille syndrome (*NOTCH2*-related Alagille syndrome is thought to be diagnosed more often in adults)
TJP2	ZO-2, tight junction protein	*TJP2*-related cholestatic liver disease; heterozygous variants linked to adult cholestasis/cirrhosis
NR1H4	FXR, bile acid nuclear receptor	*NR1H4*-related cholestatic disease (severe, typically early-onset), ICP susceptibility
MYO5B	Apical trafficking motor protein	*MYO5B*-related cholestasis, including isolated hepatic phenotypes
ABCC2	MRP2, canalicular conjugate exporter	Dubin-Johnson syndrome
SLCO1B1/3	OATP1B1/1B3, hepatocyte uptake transporters	Rotor syndrome; *SLCO1B1* variants also modify drug/statin handling

Additional/emerging genes worth considering for panel expansion:

- ***SLC51A / SLC51B*** (OSTα/OSTβ): cholestasis with congenital diarrhea; increasingly reported in adult-onset low-GGT cholestasis
- ***USP53, KIF12, ZFYVE19:*** newer PFIC-like/ cholangiopathy genes, some with associated hearing loss
- ***SERPINA1*** (alpha-1 antitrypsin deficiency): key differential/reflex test in adult cholestasis of unclear cause, especially with unexplained cirrhosis
- ***VPS33B / VIPAS39:*** ARC syndrome spectrum; typically pediatric but relevant for milder adult phenotypes
- ***SEMA7A:*** SEMA7A-related cholestatic disease; disrupts BSEP/MRP2 trafficking and is associated with low-GGT cholestasis
- ***TULP3:*** TULP3-related ciliopathy associated with progressive liver fibrosis and cirrhosis

Section ❸ : Adult phenotype clues and diagnostic considerations

The same genetic disorder may present very differently across the lifespan, and adults often exhibit milder or atypical phenotypes than those described in pediatric cohorts.

Recognition of characteristic biochemical and clinical features can help guide test selection and support interpretation of genetic findings in adults with unexplained cholestasis.

Gene	OMIM number*	Adult phenotype clue
ABCB4	#602347	Typically **high-GGT** cholestasis. Consider in patients with early or recurrent gallstones (symptom onset before age 40 years), LPAC syndrome, intrahepatic cholestasis of pregnancy, unexplained cholangiopathy, or progressive biliary fibrosis.
ABCB11	#605479, #601847	Typically **low-GGT** cholestasis with recurrent or intermittent cholestatic episodes, pruritus, or unexplained cholestatic liver disease. Disease severity is variable and may extend beyond childhood presentations.
ATP8B1	#243300, #147480	Typically **low-GGT** cholestasis accompanied by extrahepatic features such as diarrhea, pancreatitis, hearing impairment, or growth abnormalities.
JAG1 / NOTCH2	#118450 / #610205	Usually **high-GGT** cholestasis with bile duct paucity. Look for associated cardiac, skeletal, ocular, facial, or renal findings that may be subtle in adults.
TJP2	#615878	**Variable GGT** pattern. Consider in unexplained cholestasis, fibrosis, or cirrhosis. Heterozygous variants have also been associated with susceptibility to intrahepatic cholestasis of pregnancy.
NR1H4	#617049	Usually associated with severe cholestatic disease, although milder adult phenotypes and variants associated with ICP have been reported.
MYO5B	#619868	Often presents with **low-GGT** cholestasis and may occur without significant intestinal manifestations.
ABCC2	#237500	Conjugated hyperbilirubinemia without progressive cholestatic liver injury. Important benign differential diagnosis.
SLCO1B1/3	#237450	Rotor syndrome presents with benign conjugated hyperbilirubinemia and no progressive liver disease.

*Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. Available at: https://omim.org/

Clinical tip: Consider multidisciplinary hepatology genomics review for patients with suspected genetic liver disease, particularly when clinical features and genetic results are discordant or variants of uncertain significance are identified, as specialist discussion can refine diagnosis and inform further testing.

Abbreviations: ARC, arthrogryposis, renal dysfunction, and cholestasis; BSEP, bile salt export pump; DILI, drug-induced liver injury; EASL, European Association for the Study of the Liver; EDTA, ethylenediaminetetraacetic acid; FIC1, familial intrahepatic cholestasis 1; FXR, farnesoid X receptor; GGT, gamma-glutamyl transferase; ICP, intrahepatic cholestasis of pregnancy; LPAC, low phospholipid-associated cholelithiasis; MDR3, multidrug resistance protein 3; MRP2, multidrug resistance-associated protein 2; NGS, next-generation sequencing; OATP, organic anion-transporting polypeptide; OST, organic solute transporter; PFIC, progressive familial intrahepatic cholestasis; VUS, variant of uncertain significance; WES, whole-exome sequencing; WGS, whole-genome sequencing; ZO-2, zonula occludens-2.

References: European Association for the Study of the Liver. *J Hepatol*. 2024;81(2):303-325; Keitel V, Mentzinger A, Dröge C, Vilarinho S. *JHEP Rep*. 2026;8(9):101902; Nasir AB, Alkhouri N, Gish R, et al. *Dig Dis Sci*. 2026;71:838-851; Nayagam JS, Foskett P, Strautnieks S, et al. *Hepatol Commun*. 2022;6(10):2654-2664; Dröge C, Götze T, Behrendt A, Gohlke H, Keitel V. *Explor Dig Dis*. 2023;2:34-43; Bittencourt PL, Rotman V, Codes L, et al. *Hepatol Commun*. 2026;10(1):e0851; Dong C, Condat B, Picon-Coste M, et al. *JHEP Rep*. 2020;3(2):100201; Nayagam JS, Williamson C, Joshi D, Thompson RJ. *Aliment Pharmacol Ther*. 2020;52:1628-1639; Bull LN, Morotti R, Squires JE. ATP8B1 Deficiency - GeneReviews®. Updated September 9, 2021; Ayoub MD, Bakhsh AA, Vandriel SM, Keitel V, Kamath BM. *Hepatol Int*. 2023;17:1098-1112; Vandriel SM, Li L-T, She H, et al. *Liver Int*. 2025;45(9):e70251; Dixon PH, Sambrotta M, Chambers J, et al. *Sci Rep*. 2017;7:11823; Wei CS, Becher N, Friis JB, et al. *World J Gastroenterol*. 2020;26(5):550-561; Khabou B, Othman H, Guirat M, et al. *J Hum Genet*. 2025;70:331-339; Shah AA, Deswal S, Mohan N, Rastogi AN. *JPGN Rep*. 2021;2(2):e071; Gomez-Ospina N, Potter CJ, Xiao R, et al. *Nat Commun*. 2016;7:10713; Lai H, Liu X, Xin S, et al. *BMC Med Genomics*. 2022;15:90; Overeem AW, Li Q, Qiu Y-L, et al. *Hepatology*. 2020;72:213-229; Huimin Z, Yuan W, Chuanyan X, Jing C. *Front. Gastroenterol*. 2025;4:1435168; Morais MB, Machado MV. *United European Gastroenterol J*. 2022;10(7):745-753.

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