When might you consider Progressive Familial Intrahepatic Cholestasis (PFIC) in the adult cholestatic patient?

While initially characterised in paediatric patients, PFIC can manifest **later in life** after a specific trigger or patients may remain undiagnosed into adulthood[1–3]

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Explore the algorithm below to learn more about the patient presentations that may benefit from reassessment for PFIC

SYMPTOMS OF CHOLESTASIS

- **Pruritus**
- **Jaundice**
- **Fatigue**

Elevated Alkaline phosphatase (ALP) and/or GGT and/or bilirubin

Detailed history & physical examination

No likely cause identified

Ultrasound

Normal

AMA + ANA (sp100, gp210)

Negative

MRCP, FibroScan

Negative

Positive

Liver biopsy

Positive

Inconsistent with any known cause of cholestasis

POTENTIAL DIAGNOSIS

DILI, ICP, hormone-induced cholestasis

Recent history of DILI, ICP, hormone use[9,10]

History of complicated gallstones, LPAC, family history of gallstones[11]

Family history of liver disease, ICP, HCC, DILI, or episodic PFIC[9]

Dilated ducts, stone, tumour

PBC

PSC

SSC

Metabolic dysfunction-associated steatotic liver disease (MASLD)[12]

Metabolic dysfunction-associated steatohepatitis (MASH)[12]

Parenchymal or biliary disease

COULD IT BE PFIC?

Click on the buttons below to find out more about presentations that may indicate PFIC

- **Cholestatic pruritus following recent liver issue**
- **History of complicated gallstones/LPAC**
- **Family history of liver disease/ liver issue**
- **Insufficient response to treatment despite compliance**
- **AMA negative PBC**
- **Small duct PSC**
- **Lean MASLD without metabolic syndrome**[12]
- **MASLD with pruritus**[12]
- **MASH with pruritus and without metabolic syndrome**[12]
- **Idiopathic cholestasis**

MAKING A DIAGNOSIS

Click on the buttons below to learn more about diagnostic tests for suspected PFIC

Biochemical tests
Serum bile acids

Supportive genetic analysis
ATP8B1, ABCB11, ABCB4, TJP2, NR1H4 and MYO5B

Want to learn more?

For more information on **PFIC**, visit: https: //www.omim.org/entry/211600

For more information on **adult-onset PFIC**, read: Nayagam JS et al. Hepatol Commun 2022;6:2654–2664

Adapted from Dröge C et al, 2023;[7] Alkhouri N, 2023;[3] European Association for the Study of the Liver (EASL). EASL Clinical practice guidelines: management of cholestatic liver diseases. J Hepatol 2009:51:237–267.[8]

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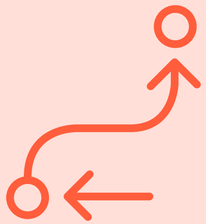
SYMPTOMS OF … | POTENTIAL DIAGNOSIS | COULD IT BE PFIC? | MAKING A DIAGNOSIS

CHOLESTATIC PRURITUS FOLLOWING RECENT LIVER ISSUE



Secondary cholestasis triggered by a liver issue can be a sign of PFIC.[1]

Consider reassessing your patient for PFIC if they present with cholestatic pruritus following a recent liver issue, including:

- Intrahepatic cholestasis of pregnancy[2]
- Drug-induced cholestasis[3]
- Hormone-induced cholestasis (cholestasis triggered by birth control, menopause, etc.)[4,5]

PFIC, progressive familial intrahepatic cholestasis.

1. Alkhouri N. Presented at AASLD 2023, Boston, US; 10–14 November; **2.** Hardikar W et al. *World J Gastroenterol* 2009;15:1126–1129; **3.** Vitale G et al. *Dig Liv Dis* 2019;51:922–933; **4.** Ganne-Carrie N et al. *J Hepatol* 2003;8:693–697; **5.** Zu Y et al. *Front Pharmacol* 2021;12:761255.

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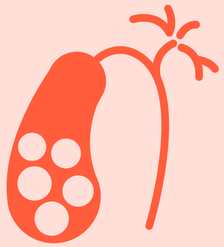
HISTORY OF COMPLICATED GALLSTONES, LPAC OR FAMILY HISTORY OF GALLSTONES



Gallstones are a known complication of PFIC[1] and low phospholipid-associated cholelithiasis (LPAC) is linked to mutations in the *ABCB4* gene,[2] which is one of the genes most associated with PFIC.[3]

Consider reassessing your patient for PFIC if they have:[2,4]

- A history of intrahepatic gallstones
- Strong family history of gallstones and incident at a young age
- LPAC leading to stones in the gallbladder or liver

PFIC, progressive familial intrahepatic cholestasis.

1. Jankowska I and Socha P. *Clin Res Hepatol Gastroenterol* 2012;36:271–274; **2.** Vitale G et al. *Cancers* 2022;14:3421; **3.** Nayagam JS et al. *Hepatol Commun* 2022;6:2654–2664; **4.** Mirza N et al. *J Child Sci* 2020;10:e134–e136.

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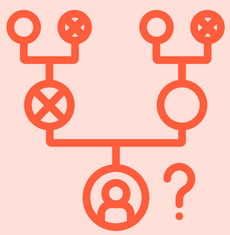
FAMILY HISTORY OF LIVER DISEASE OR LIVER ISSUE



PFIC is a hereditary condition caused by mutations in at least 12 genes, including *ATP8B1*, *ABCB11* or *ABCB4*.[1]

As these genes have also been implicated in other liver diseases, you might consider reassessing your patient for PFIC if they have a family history of:

- Intrahepatic cholestasis of pregnancy[2,3]
- Drug-induced liver injury[2]
- Hepatocellular carcinoma[2]
- Episodic PFIC[2]

PFIC, progressive familial intrahepatic cholestasis.

1. OMIM. PS211600. Available at: https://www.omim.org/clinicalSynopsis/table?mimNumber=601847,619484,619658,602347,615878,619662,617049,619849,619874,620010,619868,211600&from=PS211600. Accessed August 2024; **2.** Vitale G et al. *Dig Liv Dis* 2019;51:922–933; **3.** Hardikar W et al. *World J Gastroenterol* 2009;15:1126–1129.

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INSUFFICIENT RESPONSE TO CHOLESTATIC/CHOLANGIOPATHIC LIVER DISEASE TREATMENT DESPITE COMPLIANCE

For patients diagnosed with a cholestatic/cholangiopathic liver disease other than PFIC, poor treatment response could indicate an incorrect diagnosis.

Consider reassessing for PFIC in your patients with insufficient response to therapy for a different cholestatic/cholangiopathic liver disease despite good compliance.

PFIC, progressive familial intrahepatic cholestasis.
Dröge C et al. *Explor Dig Dis* 2023;2:34–43.

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CHOLESTASIS WITH UNUSUAL PRESENTATION

If your patient is receiving care for another liver disease but has unusual symptoms, it could be a sign of PFIC.[1]

Consider reassessing for PFIC in patients with:

- Small duct PSC[2,3]
- AMA-negative PBC[4–6]
- MASLD with pruritus[7]
- Lean MASLD without metabolic syndrome[7,8]
- Lean MASH with pruritus and without metabolic syndrome[7,8]

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IDIOPATHIC CHOLESTASIS

Variations in the genes responsible for PFIC have been identified in a number of patients with idiopathic cholestasis.[1,2]

Consider reassessing your patient if signs of cholestasis manifest without an apparent or identified cause, especially in the presence of pruritus.[1,2]

PFIC, progressive familial intrahepatic cholestasis.

1. Vitale G et al. *J Gastroenterol* 2018;53:945–958; **2.** Aamann L et al. *Scand J Gastroenterol* 2018;53:305–311.

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BIOCHEMICAL TESTS

A range of biochemical abnormalities may indicate PFIC, including elevated serum bile acid levels, elevated bilirubin levels and abnormal transaminase levels.[1,2]

	PFIC type 1	PFIC type 2	PFIC type 3
Serum bile acids	↑↑	↑↑↑	↑
Serum GGT	-	-	↑
Serum bilirubin	↑	↑	↑
Serum ALP	↑	↑	↑
Serum ALT	↑	↑	↑

Table adapted from Gunaydin et al, 2018[1]
This table only includes PFIC types 1, 2 and 3. Please see www.omim.org/entry/211600 for more information on other PFIC types.

If PFIC is suspected, assessment of these measures can help confirm a diagnosis[1,2]

↑, mild elevation; ↑↑, moderate elevation; ↑↑↑, large elevation.
ALP, alkaline phosphatase; **ALT**, alanine transferase; **GGT**, gamma-glutamyl transferase; **PFIC**, progressive familial intrahepatic cholestasis.
1. Gunaydin M et al. *Hepat Med* 2018;10:95–104; **2.** McKiernan P et al. *JHEP Reports* 2024;6:100949.

GENETIC ANALYSIS

So far, variations in at least 12 genes have been associated with PFIC.[1] These include:[1,2]

- *ATP8B1*, encoding FIC1 - PFIC type 1
- *ABCB11*, encoding BSEP - PFIC type 2
- *ABCB4*, encoding MDR3 - PFIC type 3
- *TJP2*, encoding TJP2 - PFIC type 4
- *NR1H4*, encoding FXR - PFIC type 5
- *MYO5B,* encoding MYO5B - PFIC type 10

Genetic testing can be useful to reinforce a suspected diagnosis of PFIC.[3] A lower threshold for genetic testing could lead to earlier diagnosis of PFIC, allow screening for family members,[4] and be key to facilitating individualised treatment.[3]

However, genetic testing for PFIC has certain limitations, including:

- Difficulty in predicting pathogenicity of new variants[6]
- Inconsistency in genotype-phenotype relationships[6,7]
- Mutations may reside in as-yet-undiscovered causative genes or regions of genes that are not evaluated in genetic assays, meaning testing can be inconclusive[2,7,8]

Genetic testing is not essential for a positive diagnosis of PFIC and should not delay treatment initiation. In the absence of genetic confirmation, information obtained by probing the patient's family history may support a clinical diagnosis of PFIC.[6,9,10]

PFIC, progressive familial intrahepatic cholestasis.

1. OMIM. PS211600. Available at: https://www.omim.org/clinicalSynopsis/table?mimNumber=601847,619484,619658,602347,615878,619662,617049,619849,619874,620010,619868,211600&from=PS211600. Accessed August 2024; **2.** Bull L and Thompson RJ. *Clin Liver Dis* 2018;22:657–669; **3.** Vitale G et al. *J Gastroenterol* 2018;53:945–958; **4.** Althwanay A et al. *Am J Gastroenterol* 2022;117:p e2058; **5.** Nayagam JS et al. *Hepatol Commun* 2022;6:2654–2664; **6.** McKiernan P et al. *JHEP Reports* 2024;6:100949; **7.** Davit-Spraul A et al. *Hepatology* 2010;51:1645-1655; **8.** Bakir A et al. *Ann Hum Genet* 2021;10.1111/ahg.12456; **9.** Vitale G et al. *Dig Liv Dis* 2019;51:922–933; **10.** Mirza N et al. *J Child Sci* 2020;10:e134–e136.