



Available online at  
**ScienceDirect**  
www.sciencedirect.com

Elsevier Masson France  
**EM|consulte**  
www.em-consulte.com/en



ORIGINAL ARTICLE

# Systematic review of progressive familial intrahepatic cholestasis



Alastair Baker<sup>a</sup>, Nanda Kerkar<sup>b</sup>, Lora Todorova<sup>c</sup>,  
Binita M. Kamath<sup>d</sup>, Roderick H.J. Houwen<sup>e,\*</sup>

<sup>a</sup> Paediatric Liver Centre, King's College Hospital, London, UK

<sup>b</sup> Division of Gastroenterology, Hepatology and Nutrition, Golisano Children's Hospital, University of Rochester Medical Center, Rochester, NY, USA

<sup>c</sup> Shire, Zug, Switzerland

<sup>d</sup> Division of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

<sup>e</sup> Pediatric Gastroenterology, Wilhelmina Children's Hospital, University Medical Center, Utrecht, Netherlands

Available online 17 September 2018

## KEYWORDS

Byler's disease;  
Pruritus;  
Bile secretion;  
ATP8B1;  
ABCB11;  
ABCB4

## Abstract

**Background and aims:** Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of rare genetic disorders associated with bile acid secretion or transport defects. This is the first systematic review of the epidemiology, natural history and burden of PFIC.

**Methods:** MEDLINE and Embase were searched for publications on PFIC prevalence, incidence or natural history, and the economic burden or health-related quality of life (HRQoL) of patients with PFIC. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.

**Results:** Of 1269 records screened, 20 were eligible (epidemiology, 17; humanistic burden, 5; both, 2). Incidence of intrahepatic cholestasis, including but not limited to PFIC, was 1/18 000 live births in one study that did not use genetic testing. In two studies of infants and children (2–18 years) with cholestasis, 12–13% had genetically diagnosed PFIC. Of the three main PFIC subtypes, PFIC2 was the most common (21–91% of patients). Common symptoms (e.g. pruritus, jaundice, hepatomegaly, splenomegaly) generally appeared at about 3 months

**Abbreviations:** A1ATD,  $\alpha$ -1-antitrypsin deficiency; ALGS, Alagille syndrome; ABCB4, ATP binding cassette subfamily B member 4; ABCB11, ATP binding cassette subfamily B member 11; ATP8B1, ATPase phospholipid transporting 8B1; BSEP, bile salt export pump; GGT,  $\gamma$ -glutamyl transferase; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; LT, liver transplantation; NR, not reported; NS, type of PFIC diagnosis not specified; PEBD, partial external biliary diversion; PedsQL, Pediatric Quality of Life Inventory; PFIC, progressive familial intrahepatic cholestasis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SD, standard deviation; UDCA, ursodeoxycholic acid.

\* Corresponding author: University Medical Center, Heidelberglaan 100, 3584 CX Utrecht, Netherlands.

E-mail address: [r.h.j.houwen@umcutrecht.nl](mailto:r.h.j.houwen@umcutrecht.nl) (R.H.J. Houwen).

<https://doi.org/10.1016/j.clinre.2018.07.010>

2210-7401/© 2018 Elsevier Masson SAS. All rights reserved.

of age and tended to emerge earliest in patients with PFIC2. Patients reported that pruritus was often severe and led to dermal damage and reduced HRQoL. Disease progression led to complications including liver failure and hepatocellular carcinoma, with 20–83% of patients requiring liver transplantation. Mortality was 0–87% across 10 studies (treatment varied among studies), with a median age at death of 4 years in one study.

**Conclusions:** Patients with PFIC face debilitating symptoms and poor prognosis. Further research is needed to inform patient management and clinical trial design. Published data on the epidemiology and socioeconomic burden of PFIC is limited.

© 2018 Elsevier Masson SAS. All rights reserved.

## Introduction

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of rare autosomal recessive liver disorders of childhood characterized by mutations in genes encoding proteins involved in the hepatocellular transport system [1].

Three main subtypes of PFIC (PFIC1, PFIC2, PFIC3) have been identified [1]. PFIC1, also known as Byler's disease, is caused by mutations in the *ATPase phospholipid transporting 8B1* gene (*ATP8B1*), located on chromosome 18, which encodes a phospholipid transporting transmembrane P-type adenosine triphosphatase known as FIC1 [1,2]. This 'flipase' is involved in maintaining an asymmetric distribution of phospholipids across the canalicular membrane bilayer of hepatocytes, thereby protecting the canalicular membrane from hydrophobic bile acids and maintaining its integrity [1]. PFIC2 is caused by mutations in the *ATP binding cassette subfamily B member 11* gene (*ABCB11*), located on chromosome 2, which encodes the bile salt export pump (BSEP), the main transporter of bile acids from hepatocytes to the canalicular lumen [1,3]. PFIC3 is caused by mutations in the *ATP binding cassette subfamily B member 4* gene (*ABCB4*), located on chromosome 7, which encodes multidrug-resistance protein 3 (*MDR3/ABCB4*); this protein transports phospholipids into the canalicular lumen to neutralize bile salts and prevent injury to biliary epithelia and bile canaliculi [1,4,5].

The main clinical features of PFIC include cholestasis, jaundice and pruritus, with symptoms typically appearing in infancy or early childhood [1]. PFIC is associated with a range of potentially fatal complications of the liver, including portal hypertension, liver failure, cirrhosis and hepatocellular carcinoma (HCC; PFIC2), as well as extrahepatic manifestations (PFIC1) [1]. The biochemical features of PFIC1 and PFIC2 are low levels of  $\gamma$ -glutamyl transferase (GGT) with elevated serum bile acid and decreased primary bile acid concentrations, while PFIC3 is associated with high levels of GGT [1]. Historically, diagnosis of PFIC has been based on a combination of clinical and laboratory or biochemical approaches but, more recently, genetic testing has become the gold standard.

There are no approved pharmacologic treatment options for patients with PFIC that relieve symptoms or prevent disease progression. Off-label treatments include ursodeoxycholic acid (UDCA), bile acid sequestrants and agents for the symptomatic relief of pruritus, such as antihistamines and rifampin (rifampicin) [1,6]. Not all patients respond to these approaches, however, and generally only partial relief from itching is achieved. Accordingly, invasive surgery, such as ileal bypass, partial external biliary diver-

sion (PEBD) or partial internal biliary diversion (PIBD) may be needed to lower circulating bile acid concentrations [1,6,7]. Ultimately, liver failure and intractable pruritus may indicate a need for liver transplantation (LT), most often in patients with PFIC2 [8].

There is limited information regarding the pathogenesis and burdens of PFIC. Consequently, we have conducted a systematic appraisal of the evidence on the epidemiology, clinical presentation, natural history, health-related quality of life (HRQoL) and the economic burdens of PFIC. Our aim has been to consolidate the data obtained from small studies and analyses of patient records published over the last 35 years, so that the results can be used to help inform the management of patients with PFIC and the design of future clinical studies in patients with PFIC.

## Methods

Two search strings were devised that used a combination of free text and Medical Subject Heading terms to explore:

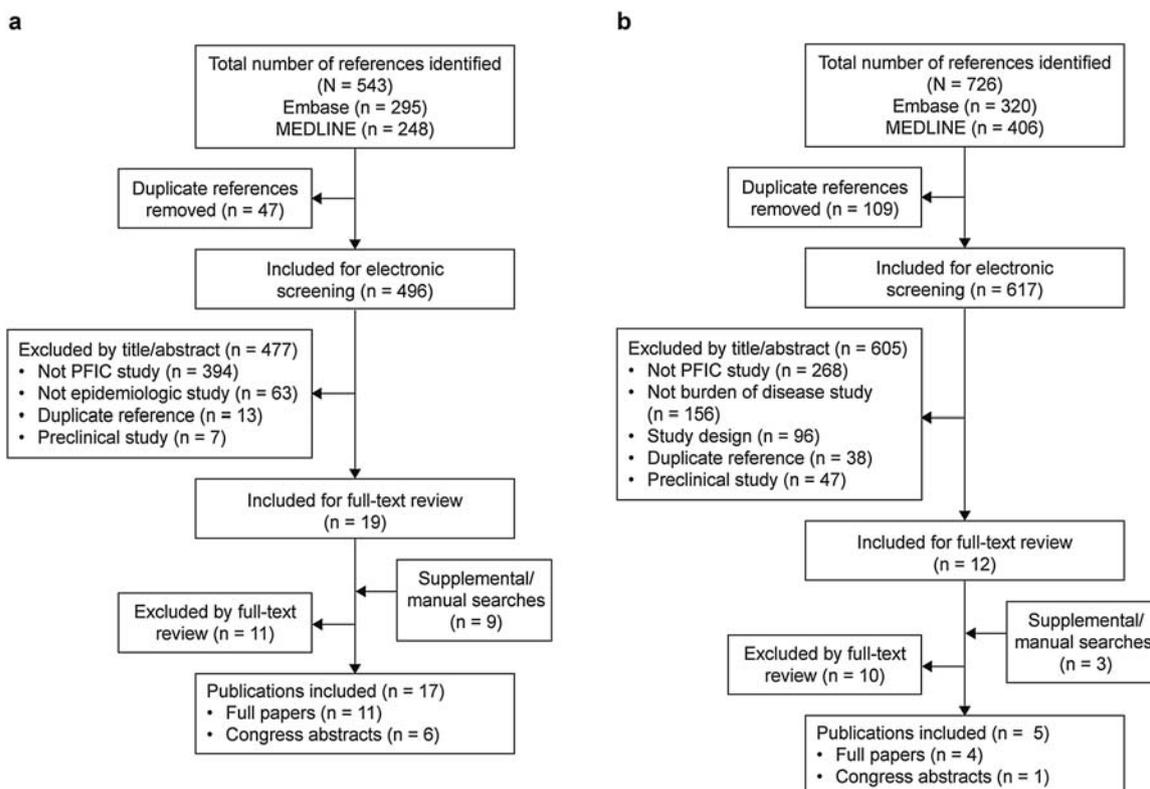
- PFIC and epidemiology or natural history;
- PFIC and health-related quality of life (HRQoL) or economic burden (Supplementary Tables S1 and S2).

On May 11–13, 2015, the OvidSP search platform was used to carry out searches of the following electronic literature databases:

- MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1946–present;
- Embase 1974–present.

The bibliographic reference lists of the studies subsequently included in the review were also manually searched. Proceedings of 11 congresses considered to be most relevant were also searched. The date range for the publication database searches was from the start of records to May 2015, but was restricted to 2012–2015 for conference proceedings because data before this period were likely to have been published as a journal article. In addition to the major publication databases, Orphanet, a specialist resource devoted to rare and orphan diseases, was searched for publications on PFIC to ensure comprehensive coverage.

Inclusion and exclusion criteria were specified in advance and documented. Identified publications were manually screened based on the title and abstract in accordance with 2009 Preferred Reporting Items for Systematic Reviews



**Figure 1** PRISMA flow diagram for systematic review of (a) epidemiology and natural history (b) HRQoL and economic burden.

and Meta-Analyses (PRISMA) guidelines [9]. Abstracts were screened for inclusion by two independent reviewers and, in the case of uncertainty, by a third reviewer. Data were extracted manually. Case studies were ineligible. Studies reporting only clinical outcomes, treatment preferences, epidemiology estimates or risk factors were ineligible. See Supplementary Tables S3–S5 for full eligibility criteria.

## Results

The searches yielded 1269 publications for screening. The numbers of included and excluded publications are shown in Fig. 1a (epidemiology and natural history) and Fig. 1b (HRQoL and economic burden). Of the 20 publications that met the eligibility criteria for inclusion in the review (Table 1), 17 publications reported the epidemiology or natural history of PFIC (summarized in Tables 2–4) and 5 publications assessed the HRQoL in patients with PFIC (summarized in Table 5); 2 publications were identified in both searches. No publications that addressed the economic burden of PFIC were identified.

## Epidemiology

Two publications reported population-level epidemiology data for PFIC (Table 1) [10,11]. A retrospective study assessed 124 infants admitted to hospitals in Norway with cholestatic jaundice during the first 3 months of life between 1955 and 1974, of whom 60 had intrahepatic cholestasis. These figures result in an incidence of intrahepatic cholestasis, including but not limited to PFIC, of approximately 1 per

18 000 live births [10]. However, molecular genetic diagnostics for PFIC were not available at the time of data collection (1955–1974). A later study that analyzed death registers and case records from two hospitals in Greenland for the period 1943–2002 reported 46 cases of PFIC1 diagnosed by liver biopsy, biochemistry and/or molecular genetic testing (*ATP8B1*) [11]. In this study, many cases occurred in patients originating from indigenous populations described by the authors as “highly inbred”. The overall study population size and incidence were not reported [11].

Six publications reported the prevalence of PFIC among patients with liver-related disease (Table 1) [12–17]. Of these, three studies used genetic testing for PFIC diagnosis: a multicenter study from North America in children with intrahepatic cholestasis [17], a Swedish tertiary referral center study that included infants with neonatal cholestasis with an onset in the first 6 months of life [14], and a world-wide multicenter study in infants with cholestasis, acute liver failure or splenomegaly [16]. In these three studies, the proportions of cases of PFIC among the study populations were 11.7% [17], 12.9% [14], and 9.0% [16], respectively. In the remaining three studies the basis of PFIC diagnosis was either clinical, biochemical and histological [13,15], or was not reported [12]. A study from India assessed children with encephalopathy, acute liver failure, cholestasis, hepatomegaly or chronic liver disease [12]; a study from Tunisia assessed children with cirrhosis [13]; and a study from Iran assessed children referred for liver needle biopsy [15]. In these three studies, the proportions of cases of PFIC among the study populations were 2.4% [12], 12.7% [13], and 5.0% [15], respectively.

**Table 1** Summary of included publications.

Reference	Study design	Study population	n	Patients with PFIC, n	Genetic diagnosis	Country/region	Study period	Reported data					
								PFIC epidemiology	PFIC subtype	At pre-sentation	At follow-up	Mortality	HRQoL and/or pruritus
Henriksen et al., 1981 [10]	Retrospective chart review	Infants with cholestatic jaundice	124	60	No	Norway	1955–1974 (follow-up in 1978)	Incidence: 1/18,000 live births	NS	Yes	Yes	43%	No
Whittington et al., 1994 [26]	Retrospective chart review	Patients with PFIC (with chronic cholestasis but excluding other chronic cholestatic conditions)	33	33	No	North America	1978–1991	No	NS	Yes	Yes	21%	No
Fischler et al., 2001 [14]	Retrospective chart review	Infants with neonatal cholestasis	85	11	Yes	Sweden	1988–1995	Prevalence: 12.9%	PFIC2: 91% Others: NS	No	No	No	No
Nielsen and Eiberg, 2004 [11]	Retrospective review of death register and hospital records	Patients with PFIC1	46	46	Yes <sup>a</sup>	Greenland	1943–2002	No	PFIC1:100%	Yes	No	87%	No
Wanty et al., 2004 [24]	Retrospective chart review	Patients with PFIC (based on chronic cholestasis)	49	49	Yes <sup>b</sup>	Belgium	NR	No	PFIC1/2: 61% PFIC3: 39%	Yes	Yes	8%	No
Chaabouni et al., 2007 [13]	Retrospective review of hospital records	Children with cirrhosis	71	9	No	Tunisia	1990–2004	Prevalence: 12.7%	NS	No	No	33%	No
Englert et al., 2007 [20]	Retrospective chart review	Patients with PFIC treated with UDCA plus PEBD and/or LT	42	42	Yes	Germany	NR	No	PFIC2: 62% PFIC3: 38%	Yes	Yes	0%	No
Monajemzadet et al., 2009 [15]	Cross-sectional, diagnostic	Children referred for liver needle biopsy excluding those with thalassemia	321	20	No	Iran	2004–2006	5.0%	NS	No	No	No	No
Lee et al., 2009 [23]	Case series	Infants with PFIC (based on chronic cholestasis)	5	5	No	Malaysia	1996–2004	No	PFIC1/2: 80% PFIC3: 20%	Yes	Yes	80%	Pruritus scores
Yang et al., 2009 [30]	Retrospective chart review	Children with PFIC who underwent PEBD	11	11	Partial	Netherlands	2000–2005	No	PFIC2: 73% Others: NS	No	No	No	HRQoL
Miyagawa-Hayashino et al., 2009 and Hori et al., 2011 [22,25] <sup>c</sup>	Retrospective chart review	Children who underwent LT	725	14	Yes	Japan	1990–2008	No	PFIC1: 78.6% PFIC2: 21.4%	No	Yes	21.4%	No
Lind et al., 2010 [29]	Prospective PFIC/ALGS database	Children/adolescents with PFIC/ALGS who underwent PEBD	8	8	NS	NR	NR	No	No	No	No	No	Yes

Table 1 (Continued)

Reference	Study design	Study population	n	Patients with PFIC, n	Genetic diagnosis	Country/region	Study period	Reported data	PFIC epidemiology	PFIC subtype	At pre-sentation	At follow-up	Mortality	HRQoL and/or pruritus
Davit-Spraul et al., 2010 [8]	Retrospective chart review	Children with hepatocellular cholestasis, pruritus, elevated serum bile acid, and normal serum GGT activity	62	62	Yes	France	1978–2007	No	PFIC1: 21% <sup>d</sup> PFIC2: 63% <sup>d</sup> Others: NS <sup>d</sup>	Yes	Yes	10%	No	
Schukfeh et al., 2012 [27]	Retrospective chart review	Children with PFIC who underwent PEBD	24	24	Partial	Germany	1994–2008	No	NS	No	No	No	No	Pruritus scores
Alam et al., 2013 [12]	Protocol-based screening study	Children with encephalopathy, acute liver failure, cholestasis, hepatomegaly, or chronic liver disease	288	7	NS	India	NR	Prevalence: 2.4%	PFIC2: 100%	No	No	No	No	No
Al Mehadib et al., 2013 [19]	Retrospective chart review	Patients with cholestasis and suspected PFIC	68	48	Yes	Saudi Arabia	2002–2012	No	PFIC1: 10.4% PFIC2: 56.3% PFIC3: 33.3%	Yes	Yes	6%	No	
Gray et al., 2013 [21]	Prospective, genetic	Infants < 2 years of age with cholestasis, acute liver failure, or splenomegaly and with DNA sequencing data	87	8	Yes	Int. (13 centres)	NR	No	PFIC1: 37.5% <sup>e</sup> PFIC2: 37.5% <sup>e</sup> PFIC3: 37.5% <sup>e</sup>	No	No	No	No	No
Ruth et al., 2014 [16]	Prospective, genetic	Infants < 2 years of age with cholestasis, acute liver failure, or splenomegaly	238	NR <sup>f</sup>	Yes	International (13 centres)	NR	Prevalence: 9%	NS	No	No	No	No	No
Vashta et al., 2015 [18]	Retrospective, postmortem	Children with hepatic disease	181	NR <sup>f</sup>	NS	North India	NR	Prevalence: 0.6%	NS	No	No	No	No	No
Kamath et al., 2015 [17]	Cross-sectional sub-study	Children with chronic intrahepatic cholestasis	214	25	Yes	North America (16 centres)	NR	Prevalence: 11.7%	PFIC1: 24.0% PFIC2: 48.0% PFIC3: 28.0%	No	No	No	No	HRQoL

A1ATD:  $\alpha$ -1-antitrypsin deficiency; ALGS: Alagille syndrome; BSEP: bile salt export pump; GGT:  $\gamma$ -glutamyl transferase; HRQoL: health-related quality of life; Int: international; LT: liver transplantation; NR: not reported; NS: type of PFIC diagnosis not specified; PEBD: partial external biliary diversion; PFIC: progressive familial intrahepatic cholestasis; UDCA: ursodeoxycholic acid.

<sup>a</sup> PFIC diagnosed by molecular testing, liver biopsy, and/or biochemistry.

<sup>b</sup> Genetic analysis was performed where possible only for PFIC2 mutations.

<sup>c</sup> Miyagawa-Hayashino et al. (journal article) and Hori et al. (subsequent congress abstract) reported on the same study population. Hori et al. included one additional patient (who had PFIC2 and survived); and reported death of one more of the original patients (who had PFIC1).

<sup>d</sup> PFIC subtype remained unknown in 10 patients (16%).

<sup>e</sup> There were 3/8 patients with each subtype; one patient had both PFIC1 and PFIC3.

<sup>f</sup> Proportion, but not number, of cases reported.

**Table 2** Clinical presentation of patients with PFIC.

Reference	Age at onset of PFIC/first symptoms	Clinical features, n/N (%) in patients with PFIC
<b>PFIC1/PFIC2/PFIC3</b>		
Henriksen et al., 1981 [10]	First 3 months of life	Cholestasis: 60/60 (100) Jaundice with hepatomegaly and/or splenomegaly: 60/60 (100) Pale stools and dark-colored urine: 60/60 (100)
Whittington et al., 1994 [26]	3.1 ± 3.0 months (mean ± SD) <sup>a</sup>	Pruritus: 32/33 (97); 25/33 (76) with pruritus grade ≥ 3+ [constant itching with significant excoriations], based on Whittington scale Hepatomegaly: 32/33 (97) Rickets: 25/33 (76) Recurrent and severe epistaxis (no coagulopathy or thrombocytopenia): 17/33 (52) Vitamin E deficiency: 17/33 (52) Persistent vitamin E neuropathy (mild-to-severe): 13/33 (39) Wheezing and cough: 10/33 (30) Cholelithiasis: 9/33 (27) Bleeding diathesis: 8/33 (24) Severe osteopenia: 2/33 (6) Sensorineural hearing loss: 2/33 (6) Mild mental retardation: 1/33 (3)
<b>PFIC1/PFIC2</b>		
Schukfeh et al., 2012 [27]	Age at diagnosis: 21 months [4 months–17 years]	Chronic cholestatic liver disease: 24/24 (100) Jaundice: 13/24 (54) Elevated serum bile acids: 24/24 (100) Normal GGT: 23/24 (96) Pruritus: 18/24 (75)
Lee et al., 2009 [23]	3–4 days	Moderate-to-severe neonatal cholestatic jaundice: 4/4 (100) Hepatomegaly: 4/4 (100) Slightly pigmented or pale stools: 4/4 (100) Pruritus: 4/4 (100); 3/4 (75) with pruritus grade ≥ 3+, based on Whittington scale Splenomegaly: at least 2/4 (50) <sup>b</sup>
Wanty et al., 2004 [24]	2 months [0–58] (mean [range])	Pruritus: 23/24 (96) <sup>c</sup> Hepatomegaly: 19/21 (90) <sup>c</sup> Cholestasis: 20/25 (80) <sup>c</sup> Jaundice: 19/27 (70) <sup>c</sup>
<b>PFIC1</b>		
Al Mehadib et al., 2013 [19]	< 18 months	Jaundice: 5/5 (100) Hepatomegaly: 5/5 (100) Poor growth: 5/5 (100) Diarrhea: 4/5 (80) Splenomegaly: 3/5 (60)
Davit-Spraul et al., 2010 [8]	2 months [1–5] (median [range])	Jaundice, discolored stools, and/or hepatomegaly at ≤ 1 month: 2/13 (15) Jaundice, discolored stools, hepatomegaly, and/or pruritus at ≤ 3 months: 8/13 (61) Diarrhea: 8/13 (61) Elevated sweat chloride levels: 2/13 (15) Pancreatitis: 1/13 (8)
Nielsen and Eiberg, 2004 [11]	1–2 months	Jaundice with protuberant abdomen <sup>d</sup> Hepatomegaly <sup>d</sup> Itching <sup>d</sup> Bleeding episodes <sup>d</sup> Failure to thrive <sup>d</sup> Rickets <sup>d</sup>

Table 2 (Continued)

Reference	Age at onset of PFIC/first symptoms	Clinical features, n/N (%) in patients with PFIC
<b>PFIC2</b>		
Al Mehadib et al., 2013 [19]	≤ 2 years	Jaundice: 22/27 (81) Rickets: 6/27 (22) Pruritus: 3/27 (11)
Davit-Spraul et al., 2010 [8]	2 months [1–60] (median [range])	Jaundice, discolored stools, and/or hepatomegaly at ≤ 1 month: 16/36 (44) Jaundice, discolored stools, hepatomegaly, and/or pruritus (≤ 3 months): 26/36 (72) Cholelithiasis: 10/36 (28) Vitamin K deficiency (bleeding): 3/36 (8) Cirrhosis: 1/21 (5) <sup>c,e</sup> HCC: 1/21 (5) <sup>c,e</sup> Vitamin D deficiency (rickets): 1/36 (3)
<b>PFIC3</b>		
Englert et al., 2007 [20]	3.2 [2 months–10 years] (mean [range])	Pruritus: 18/26 (69) Cholestasis: 15/26 (58) Liver cirrhosis: 12/26 (46) Growth retardation: 10/26 (38)
Al Mehadib et al., 2013 [19]	≥ 2 years	Jaundice: 5/16 (31) Pruritus: 4/16 (25) Rickets: 1/16 (6)
Wanty et al., 2004 [24]	3 months [0–36] (median [range])	Jaundice: 14/17 (82) <sup>c</sup> Hepatomegaly: 13/17 (76) <sup>c</sup> Cholestasis: 8/14 (57) <sup>c</sup> Pruritus: 7/17 (41) <sup>c</sup>
Lee et al., 2009 [23]	3–4 days (3 days in 4 patients and 4 days in 1 patient)	Neonatal jaundice within first week: 1/1 (100) Hepatomegaly: 1/1 (100) Pale stools: 1/1 (100) Pruritus: 1/1 (100); grade ≥ 4+ [cutaneous mutilation hemorrhage and scarring evident], based on Whittington scale Possible splenomegaly <sup>b</sup>

GGT:  $\gamma$ -glutamyl transferase; HCC: hepatocellular carcinoma; PFIC: progressive familial intrahepatic cholestasis; SD: standard deviation.

<sup>a</sup> One patient with clinical presentation at 17 years was excluded from this calculation.

<sup>b</sup> Three patients with PFIC of unspecified subtype had splenomegaly.

<sup>c</sup> Among patients with available data.

<sup>d</sup> n/N not reported.

<sup>e</sup> At diagnosis or before age 1 year.

One postmortem study in India carried out autopsies on children (aged 0–14 years) with signs and symptoms of hepatic diseases and reported a 0.6% prevalence of PFIC [18].

### Distribution and biochemical characteristics of main PFIC subtypes

Nine studies reported the distribution of subtypes among patients with PFIC [8,14,17,19–25]. PFIC2 was generally the most common subtype among patients diagnosed via genetic testing: PFIC2 was detected in 37.5–90.9% of patients [8,14,17,19,21], while PFIC1 and PFIC3 were detected in 10.4–37.5% [8,14,17,19,21] and 28.0–37.5% of patients [17,19,21], respectively. In contrast, a study in Japanese patients with PFIC who had undergone LT reported a higher frequency of PFIC1 (11/14, 78.6%) than PFIC2 (3/14, 21.4%)

[22]. One publication identified a patient with both PFIC1- and PFIC3-causing mutations [21]. In another study exploring PFIC1 and PFIC2 genotypes, 18 different mutations in *ATP8B1* and 41 mutations in *ABCB11*, respectively, were identified [8]. In the three studies that reported values for all three main PFIC subtypes, the relative incidences of PFIC1, PFIC2 and PFIC3 were 10.4%, 56.3% and 33.3% [19]; 37.5%, 37.5% and 37.5% [21]; and 24%, 48% and 28% [17], respectively (Table 1).

Serum GGT levels were normal or minimally elevated in patients with PFIC1 or PFIC2 [8,19,23], but significantly elevated in patients with PFIC3 [19,23]. PFIC2 was associated with elevated serum alanine aminotransferase and  $\alpha$ -fetoprotein levels, low biliary bile acid concentrations, severe lobular lesions with giant hepatocytes and negative BSEP canalicular staining [8].

**Table 3** Disease progression in patients with PFIC.

Reference	Study period	Clinical features at follow-up, n/N (%) in patients with PFIC	Liver transplantation (LT)		Age at LT	Clinical features/outcome post-LT, n/N (%)
			Patients, n/N (%)	Indications, n/N (%)		
PFIC1/PFIC2/PFIC3 Henriksen et al., 1981 [10]	1955–1974 (follow-up in 1978)	Hepatomegaly: 6/32 (19) <sup>a</sup> Splenomegaly: 4/32 (13) <sup>a</sup> Idiopathic neonatal cholestasis: 8/32 (25) <sup>a</sup> Cholestasis with lymphedema: 5/32 (16) <sup>a</sup> Other familial cholestases: 4/32 (13) <sup>a</sup> Septicemia: 3/32 (9) <sup>a</sup> Inspissated bile syndrome: 1/32 (3) <sup>a</sup> Mucopolysaccharidosis: 1/32 (3) <sup>a</sup> Subpopulation biopsied (n = 7): cirrhosis: 2/7 (29) <sup>b</sup> ; fibrosis: 1/7 (14) <sup>b</sup> ; bile duct hypoplasia: 1/7 (14) <sup>b</sup>	0/32 (0)	NR	NR	NR
Lee et al., 2009 [23]	1996–2004	Giant cell hepatitis: 4/5 (80) Developmental delay: 1/5 (20) Severe pruritus (grade ≥ 3+ based on Whittington scale): 4/5 (80) Failure to thrive: 5/5 (100) Cirrhosis: 4/5 (80)	1/5 (20)	NR	22 months	Death post-LT (sepsis): 1/1 (100)
Schukfeh et al., 2012 [27]	1994–2008 (median follow-up 9.8 years [1.6–14.3])	PEBD without LT after 1 year: 21/24 (88); normalisation of serum bile acid levels: 13/21 (62); signs of improved liver function and reduced liver damage: 13/21 (62); pruritus score ≤ 3: 13/21 (62); PEBD failure: 8/21 (38) LT within 1 year after PEBD: 3/24 (12.5)	9/24 (37)	Liver cirrhosis: 7/9 (78) PEBD failure: 6/9 (67)	24 months [4 months to 4.4 years] (median [range])	NR

Table 3 (Continued)

Reference	Study period	Clinical features at follow-up, n/N (%) in patients with PFC	Liver transplantation (LT)			Clinical features/outcome post-LT, n/N (%)
			Patients, n/N (%)	Indications, n/N (%)	Age at LT	
Wanty et al., 2004 [24]	The 15 years before publication	Treatment with UCDA: 20/49 (41); favourable liver enzyme response and reduced pruritus: 10/20 (50); partial response in liver enzymes and persisting pruritus: 10/20 (50); untreated patients: 29/49: NR	38/49 (78)	NR	PFIC1/PFIC2: 50 months [19–189] PFIC3: 63 months [17–129] (median [range])	Death post-LT: 3/38 (8) (1 sepsis following surgery, 1 post-LT hepatitis C, 1 unknown cause)
Whittington et al., 1994 [26]	1987–1991	Pruritus and other symptoms persistently severe despite treatment with medication(s), 33/33 (100) Partial ileal bypass, 2/33 (6); reversal of cholestasis, 2/2 (100) Partial cutaneous biliary diversion: 14/33 (42); adequate response: 13/14 (93); complete relief of cholestasis: 9/14 (64); partial relief of cholestasis: 1/14 (7); death 1/14 (7); secondary LT: 4/14 (29) Death at follow-up: 7/33 (21); liver failure: 2/7 (29); hepatocellular carcinoma: 2/7 (29); LT complications: 3/7 (43)	14/33 (42)	Decompensated cirrhosis: 13/14 (93); unsuccessful biliary diversion: 4/14 (29) Mutilating pruritus: 1/14 (7)	6.2 years [8 months–11 years] (mean [range])	Death post-LT: 3/14 (21) (All due to complications of LT)
PFIC2/PFIC3 Englert et al., 2007 [20]	NR	Pruritus: 32/42 (76) Cholestasis: 27/42 (64) Liver cirrhosis: 25/42 (60) Successful treatment with medication: 2/42 (5) Growth retardation: 19/42 (45) Biliary diversion: 17/42 (40); successful: 5/17 (29); referred for secondary LT: 12/17 (59)	35/42 (83) (2/35 awaiting LT)	Severe pruritus, NR Growth retardation, NR Liver cirrhosis, NR Cholangitis and pruritus, NR	NR	Death post-LT: 0/33 (0) Significant catch-up of growth retardation: 8/19 (83)

Table 3 (Continued)

Reference	Study period	Clinical features at follow-up, n/N (%) in patients with PFIC	Liver transplantation (LT)			Clinical features/outcome post-LT, n/N (%)
			Patients, n/N (%)	Indications, n/N (%)	Age at LT	
<b>PFIC1</b>						
Al Mehaidib et al., 2013 [19]	2002–2012	NR	2/5 (40)	NR	NR	NR
Davit-Spraul et al., 2010 [8]	1978–2007	Recurrent or permanent jaundice: 13/13 (100) Cirrhosis: 2/5 (40) <sup>c,d</sup> Pruritus: 13/13 (100) Hepatomegaly: 13/13 (100) Splenomegaly: 4/13 (31) Positive response to UDCA: 5/13 (38) Successful biliary diversion: 1/1 (100)	6/13 (46)	Severe cholestasis with no liver failure or HCC: 6/6 (100)	4 years [1.5–7.5] (median [range])	Diarrhea: 5/6 (83) Liver steatosis: 3/6 (50) Growth retardation: 4/6 (67) Deafness: 2/6 (33) Pancreatitis: 2/6 (33) Liver failure requiring second LT: 2/6 (33) Death post-LT: 2/6 (33)
Miyagawa-Hayashino et al., 2009 [25] <sup>e</sup> Hori et al., 2011 [22] <sup>e</sup>	1990–2008 (follow-up for 4.2–16.5 years) 2011 update	Severe cholestasis with cirrhosis, undergoing LT: 11/11 (100)	11/11 <sup>f</sup>	End-stage liver disease, severe pruritus, significant growth failure: 11/11 (100)	4 years [1–18] (median [range])	Steatosis: 8/11 (73) Steatohepatitis: 7/11 (64): bridging fibrosis: 4/7 (57) <sup>b</sup> ; cirrhosis: 2/7 (29) <sup>b</sup> Diarrhea: 7/11 (64) Chronic pancreatitis: 2/11 (18) Deaths post-LT: 3/11 (18) <sup>c</sup>

Table 3 (Continued)

Reference	Study period	Clinical features at follow-up, n/N (%) in patients with PFIC	Liver transplantation (LT)			Clinical features/outcome post-LT, n/N (%)
			Patients, n/N (%)	Indications, n/N (%)	Age at LT	
<b>PFIC2</b>						
Al Mehadib et al., 2013 [19]	2002–2012	NR	15/27 (56) Death awaiting LT: 3/27 (11)	NR	NR	NR
Davit-Spraul et al., 2010 [8]	1978–2007	Recurrent/permanent jaundice: 29/36 (81) Cirrhosis: 15/26 (58) <sup>c,d</sup> Pruritis: 36/36 (100) Hepatomegaly: 35/36 (97) Splenomegaly: 15/36 (42) HCC: 3/26 (12) <sup>c,d</sup> Positive response to UDCA: 9/29 (31) Successful biliary diversion: 1/9 (11)	19/36 (53) (4/19 awaiting LT)	Severe cholestasis: 8/19 (42) Severe cholestasis and liver failure: 6/19 (32) Severe cholestasis, liver failure and HCC: 5/19 (26)	NR	Deaths during/post-LT: 4/19 (21) No extrahepatic manifestations in patients surviving LT: 14/19 (74)
<b>PFIC3</b>						
Hori et al., 2011 [22] <sup>f</sup>	1990–2011	Severe cholestasis with cirrhosis, undergoing LT: 3/3 (100)	3/3 (100) <sup>f</sup>	End-stage liver disease, severe pruritus, significant growth failure: 3/3 (100)	NR	No steatosis, fibrosis or deaths post-LT, 3/3 (100)
Al Mehadib et al., 2013 [19]	2002–2012	NR	1/16 (6)	NR	NR	NR
HCC: hepatocellular carcinoma; LT: liver transplantation; NR: not reported; PEBD: partial external biliary diversion; PFIC: progressive familial intrahepatic cholestasis; UCDA: ursodesoxycholic acid.						
<sup>a</sup> Among patients who were alive at follow-up and had a follow-up examination.						
<sup>b</sup> Among patients who were alive at follow-up and had a liver biopsy.						
<sup>c</sup> Among patients with available data.						
<sup>d</sup> After 1 year of age.						
<sup>e</sup> Miyagawa-Hiyashino et al. (journal article) and Hori et al. (subsequent congress abstract) reported on the same study population. One additional patient with PFIC1 died according to Hori et al.						
<sup>f</sup> Miyagawa-Hiyashino et al. did not report on patients with PFIC2 (n = 2) in the cohort; Hori et al. reported on one additional patient with PFIC2 (total n = 3).						

**Table 4** Mortality in patients with PFIC.

Reference	Mortality, n/N (%)	Reasons for death, n/N	Age of death	Treatment, n/N (%) <sup>a</sup>
Al Mehaidib et al., 2013 [19]	3/48 (6)	NR	NR	Awaiting LT: 3/48 (6) LT: 18/48 (38)
Davit-Spraul et al., 2010 [8]	6/62 (10)	Post-LT: 3/6 During LT: 1/6 Liver failure: 1/6 Cerebral bleeding: 1/6 NA	PFIC1: 15 years [7–23] PFIC2: 1 year [3–4] PFIC NS: 3.2 years (median [range]) NA	UDCA: 53/62 (85) PEBD: 15/62 (24) LT: 25/62 (40)
Englert et al., 2007 [20]	0/42 (0)	NA	NA	UDCA: 42/42 (100) PEBD: 17/42 (40) <sup>b</sup> LT: 35/42 (83) <sup>b</sup> NR
Henriksen et al., 1981 [10]	26/60 (43)	Acute complications secondary to cholestasis (infection, dehydration, GI bleeding): 16/26 HCC secondary to cholestasis: 3/26 Other: 7/26	NR	NR
Miyagawa-Hayashino et al., 2009 [25] <sup>c</sup> Hori et al., 2011 [22] <sup>c</sup>	3/14 (21)	Rupture of splenic artery aneurysm post-LT: 1/3 Chronic rejection post-LT: 1/3 NR: 1/3	13.8 years; 5.5 years; NR	LT: 14/14 (100) <sup>d</sup>
Lee et al., 2009 [23]	4/5 (80)	Cirrhosis with liver failure: 2/4 Coagulopathy, massive upper GI bleed: 1/4 Sepsis after LT: 1/4	9–51 months	UDCA: 5/5 (100) Rifampin: 4/5 (80) LT: 1/5 (20) NR
Nielsen and Eiberg, 2004 [11]	40/46 (87)	Infections <sup>e</sup> Bleeding episodes <sup>e</sup> Liver failure <sup>e</sup>	NR	NR
Wanty et al., 2004 [24]	4/49 (8)	Sepsis and massive fluid loss post-PEBD: 1/4 Sepsis post-LT: 1/4 Chronic aggressive hepatitis C post-LT: 1/4 Unknown cause post-LT: 1/4	NR	UDCA: 20/49 (41) PEBD: 5/49 (10) LT: 38/49 (78)
Whittington et al., 1994 [26]	7/33 (21)	Liver failure: 2/7 HCC: 2/7 LT-related complications: 3/7	3.9 ± 2.4 years (mean ± SD)	UDCA: 6/33 (18) PEBD: 18/33 (55) <sup>f</sup> LT: 14/33 (42)

GI: gastrointestinal; HCC: hepatocellular carcinoma; LT: liver transplantation; NA: not applicable; NR: not reported; PEBD: partial external biliary diversion; PFIC: progressive familial intrahepatic cholestasis; SD: standard deviation; UDCA: ursodeoxycholic acid.

<sup>a</sup> More than one treatment possible.

<sup>b</sup> LT or PEBD was an inclusion criterion. LT includes 2/35 awaiting surgery.

<sup>c</sup> Miyagawa-Hiyashino et al. (journal article) and Hori et al. (subsequent congress abstract) reported on the same study population. Hori et al. included one additional patient (who had PFIC2 and survived); and reported death of one more of the original patients (who had PFIC1).

<sup>d</sup> LT was an inclusion criterion.

<sup>e</sup> n/N not reported.

<sup>f</sup> Includes four unsuccessful PEBDs.

**Table 5** Summary of studies exploring health-related quality of life and pruritus in patients with PFIC.

Reference	Cohort characteristics	Results
Kamath et al., 2015 [17]	49 children aged 5–18 years with chronic intrahepatic cholestasis (non-ALGS or A1ATD); 25 with genetic diagnosis (PFIC1, 6; PFIC2, 12; PFIC3, 7)	Children with IHC had lower total PedsQL self-report scores than healthy peers (73 vs. 84; effect size, 0.87)
Lee et al., 2009 [23]	5 infants with PFIC (based on chronic unremitting infantile cholestasis and biomarkers typical of cholestasis [including increased levels of conjugated bilirubin and alkaline phosphatase with low-to-normal levels of serum GGT])	Pruritus severity score based on Whittington scale (0–4): 1 patient with pruritus grade 1+ (rubbing or mild scratching when not distracted); 3 patients with pruritus grade 3+ (abrasions evident); 1 patient with pruritus grade 4+ (cutaneous mutilation, hemorrhage, and scarring evident)
Lind et al., 2010 [29]	8 children with PFIC or ALGS who had undergone PEBD (median age, 9.2 years; range, 6.3–14.5 years)	Self-reported and parent-proxy PedsQL overall HRQoL, Physical Health, and Psychosocial Health summary scores were lower in patients with PFIC/ALGS than in healthy peers Median score for severity of pruritus in patients with PFIC/ALGS: 2.5 (Infant Dermatitis Scale: 1 = none; 5 = severe); significantly correlated with overall HRQoL ( $r=0.74$ )
Schukfeh et al., 2012 [27]	24 children (16 boys and 8 girls) with PFIC undergoing PEBD in a medical school in Germany, 1994–2008	Overall, the median preoperative Kardoff pruritus score was 3 (range, 0–5) In patients in whom PEBD surgery was successful, postoperative pruritus severity scores were significantly lower than preoperative scores: preoperative median pruritus score: 3 (range, 0–5); postoperative median pruritus score: 0 (range, 0–3) Pruritus scores were unchanged in patients in whom surgery was unsuccessful: preoperative median pruritus score: 2 (range, 0–4); postoperative median pruritus score: 2 (range, 0–4)
Yang et al., 2009 [30]	11 children with PFIC undergoing PEBD at a university medical center in the Netherlands, 2002–2005; diagnosis primarily on clinical grounds, laboratory parameters, and liver biopsy; 8 with genetically confirmed PFIC2	Median follow-up: 3.1 years (range, 2.0–5.7) 2 years after PEBD, 5/11 children (45%) did not experience pruritus, 3/11 (27%) had mild pruritus, and 3/11 (27%) continued to experience severe pruritus with significant scratch marks Sleep of patients and parents improved, and all patients resumed their school activities, contributing to improved HRQoL

A1ATD:  $\alpha$ -1-antitrypsin deficiency; ALGS: Alagille syndrome; GGT: gamma-glutamyl transferase; HRQoL: health-related quality of life; IHC: intrahepatic chronic cholestasis; PEBD: partial external biliary diversion; PedsQL: Pediatric Quality of Life Inventory; PFIC: progressive familial intrahepatic cholestasis.

### Clinical manifestations of PFIC

Nine publications described symptoms or other clinical features of PFIC at presentation (Table 2) [8,10,11,19,20,23,24,26,27] and 10 reported on disease progression (Table 3) [8,10,19,20,22–27].

Multiple symptoms were reported at presentation, including: jaundice, hepatomegaly, itching/pruritus, pale stools, splenomegaly, diarrhea, discolored stools, failure to thrive, vitamin E deficiency, vitamin D deficiency and pancreatitis, with the last of these being confined to PFIC1

(Table 2) [8,10,11,19,20,23,24,26,27]. Symptoms of PFIC1 and PFIC2 generally appeared within the first 3 months of life [8], with a tendency for earlier appearance in patients with PFIC2 [8,19,20,24]. In one study, symptoms appeared in the first month of life in 15% of patients with PFIC1 and 44% of patients with PFIC2, and by 3 months of age in 61% of patients with PFIC1 and 72% of patients with PFIC2 [8]. No differences between patients with PFIC1 and PFIC2 were seen in the development of jaundice, pruritus, hepatomegaly or splenomegaly over the first few months of life [8] whereas those with PFIC3 may not present with jaun-

dice, hepatomegaly or pruritus until after 2–3 years of age [19,24].

Itching or pruritus at presentation were reported in seven publications (Table 2), with frequencies ranging from 11% to 100% of patients [8,11,19,20,23,24,26]. Based on the Whittington scale (0, none; 1+, rubbing or mild scratching when not distracted; 2+, active scratching without evident skin abrasions; 3+, abrasions evident; 4+, cutaneous mutilation, hemorrhage and scarring evident) [28], pruritus was reported to be often severe (grade 3+ or more) in 76–80% of patients and was not consistent with the degree of bilirubin elevation [23,26]. Pruritus appeared to correlate with a higher level of serum bile acid in patients with low levels of GGT, although this effect was not statistically significant [24].

Some patients with PFIC2 also presented with early signs of vitamin D deficiencies (rickets, 3–22%), vitamin K deficiencies (bleeding, 8%) or cholelithiasis (28%) [8,19]. Other extrahepatic manifestations at presentation were evident in PFIC1 (but not PFIC2), including diarrhea (61%), pancreatitis (8%) and elevated sweat chloride (15%) [8]. PFIC3 was also associated with rickets (6%) [19]. None of the identified studies reported any other extrahepatic symptoms at presentation.

At follow-up, symptoms or other clinical features reported in patients with PFIC (Table 3) included jaundice, hepatomegaly, pruritus, splenomegaly, diarrhea, failure to thrive, growth retardation, severe cholestasis and liver failure (with possible symptomatic improvement, persistence or recurrence depending on interventions); there were also reports of pancreatitis in patients with PFIC1 and HCC in patients with PFIC2 (Table 3) [8,10,19,20,22–26]. Pruritus was reported in 76–100% of patients at follow-up [8,20,23,26,27] and often remained severe despite therapy [23,26].

Progression to severe liver disease was more common and occurred earlier in patients with PFIC2 than in those with PFIC1, occasionally manifesting as early as 7 months of age [8]. In patients under the age of 1 year, those with PFIC1 generally had no or mild portal and lobular fibrosis, no cirrhosis, no HCC and no necrosis, whereas those with PFIC2 had mild-to-severe portal and lobular fibrosis with bridging fibrosis, cirrhosis and sometimes necrosis. In patients over 1 year of age, major portal and lobular fibrosis was observed both in children with PFIC1 and those with PFIC2, but lesions were more pronounced in the latter [8]. Among patients undergoing LT, liver failure and/or HCC was detectable in about 60% of those with PFIC2 but in none of those with PFIC1 [8].

## Mortality

Ten publications reported PFIC mortality data (Tables 4 and 5) [8,10,11,19,20,22–26], with mortality rates ranging from 0% to 87% [11,19]. The rates of LT for patients with PFIC1 and PFIC2 (40–100%; Table 3) suggest that the highest reported mortality figure (87% [11]) is probably most representative of the natural history of untreated PFIC. Reasons for death included infections, bleeding (cerebral, gastrointestinal, splenic), liver failure, LT-related complications, HCC, and complications secondary to cholestasis, including

acute infections, dehydration and gastrointestinal bleeding (Table 4).

## Health-related quality of life and pruritus

Five publications evaluated the HRQoL or pruritus associated with PFIC (Table 5) [17,23,27,29,30]. Of these, only two publications assessed the impact of PFIC or pruritus on HRQoL [17,29]. Kamath and colleagues assessed HRQoL in children with chronic intrahepatic cholestasis, including those with PFIC [17]. Of 49 patients with chronic intrahepatic cholestasis, 25 had genetically confirmed PFIC. HRQoL was assessed using the Pediatric Quality of Life Inventory (PedsQL) Measurement Model; scores range from 0 to 100 with higher scores indicating better HRQoL. Children with chronic intrahepatic cholestasis had lower total PedsQL self-reported scores compared with healthy controls (73 vs. 84; effect size, 0.87); parent-reported scores were similar in both groups (79 vs. 82) [17]. Lind and colleagues used the PedsQL and the Infant Dermatitis Scale to assess HRQoL associated with pruritus in patients aged 6–18 years with PFIC or Alagille syndrome, compared with healthy peers [29]. HRQoL, physical health and psychosocial summary scores were lower in patients with pruritus than in healthy peers [29].

Three publications identified pruritus as the most bothersome symptom associated with PFIC [23,27,30]. A retrospective chart review assessed the severity of pruritus using the Whittington scale in five Malaysian patients with PFIC. Of the five patients, three had moderate pruritus with abrasions; one had severe pruritus with cutaneous mutilation, hemorrhage, and scarring; and one reported mild scratching and rubbing [23]. A German study in 24 patients with PFIC assessed the severity of pruritus using a 6-point pruritus score; the median was grade 3 (permanent scratch marks) [27]. A Dutch retrospective chart review of 11 patients with PFIC who had received PEBD identified the patients' main complaint as intractable pruritus with significant excoriations [30].

## Discussion

Patients with PFIC experience shortened life expectancy, debilitating symptoms and poor HRQoL. This systematic review consolidates the information available on the epidemiology, natural history, and burden of PFIC. Although genetic testing now allows definitive diagnosis, we found significant knowledge gaps in the epidemiology of PFIC and its subtypes. We also found limited evidence about mortality, the HRQoL of patients with PFIC, and a lack of published information on the economic burden of the disorder.

Published epidemiologic evidence on the global incidence and prevalence of PFIC was found to be very limited. It was difficult to compare results across studies because of differences in methods and patient populations, as well as the absence of molecular genetic diagnostics to differentiate PFIC from other similar conditions in earlier studies. When reviewing the literature, numerous authors have indicated that PFIC is estimated to affect 1 in 50,000–100,000 births [1,31]. However, the source of this estimate could not be identified by this systematic literature analysis and this

rate is not supported by observational or clinical evidence. Population epidemiology data identified in the present systematic review was limited either to an estimate based on non-genetic diagnoses and average birth rates in Norway [10], or to case reports from a small indigenous population in Greenland [11]. Confirmation of PFIC diagnosis by molecular genetic testing allows accurate assessment of its prevalence. Among studies assessing children admitted to hospital with liver-related diseases, publications of studies using molecular genetic diagnosis reported a prevalence of PFIC of 12–13% in children with cholestasis and 9% in those with cholestasis, acute liver failure, or splenomegaly [14,16,17]. This suggests that PFIC accounts for a considerable proportion of childhood liver disease. Although originally reported mostly in Caucasian patients [23], PFIC has also been diagnosed in individuals from other populations. However, in general, these diagnoses were not based on genetic testing and the actual prevalence might be higher than reported [12–18,23].

Of the three main PFIC subtypes, PFIC2 was generally more common than PFIC1 and PFIC3 in studies conducted in the USA and Europe, but PFIC1 was the most common subtype in a study conducted in Japan [22]. Further research is needed for accurate estimates of the prevalence and incidence of PFIC and its subtypes, and for improved understanding of geographic and ethnic variations.

Pruritus was a primary symptom of PFIC, experienced by 11–100% of patients at presentation and by 76–100% of patients at follow-up. Pruritus was often severe; was associated with abrasions, cutaneous mutilation, hemorrhage, and scarring; and led to significantly diminished HRQoL (assessed using the PedsQL) in patients with PFIC compared with healthy peers [17]. Symptoms of PFIC also included jaundice, hepatomegaly, splenomegaly, diarrhea, and failure to thrive. These generally appeared by about 3 months of age in patients with PFIC1 or PFIC2 [8], whereas patients with PFIC3 sometimes did not present with symptoms until after 2–3 years of age [19,24]. Patients with PFIC2 were more likely than patients with PFIC1 or PFIC3 to experience progression to severe liver disease or HCC and to require LT. Progression to HCC appeared to be a common and early outcome in patients with PFIC2. Furthermore, an immunohistochemical and mutational analysis study of liver samples obtained from 10 children with HCC aged 13–52 months showed that the majority had evidence of bile acid transporter deficiencies and mutations in *ABCB11* [32]. No publications were identified reporting data on PFIC in adults, indicating the need for further research in this area.

Limited evidence was identified on the HRQoL of patients with PFIC. Two studies reported that children with PFIC had lower HRQoL than healthy peers (using the generic PedsQL questionnaire). HRQoL was also lower in patients with PFIC or Alagille syndrome than in patients with  $\alpha$ -1 antitrypsin deficiency, another chronic liver disease [17]. The development of disease-specific instruments may help with future assessment of the impact of specific symptoms of PFIC (e.g. pruritus) on HRQoL.

No publications reporting data on PFIC-related costs, resource utilization, or overall economic burden were identified. While rare, PFIC is both severe and life-threatening, and management of patients may involve extended and repeated hospitalization, surgery, transplan-

tation, and other costly interventions. Furthermore, the symptoms of PFIC can be debilitating and, as most patients are children and infants, there is likely to be an associated economic burden imposed on parents and other caregivers. Further research is needed to quantify the economic burden of PFIC.

## Conclusion

Clinical features and prognosis vary depending on the subtype of PFIC. For instance, outcomes after LT can be poor in patients with PFIC1 [25], as the disease is multisystemic and hence the bowel and lung manifestations are not necessarily improved post-LT. These differences underscore the importance of prompt genetic confirmation of the diagnosis to provide additional guidance to physicians and patients about the likely disease course. Prenatal genetic diagnosis could also be considered. PFIC1, PFIC2 and PFIC3 are the main subtypes of PFIC, but genetic testing can also detect other inherited cholestatic liver diseases including *TJP2* deficiency (encoding tight junction protein 2), which is sometimes referred to as PFIC4 [33], and cholestasis associated with genetic defects in *MYO5B* (encoding myosin VB) [34]. Next generation sequencing of targeted gene panels has proven value in rapidly and reliably discriminating cholestatic disease of childhood [35].

Current clinical information is variable and based on small and often anecdotal studies in a limited number of geographical regions. The increasing availability of molecular genetic diagnostics, coupled with specific new codes in the International Statistical Classification of Diseases and Related Health Problems, will allow more accurate prospective and retrospective assessment of patients with PFIC. Creating and unifying patient registries will help to align all available information on the population of patients with PFIC, including genotyping data. Further studies are required to better characterize the subtypes of PFIC, not only to improve clinical understanding but also to inform the management of individuals with PFIC and the design of future therapeutic trials in patients with these genetic conditions. Evaluation of the economic costs of PFIC and the HRQoL of patients may help to encourage recognition of the burden imposed by this debilitating and potentially underdiagnosed family of diseases, and to ensure that adequate attention is paid to patients' needs.

## Funding

This work was funded by Shire International GmbH. Shire develops and markets treatments for genetic diseases including progressive familial intrahepatic cholestasis.

## Writing assistance

Under the direction of the authors, Dr. Obaro Evuarherhe and Dr. Elizabeth Gandhi, employees of Oxford PharmaGenesis, Oxford, UK, provided writing assistance for this publication. Editorial assistance in formatting, proofreading, copy editing and fact checking was also provided by Oxford PharmaGenesis. Shire International GmbH provided funding to

Oxford PharmaGenesis for support in writing and editing this manuscript.

## Author contributions

All authors were involved in the study concept and design, analysis and interpretation of the data, and the drafting and critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript for submission.

## Disclosure of interest

L. Todorova is a former employee of Shire and owns stock or stock options.

The following authors have received compensation for serving as consultants or speakers for, or they or the institutions they work for have received research support or royalties from, the companies or organizations indicated: A. Baker (Shire), N. Kerkar (Retrophin, Alexion), B.M. Kamath (Retrophin, Shire), R.H.J. Houwen (Alexion, Albireo).

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.clinre.2018.07.010>.

## References

- [1] Srivastava A. Progressive familial intrahepatic cholestasis. *J Clin Exp Hepatol* 2014;4:25–36.
- [2] Bull L, et al. A gene encoding a P-type ATPase mutated in two forms of hereditary cholestasis. *Nat Genet* 1998;18:219–24.
- [3] Strautnieks SS, et al. A gene encoding a liver-specific ABC transporter is mutated in progressive familial intrahepatic cholestasis. *Nat Genet* 1998;20:233–8.
- [4] Deleuze JF, et al. Defect of multidrug-resistance 3 gene expression in a subtype of progressive familial intrahepatic cholestasis. *Hepatology* 1996;23:904–8.
- [5] Delaunay JL, et al. A functional classification of ABCB4 variations causing progressive familial intrahepatic cholestasis type 3. *Hepatology* 2016;63:1620–31.
- [6] van der Woerd WL, Houwen RH, van de Graaf SF. Current and future therapies for inherited cholestatic liver diseases. *World J Gastroenterol* 2017;23:763–75.
- [7] Bustorff-Silva J, et al. Partial internal biliary diversion through a cholecystojejunocolonic anastomosis—a novel surgical approach for patients with progressive familial intrahepatic cholestasis: a preliminary report. *J Pediatr Surg* 2007;42:1337–40.
- [8] Davit-Spraul A, et al. ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC): phenotypic differences between PFIC1 and PFIC2 and natural history. *Hepatology* 2010;51:1645–55.
- [9] Liberati A, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62:e1–34.
- [10] Henriksen NT, Drablos PA, Aagaens O. Cholestatic jaundice in infancy. The importance of familial and genetic factors in aetiology and prognosis. *Arch Dis Child* 1981;56:622–7.
- [11] Nielsen IM, Eiberg H. Cholestasis Familiaris Groenlandica: an epidemiological, clinical and genetic study. *Int J Circumpolar Health* 2004;63(Suppl. 2):192–4.
- [12] Alam S, et al. Protocol-based management of metabolic liver disease in children at a tertiary care specialized center. *Hepatol Int* 2013;7:S112.
- [13] Chaabouni M, et al. Epidemiological, etiological and evolutionary aspects of children cirrhosis in a developing country: Experience of the pediatric department of SFAX University hospital, Tunisia. [French]. *Tunis Med* 2007;85:738–43.
- [14] Fischler B, Papadogiannakis N, Nemeth A. Aetiological factors in neonatal cholestasis. *Acta Paediatr* 2001;90:88–92.
- [15] Monajemzadeh M, et al. Liver needle biopsy in Iranian pediatric patients: diagnostic significance and pattern of liver diseases. *Indian J Pathol Microbiol* 2009;52:10–3.
- [16] Ruth ND, et al. Identifying incidence of inherited metabolic disorders in patients with infantile liver disease. *J Hepatol* 2014;1:S505.
- [17] Kamath BM, et al. Quality of life and its determinants in a multicenter cohort of children with Alagille syndrome. *J Pediatr* 2015;167:390–6 [e3].
- [18] Vasishta R, et al. Spectrum of significant liver diseases at autopsy in children in a tertiary care institute. *Lab Invest* 2015;95:12A.
- [19] Al Mehadib A, Al Shahrani A. Progressive familial intrahepatic cholestasis in Arabs. *J Hepatol* 2013;58:S555–6.
- [20] Englert C, et al. Liver transplantation in children with progressive familial intrahepatic cholestasis. *Transplantation* 2007;84:1361–3.
- [21] Gray Z, et al. Identifying incidence of inherited metabolic disorders in patients with infantile liver disease. *J Pediatr Gastroenterol Nutr* 2013;56(suppl. 2):88.
- [22] Hori T, et al. Progressive familial intrahepatic cholestasis: a single-center experience of living-donor liver transplantation during two decades in Japan. *Clin Transplant* 2011;25:776–85.
- [23] Lee WS, Chai PF, Looi LM. Progressive familial intrahepatic cholestasis in Malaysian patients—a report of five cases. *Med J Malaysia* 2009;64:216–9.
- [24] Wanty C, et al. Fifteen years single center experience in the management of progressive familial intrahepatic cholestasis of infancy. *Acta Gastroenterol Belg* 2004;67:313–9.
- [25] Miyagawa-Hayashino A, et al. Allograft steatohepatitis in progressive familial intrahepatic cholestasis type 1 after living-donor liver transplantation. *Liver Transpl* 2009;15:610–8.
- [26] Whittington PF, et al. Clinical and biochemical findings in progressive familial intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr* 1994;18:134–41.
- [27] Schukfeh N, et al. Normalization of serum bile acids after partial external biliary diversion indicates an excellent long-term outcome in children with progressive familial intrahepatic cholestasis. *J Pediatr Surg* 2012;47:501–5.
- [28] Whittington PF, Whittington GL. Partial external diversion of bile for the treatment of intractable pruritus associated with intrahepatic cholestasis. *Gastroenterology* 1988;95:130–6.
- [29] Lind RC, et al. Quality of life in children after a partial external biliary diversion for progressive familial intrahepatic cholestasis or Alagille's disease. *J Pediatr Gastroenterol Nutr* 2010;50:E155.
- [30] Yang H, et al. Partial external biliary diversion in children with progressive familial intrahepatic cholestasis and Alagille disease. *J Pediatr Gastroenterol Nutr* 2009;49:216–21.

- [31] Baussan C, et al. Genetic cholestatic liver diseases: the example of progressive familial intrahepatic cholestasis and related disorders. *Acta Gastroenterol Belg* 2004;67:179–83.
- [32] Knisely AS, et al. Hepatocellular carcinoma in ten children under five years of age with bile salt export pump deficiency. *Hepatology* 2006;44:478–86.
- [33] Sambrotta M, et al. Mutations in TJP2 cause progressive cholestatic liver disease. *Nat Genet* 2014;46:326–8.
- [34] Qiu YL, et al. Defects in myosin VB are associated with a spectrum of previously undiagnosed low gamma-glutamyl-transferase cholestasis. *Hepatology* 2017;65:1655–69.
- [35] Nicastro E, D'Antiga L. Next generation sequencing in pediatric hepatology and liver transplantation. *Liver Transpl* 2018;24:282–93.