ESPGHAN provides a variety of educational activities, events and information that are available throughout the year. The ESPGHAN Education Partner Programme (EPP) was launched in 2015. Based on the 2015 adopted ESPGHAN Code of Conduct, the EPP has been developed to ensure the on-going development and implementation of an up-to-date, independent, high quality educational programme for health care professionals. The dedicated support and financial commitment from our partners helps to enhance and stabilize support for ESPGHAN’s educational activities. The EPP educational activities for 2017 are:

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<td>June 25-30, 2017</td>
<td>Bari, Italy</td>
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<td>ESPGHAN Danube/Balkan Summer School (EPP)</td>
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<td>ESPGHAN Young Investigator Forum (EPP)</td>
<td>September 20-23, 2017</td>
<td>Bergen, The Netherlands</td>
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<td>ESPGHAN AHP Summer School (EPP)</td>
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<td>ESPGHAN Paediatric GI Motility Hands-On Training Course (EPP)</td>
<td>September 26-27, 2017</td>
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<td>ESPGHAN School of Paediatric Liver Transplantation (2nd Transplant School Meeting)</td>
<td>September 27-30, 2017</td>
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<td>ESPGHAN GI School (EPP)</td>
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<td>ESPGHAN 3rd Paediatric IBD Masterclass (EPP)</td>
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<td>ESPGHAN Master Class on Gastrointestinal Immunology (EPP)</td>
<td>November 2017</td>
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<td>Chronic Liver disease in children: treatment and follow up</td>
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We sincerely thank the following EPP partners for their generous support and commitment:
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FAMILIAL CHOLESTASIS
January 26–28, 2017
Budapest, Hungary

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ABOUT ESPGHAN

WHO WE ARE
We are a multi-professional organisation dedicated to the promotion of the health of children with special regard to the gastrointestinal tract, the liver and nutritional status. Our members include clinicians, scientists, trainees, and allied health professionals.

WHAT WE DO
• provide representation for professionals involved in paediatric gastroenterology, hepatology and nutrition
• promote basic, translational and clinical science
• lobby for stronger support of research
• offer the highest standards of education to our members and other involved professionals
• focus attention on new investigators and trainees to ensure they are supported and encouraged
• serve as a source of competent advice for governments, international agencies, and relevant stakeholders

HOW WE DO IT
We achieve the above by knowledge creation, the dissemination of science based information, the promotion of best practice in the delivery of care, and the provision of high quality education for paediatric gastroenterology, hepatology and nutrition professionals in Europe and beyond.

HOW TO JOIN US
For information on different membership types and application procedure please visit our website www.espghan.org or contact the ESPGHAN Office via office@espghan.org.
Dear colleagues,

It is our great pleasure to welcome you to the ESPGHAN monothematic conference on Progressive Familial Intrahepatic Cholestasis (PFIC) in the beautiful city of Budapest. PFIC is an expanding family of disorders, diagnosed on mutations in the genes encoding key proteins in hepatic and sometimes extra-hepatic physiology. The first described conditions have been labeled PFIC type 1, type 2 and type 3, based on defective functions of specific canalicular transport proteins. More recently, however, additional mutations in other genes have been identified, that are also responsible for clinical phenotype of progressive cholestasis. The identification of responsible genes has significantly increased our insights in hepatic and biliary physiology. On the other hand, these different disorders have led to many new clinical challenges regarding optimal diagnosis, treatments and evolution of the disease into adulthood. The mutation analysis can also detect adult patients with a clinical phenotype different from the one at paediatric age. Presently, many of the affected children develop end-stage liver disease and need liver transplantation in childhood. Alternative therapies such as choleresis stimulation and partial biliary diversion have emerged, or are being developed - e.g. gene therapy.

The monothematic conference aims to provide an overview of the state-of-the-art knowledge of the pathophysiology of the classic and novel PFIC syndromes across the lifespan, their clinical aspects, present and emerging treatments, and to encourage collaboration between scientists and clinicians.

We are delighted to welcome you to Budapest!

Henkjan Verkade
Nedim Hadzic
Ronald Oude Elferink
Jörg Jahnel
Antal Dezsofi
Piotr Czubowski
Faculty

MONOTHEMATIC CONFERENCE: FAMILIAL CHOLESTASIS

January 26–28, 2017
Budapest, Hungary

Organizing Committee

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Institute of Pathology, Medical University Graz, Graz, Austria

Coen Paulusma, M.Sc, PhD
Scientist, Academic Medical Center (AMC), Amsterdam, The Netherlands
Faculty

MONOTHEMATIC CONFERENCE:
FAMILIAL CHOLESTASIS

January 26–28, 2017
Budapest, Hungary

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Heinrich-Heine University, Düsseldorf, Germany.

Dominique Debray, MD, PhD
Pediatric Hepatology Unit, Necker Hospital, Paris, France

Prof. Ulrich Baumann, MD, FRCPCH,
Professor of Paediatric Gastroenterology and Hepatology, Hannover Medical
School, Germany

Prof. Catherine Williamson, MD, PhD
Chair in Women’s Health Clinical Academic Group, King’s Kollege Londa, United Kingdom

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Expertise in Hepatology, Pediatrics, Cell Biology, Hôpital Bicêtre (Hôpitaux Universitaires
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Children’s Hospital Tübingen, Germany

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Academic Medical Center (AMC), Amsterdam, The Netherlands

Prof. Amit Nathwani, MD, PhD
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Prof. Irena Jankowska, MD, PhD
The Children’s Memorial Health Institute, Warsaw, Poland
Programme

MONOTHEMATIC CONFERENCE: FAMILIAL CHOLESTASIS

January 26–28, 2017
Budapest, Hungary

DAY 1: Thursday, January 26, 2017

15.00–15.10 Welcome and Introduction

15.10–16.30 Basic aspects
Chairperson: Henkjan J. Verkade, Antal Dezsofi

Bile flow in health and disease
Ronald Oude Elferink (The Netherlands)

History and overview of PFIC syndrome
Richard Thompson (United Kingdom)

Animal models of PFIC
Coen Paulusma (The Netherlands)

16.30–17.00 COFFEE BREAK AND POSTER WALK

Poster presentation

Long-term outcome of the patient with PFIC1 after successful partial external biliary diversion (PEBD) in early childhood
Alexandra Marach-Mocarska (Poland)

Clinical and Laboratory features in Children with Progressive Familial Intrahepatic Cholestasis in United Arab Emirates
Amer Azaz, Mohamed Miqdady (Saudi Arabia)

Hungarian experience with progressive familial cholestasis (PFIC)
Anna Fodor, Doloresz Szabo, Zsuzsanna Vajnisek, Laszlo Szarnyi, Antal Dezsofi (Hungary)

17.00–18.45 Physiology and pathophysiology of PFIC syndrome
Chairperson: Nedim Hadzic, Ekkehard Sturm

Histology and immunohistochemistry of PFIC syndromes
Alex Knisely (Austria)

Genetic variations of main types and their significance (polymorphisms, etc.)
Verena Keitel-Anselmino (Germany)

Other forms of familial cholestasis
Dominique Debray (France)

Case report presentation

Genetic Profiling of Children with Cholestatic Liver Disease: Experience of a Large Pediatric Liver Transplant Center
Mohammad Shagrani (Saudi Arabia)

19.00 DINNER AT THE HOTEL PRESIDENT
DAY 2: Friday, January 27, 2017

8.30–10.15 Clinical aspects I (Management and complications)
Chairperson: Ulrich Baumann, Jörg Jahnel

The mechanism of cholestatic pruritus
Ronald Oude Elferink (The Netherlands)

Medical treatments
Henkjan J. Verkade (The Netherlands)

Surgical non-transplant options (biliary diversions, nasobiliary drainage)
Irena Jankowska (Poland)

10.15–10.45 COFFEE BREAK AND POSTER WALK

10.45–12.30 Clinical aspects II
Chairperson: Dominique Debray, Piotr Czubkowski

Extrahepatic features of PFIC
Nedim Hadzic (United Kingdom)

LTx in PFIC; whom and when to transplant?
Ulrich Baumann (Germany)

Recurrent disease after LT for PFIC 1 and 2
Richard Thompson (United Kingdom)

Case report presentation
Genetic variations underlying progressive familial intrahepatic cholestasis (PFIC) in the Indian population
Rakesh Aggarwal (India)
# Programme

## MONOTHEMATIC CONFERENCE: FAMILIAL CHOLESTASIS

**January 26–28, 2017**  
**Budapest, Hungary**

### 12:30–13.30 LUNCH BREAK AND POSTER WALK

**Poster presentation**
- 14-year-old girl with PFIC-2 – case report  
  Magda Naorniakowska (Poland)
- A complicated post transplant course in patient with PFIC Type 1  
  Mirna Natalija Anicic (Croatia)
- New FXR mutation leads to intrahepatic cholestasis and liver failure  
  Mordechai Slae (Israel)
- Charged multivesicular protein 5, a newly identified bile salt transport pump (BSEP)-interacting protein, involves the membrane targeting of BSEP  
  Shang – Hsin Wu (Taiwan)

### 13.30–15.45 Clinical aspects III (PFIC beyond paediatric hepatology)

**Chairperson:** Richard Thompson, Irena Jankowska

**PFIC, oral contraceptives and pregnancy**  
*Catherine Williamson (United Kingdom)*

**Atypical presentations of PFIC at pediatric and adult age: MDR3 def, BRIC, gallstones and others**  
*Emanuel Gonzales (France)*

**Malignancies in PFIC**  
*Alex Knisely (Austria)*

**Drug toxicity and PFIC. Which and why?**  
*Bruno Stieger (Switzerland)*

**Case report presentation**
- Predicting development of hepatocellular carcinoma among patients with progressive familial intrahepatic cholestasis type 2  
  Tanguy Demaret (Belgium)

### 16.30 SOCIAL PROGRAM AND COURSE DINNER

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<td>17.30–18.00</td>
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<tr>
<td>18.00–18.30</td>
<td>SIGHTSEEING - INNERCITY PARISH CHURCH</td>
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<td>18.30–20.00</td>
<td>GUIDED SIGHTSEEING TOUR BY BUS</td>
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<td>20.30</td>
<td>DINNER AT THE HOTEL PRESIDENT</td>
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DAY 3: Saturday, January 28, 2017

9.00–10.15 PFIC and personalised medicine
Chairperson: Alex Knisely, Ronald Oude Elferink
History of gene therapy: ups and downs!
*Piter Bosma (The Netherlands)*
Developments in liver-directed gene therapy
*Amit Nathwani (United Kingdom)*
New medical options (FXR agonists/norUDCA/ASBT inhibition)
*Ekkehard Sturm (Germany)*

10.15–10.30 COFFEE BREAK

Case report presentation
Two siblings with TJP2 Mutations
*Christina Goncalves (Portugal)*

10.30–11.45 PFIC and personalised medicine
Chairperson: Alex Knisely, Ronald Oude Elferink
Emerging therapies (molecular chaperons, hepatocyte transplantation)
*Emanuel Gonzales (France)*
Ideas for collaboration, networks (ERN) and further research
*Ekkehard Sturm (Germany)*

Conclusions and closure

11.45–12.45 Lunch and farewell
Genetic Profiling of Children with Cholestatic Liver Disease: Experience of a Large Pediatric Liver Transplant Center

Mohammad Shagrani¹,², Jessica Burkholder¹, Dieter Broering¹, Mohamed Abouelhoda³,⁴, Nada Altassan³,⁴, Fowzan S Alkuraya¹

¹Organ Transplant Centre, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; ²College of Medicine, Alfaisal University, Riyadh, Saudi Arabia; ³Saudi Human Genome Project, King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia; ⁴Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Introduction: Advanced cholestatic liver disease is a leading referral to pediatric liver transplant centers. In our country (S.A.) genetic familial and metabolic liver diseases are the leading indication for liver transplantation which is not the case in any other population as biliary atresia is the leading cause anywhere else. This is reflecting the urgency for the need of our own gene panel.

Methods: Recent advances in the molecular classification of this group of disorders promise a highly personalized management although the genetic heterogeneity also poses a diagnostic challenge. Using a next-generation sequencing-based multi-gene panel for the first time, we performed retrospective analysis of 98 pediatric patients who presented with advanced cholestatic liver disease.

Result: A likely causal mutation was identified in the majority (66%) which higher than any published data so far. We did manage to reverse diagnosis in 50% of cases present as primary diagnosis as Wilson disease to be MDR 3 disease (PFIC3) Progressive familial intrahepatic cholestasis which will change the whole management, we diagnose 7 children with TJP2 (Tight junction protein 2) rarely been reported to cause cholestatic liver disease and we showed that it has clear oligogenic presentation. In our cohort it showed that PFIC3 and PFIC2 are more prevalence than PFIC1. In addition to refining the clinical diagnosis, the panel results provided molecular explanation for a number of important clinical observations including risk of recurrence post-transplantation, which highlights the promise of applying our assay prospectively to personalize the management of these patients.

Conclusion: In summary, we describe the successful use of a next generation sequencing-based multi-gene panel to molecularly characterize a large cohort of pediatric patients with advanced cholestatic liver disease. Our results highlight the important contribution of genetic causes in this cohort and the promise of this approach when applied prospectively to personalize the diagnosis and management of these patients. We are totally believe that this new genetic panel in KFSHRC will change the future of pediatric liver diseases in all aspects and will open a new era of translation and personalized medicine research.
Long-term Outcomes of Six Patients After Partial External Biliary Diversion for Progressive Familial Intrahepatic Cholestasis

Basak Erginel B, Gun Soysal F, Celik A, Salman T, Cantez S, Durmaz Ugurcan O

Istanbul University Istanbul Medical Faculty; 1Department of Pediatric Surgery; 2Department of Pediatric Gastroenterology, Hepatology and Nutrition

Aims: Background: Partial internal biliary diversion (PIBD) is an alternative approach for the treatment of devastating pruritus in patients with progressive familial intrahepatic cholestasis (PFIC). In these patients quality of life can be improved and progression of liver disease can be delayed while waiting for liver transplantation. The aim of our study was to evaluate six patients with PFIC who have undergone PIBD in long-term follow-up.

Methods: Retrospective review of the records of six patients who underwent PIBD for PFIC between 2008 and 2010 was conducted to evaluate age, growth, clinical and laboratory studies for long-term outcome.

Results: Serum postoperative bile acid levels were reduced from a mean 340.1 μmol/L (range 851-105) preoperatively to a mean of 96.3 μmol/L at post-operative fifth year. The difference between pre and postoperative bile acid levels were statistically significant (p=0.018). AST decreased from 79,1 U/L (range 43-150 U/L) to 64,6 U/L (range 18-172 U/L), ALT decreased from 102,8 U/L (range 35-270U/L) to 84,6 U/L and total bilirubin decreased from 2,9 μmol/L (range 0,35-6,4 μmol/L) to 1,53 μmol/L (range 0,3- 2,4). Again, the decrease in total bilirubin levels were significant (p=0.043). Pruritus was diminished from a mean of +4 (range 4-4) preoperatively to a mean of +2 (4-0) (Table). One patient who underwent liver transplantation due to relapsing pruritus died from post-operative sepsis in the early post-operative period at the fifth year after PIBD. Five symptom-free patients have not required liver transplantation at a mean period of 6.1 ± 0.83 years (5.1-7.0 years) follow-up.

Table 2. Bile acid values and pruritus score of each patient pre-operatively and five years post-operatively .

<table>
<thead>
<tr>
<th>Patients</th>
<th>Bile acids(μmol/L)</th>
<th>Pruritus</th>
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<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
</tr>
<tr>
<td>1</td>
<td>216</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>212</td>
<td>3.1</td>
</tr>
<tr>
<td>3</td>
<td>851</td>
<td>170.1</td>
</tr>
<tr>
<td>4</td>
<td>452</td>
<td>310</td>
</tr>
<tr>
<td>5</td>
<td>105</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>205</td>
<td>6.6</td>
</tr>
<tr>
<td>Mean</td>
<td>340.1</td>
<td>96.3</td>
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Conclusion: PIBD can serve as an effective surgical procedure in the long-term and can delay the need for liver transplantation in children with PFIC by alleviating cholestatic injury in the liver and by reducing jaundice and pruritus.
Genetic variations underlying progressive familial intrahepatic cholestasis (PFIC) in the Indian population

Anjali Sharma, Ujjal Poddar*, Shikha Agnihotry, Amit Goel, Rakesh Aggarwal
Departments of Gastroenterology and *Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Aims and objectives: PFIC is an important cause of cholestatic liver disease in children. It is caused by genetic variations in ATP8B1, ABCB11 or ABCB4 genes, which encode proteins that transport bile salts into biliary canaliculi. Since there are no data on genetic variations in patients with PFIC in the Indian population, which is genetically quite diverse, we decided to study variations associated with PFIC in India.

Methods: We studied unrelated children with clinical, biochemical and histological features suggestive of PFIC. All the coding exons and flanking splice regions of ATP8B1, ABCB11 and ABCB4 genes were sequenced and compared with the reference sequences. Sequence variations were looked for in parents, a group of healthy persons, and various variation databases, and their effect on protein function was assessed using bioinformatic tools. Variations were interpreted using standards and guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Our institution’s ethics committee approved the study and parents provided informed consent.

Results: Among 25 children studied (age range: 1 mo to 12 y; 19 male), 9 (36%) had ‘pathogenic’ or ‘likely pathogenic’ (P/LP) genomic variations (ATP8B1: 4, ABCB11: 3 and ABCB4: 2); each patient had a different variation. These variations included four single amino acid substitutions (ATP8B1: c.1660G>A/p.Asp554Asn and c.2941G>A/p.Glu981Lys; ABCB11: c.548T>C/p.Met183Thr; ABCB4: c.431G>A/p.Arg144Gln), one single nucleotide substitution that created a premature stop codon at its location (ABCB4: c.475C>T/p.Arg159Ter), (iii) one single-nucleotide deletion leading to frame-shift and premature termination (ABCB11: c.1360delG/p.Val454Ter); (iv) one 3-nucleotide deletion leading to in-frame loss of an amino acid (ATP8B1: c.1587_1589delCTT/p.Phe529del), (v) a complex inversion of 4 nucleotide with a single-nucleotide deletion leading to frame-shift and premature termination (ATP8B1: c.589_592inv;592_593insA/p.Gly197LeufsTer10), and (vi) a splice-site variation likely to cause abnormal splicing (ABCB11: IVS8+1G>C). The P/LP variations were homozygous in seven patients, and heterozygous in two (ABCB11: IVS8+1G>C and c.1360delG). Three variations were novel (ATP8B1: c.589_592inv;592_593insA; ABCB11: IVS8+1G>C and c.1360delG). The variations were more common in patients with history of consanguinity (5/7; 71%) than in those without (4/18; 22%) (p<0.05).

Conclusions: P/LP sequence variations, including some novel variations, in the three PFIC genes were identified in 36% of Indian children with PFIC. None of the variations was particularly common. No exonic or splice-site variation in the three genes was identified in nearly two-thirds of patients. Thus, it may be useful to look for variations in other genes involved in bile salt transport or in promoter/intronic regions of ATP8B1, ABCB11 and ABCB4 genes in the Indian population.
Two siblings with TJP2 Mutations

Cristina Gonçalves, Sandra Ferreira, Susana Nobre, Lina Ramos, Isabel Gonçalves
Pediatric and Adult Liver Transplantation Unit, Coimbra Hospital and University Centre, Coimbra, Portugal

Scientific evidence about bile acids transporters, their disorders and the development of genetics techniques are challenging. Patients with liver disease previously of unknown aetiology are becoming diagnosed with “new disorders” associated with deficiency in transporters or proteins of the biliary duct. The authors present the case of two siblings with cholestasis presenting in the neonatal period and progressive liver disease.

Case 1: 15-year-old girl, presented with neonatal cholestasis with severe pruritus and coloured stools since the age of 2 months. Laboratory evaluation showed high LFT’s (AST/ALT) with normal GGT. Additionally, abdominal US disclosed a heterogeneous liver with a nodular lesion on S7 (1.6x1.5x0.9 cm). A-fetoprotein levels were normal. Metabolic and Hormonal evaluations were normal. Sequencing of ATP8B1 and ABCB11 genes did not show any pathological mutations. Due to severe pruritus and refractoriness to UDCA, rifampicin therapy was started with dramatic clinical improvement, lowering bilirubin and LFT’s and improving pruritus. She remains stable without portal hypertension features; liver mass dimensions also remained stable. Liver biopsy was repeated at the age of 14 disclosing septal fibrosis (F3/F4) with focal regeneration. A NGS Familial Cholestasis Panel was performed and a homozygous mutation on TJP2 gene was found (c.1136T>A(p.Leu379Gln)).

Case 2: 4-year-old girl, young sister of patient 1, presented at 2 months of age with cholestasis without reference to acoic stools. Severe pruritus was also noticed. Clinical and laboratory profile was similar to the older sister. However, coagulopathy was also found (Maximum INR:1.62). Abdominal ultrasound disclosed a heterogeneous liver with suggestion of nodules. Alfa-fetoprotein was high (>2000). Due to poor response to UDCA, rifampicin was added and a clinical improvement was noticed, with resolution of cholestasis and pruritus. However, portal hypertension developed, but the girl remains stable without complications. Such as in her sister, an NGS Familial Cholestasis Panel was performed and the same homozygous mutation on TJP2 gene was found (c.1136T>A(p.Leu379Gln)).

TJP2 encodes the protein zona-occludens - 2, which is a cytosolic component of cell junction in epithelia. Mutations in TJP2 gene were recently described in associated with normal GGT-neonatal cholestasis associated with extra-hepatic features (neurological, hearing, lung), although liver is the most involved tissue. This cases describe two siblings with FiC-profile cholestasis associated with TJP2 mutation, that were previously undiagnosed. The good clinical response to rifampicin remains to be clarified.
Predicting development of hepatocellular carcinoma among patients with progressive familial intrahepatic cholestasis type 2

Varma Sharat1, Raphael Fredrick2, Davit-Spraul Anne3, Charlotte Mussini1, Xavier Stephenne1, Emmanuel Jacquemin3, Sokal EM1, Emmanuel Gonzales1

1 Université catholique de Louvain, Brussels, Belgium; 2 Medicinal Chemistry Research Group, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; 3 Bicêtre Hôpital, Paris-Sud University, AP-HP, France

Background and aims: Progressive familial intrahepatic cholestasis type 2 (PFIC2) is an autosomal recessive disorder due to defective bile salt export pump (BSEP) which results in cholestatic liver disease and in some cases in hepatocellular carcinoma (HCC). As intra-hepatocytic bile accumulation is considered to be the driver of oncogenesis in PFIC2, we hypothesized that risk of HCC would correlate to functional loss of BSEP.

Methods: From two participating centers, sixty-two children with PFIC2 were identified, of which seven who developed HCC were included. Clinical, genetic, histological information was collected and 3D homology modeling was done to determine the severity of structural alterations in BSEP. Functional ability of BSEP was assessed by the clinical response to medical therapy and severity of structural change in the BSEP as assessed by 3D homology modeling.

Results: PFIC2 was diagnosed at a mean age of 3.7 months (1-10 months) and HCC was discovered 52 months later (11-150 months). At diagnosis BSEP canalicular immunostaining was negative in 85% (6 of 7). HCC was suspected because of elevated AFP in 5 and of visualization of suspicious ultrasonographic lesion in 6 patients. In one patient HCC was discovered fortuitously after LT. Functional ability of BSEP was retained in 2 patients. These patients demonstrated clinical response to medical therapy and had mild structural alteration of BSEP on 3D modeling.

Conclusion: There is high incidence of HCC in PFIC2 patients (11%, 7/62). HCC can occur in presence of normal AFP and in patients with mutations that are predicted to lead to severe functional loss.
Hungarian experience with progressive familial cholestasis (PFIC)

Anna Fodor, Dolóresz Szabó, Zsuzsanna Vojnisek, László Szőnyi, Antal Dezsőfi
First Dept. of Pediatrics, Semmelweis University, Budapest, Hungary

Aim: We retrospectively reviewed patient documentations from January 1995 till October 2016 at the First Dept. of Pediatrics, Semmelweis University Budapest, Hungary.

Patients: During this period we diagnosed 2 patients with PFIC1 and 10 with PFIC2. The average age at diagnosis was 3 months (2.75±1.31; 1-5 months). There was no consanguinity in the families. In all patients the main presenting symptoms were cholestasis, pruritus, besides elevated AST, ALT but normal GGT and coagulopathy.

Diagnosis: Diagnostic evaluation included the exclusion of other causes of neonatal cholestasis (viral infections, metabolic liver diseases, cystic fibrosis, alpha-1 antitrypsin deficiency, etc.) The final diagnosis was made on genetic testing in 58% (analysis of ATP8B1 and ABCB11 genes), immunohistochemistry in 33% (negative immunoreaction of bile salt export pump - BSEP) and in the others were made on typical symptoms, histopathology and exclusion of other diseases.

Therapy: All patients received ursodeoxycholic acid therapy and were supplemented with fat soluble vitamins. Two patients had partial biliary diversion (in age of 2 and 3 years) and 1 had cholecystectomy.

Outcomes: Eight of the 12 patients underwent liver transplantation (LTx), 50% was cadaveric and 50% was living related LTx. The medium age for LTx was 3 years (3.26±4.19; 1-12 years). The indication for LTx was end stage liver disease in 6 cases and uncontrollable pruritus in 2 cases. After LTx we have observed severe complications, such as periportal fibrosis, biliary anastomotic stricture, cava inferior syndrome, low grade cellular rejection, high grade steatosis hepatitis, post-transplant lymphoproliferative disease. All two patients with PFIC1 developed intense diarrhea after LTx. Till now one patient died in acute on chronic liver failure.
Outcome of Children with PFIC After Living Donor Liver Transplantation

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Objective: Progresif familial intrahepatic cholestasis is uncommon causes of liver failure during childhood. Despite our understanding increased in disease pathogenesis, medical therapy may not prevent the development of end stage liver disease.

Aim: to evaluate outcome of transplanted children with PFIC.

Methods: Patients data were collected from medical records and clinic charts. Patient demographics, clinical and laboratory data, surgical details, complications, and graft and patient survival are reviewed. Posttransplant immunosuppression consisted of a double regimen of tacrolimus and steroid. Statistical analysis was performed with SPSS version 16.0. Survival analysis was estimated using the Kaplan-Meier survival method. Numeric values are expressed as median and range unless otherwise stated.

Results: Between June 2009 and September 2016, 270 children underwent liver transplantation. Of the 62 children, 38 had PFIC type 2, 12 had PFIC type 1 and 11 had PFIC type 3. Median age at the transplantation was 50 mos (3-77), PELD and weight was 19 (4-41), 9.2 kg (4-54), respectively. The indications of LT was liver failure (n=38), variceal bleeding due to portal hypertension (n=12), intractable pruritis (n=16), growth failure. Six of them underwent to partially internal biliary diversion prior to LT. Median followed up was 50 months (range3-77). Survival for 1, 2 and 6 years was 95%, 95% and 95% respectively. One patient underwent retransplantation due to chronic rejection on posttransplant 31 months. Posttransplant complications were infection (n=10), hemofagositic lymphpohistocytosis (n=3), PTLD and lymphoma (n=2), biliary problems (n=7), food allergy (n=8) and diarrhea (n=3). Two patients who developed low GGT cholestasis were successfully treated steroid and AntiCD-20 monoclonal antibody. Graft-biopsy specimens obtained during periods of such elevations did not show signs of both acute and chronic rejection. No donor had early or late postoperative complications.

Conclusion: PFIC is common indication for LT in our population. The outcome is promising. But we need to close follow up disease recurrence and extraintestinal involvement after transplantation.
Hepatocarcinoma in a child with PFIC 2: an unlucky complication.

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Progressive familial intrahepatic cholestasis (PFIC) are inherited rare liver disorders of childhood, due to mutations in hepatocellular transport system genes. PFIC type 2 is caused by mutations in ABCB11 gene (chromosome 2q24), which encodes bile salt export pump (BSEP). In PFIC2, the clinical presentation is more severe, with permanent jaundice from the first months of life and severe pruritus. These patients evolve to end-stage liver cirrhosis within the first years of life. Although hepatocellular carcinoma (HCC) is rare in children, patients with BSEP deficiency are at risk of hepatobiliary malignancy (HCC, cholangiocarcinoma) before 1 year of age. Thus, these patients need a close monitoring for hepatocellular carcinoma with serum alpha-fetoprotein (AFP) evaluation every 6 months and liver ultrasonography (US) every year. However, liver US can be negative for focal nodules and advanced radiological investigation such as computed tomography (CT) may be often necessary. We described a case report of a girl affected by PFIC 2, diagnosed at 10 months of age with liver immunostaining, showing absence of BSEP, and subsequent genetic confirmation. The child received ursodeoxycholic acid and fat-soluble vitamins supplements. However, during the follow-up, clinical conditions worsened with increasing itching, persistent hyperbilirubinemia, coagulopathy and severe growth failure. At 28 months of age, the child was admitted for liver transplant work up. Histopathology on the explanted liver showed three unexpected nodules in lobe dx (maximum diameter of 1 cm) in the context of the micronodular and fibrotic parenchyma. Histopathological examination confirmed HCC. US evaluations, performed monthly before the transplant, were always negative for focal nodules. Serum AFP concentration was found just elevated (mean value 16 ng/mL, normal value <5 ng/mL), one time before the liver transplantation. However, because of normal US liver pattern, further radiological investigations were not performed. Chest and abdominal CT and bone scintigraphy, performed after liver transplantation, were negative for metastasis. One year after successful transplantation, there are no signs of malignancy detectable by clinical and radiological methods. The child is well and continues follow-up with AFP levels and liver US evaluation every 2 months. Low elevation of AFP was recorded (mean value 20 ng/mL, normal value <5 ng/mL); however, chest and abdominal CT scan, performed after 6 months and 1 year from liver transplantation. In conclusion, any case of PFIC 2 needs routine screening for HCC. Serum AFP concentration and US evaluation can be not sufficient to exclude HCC. The detection of HCC could be often incidental and performed only by histopathology examination on explanted liver. Advanced radiological examination as well as careful macroscopic examination of their explanted liver are essential to exclude HCC.
Familial Cholestasis Differential; Case Report of Biliary Atresia in a 1 Year Old in Uganda

BIODATA
Name: T.G
Age: 11 months
Sex: Female
Address: Masindi, Midwestern Uganda
Date of Admission: 27th October 2016
Date of Death: 20th November 2016

Baby T.G has been unwell since birth.

At admission, mother reported that the child was not gaining weight, neither was she progressing developmentally milestone-wise.

Child had reportedly been passing loose pale stools, often contained unaltered food content as it was ingested 3-4 times per day since birth after the meconium passage.

The mother also reported that baby T.G had been passing unusually dark urine, none bloody and not associated with crying on micturation since her first few days of life.

At about 6 weeks of age, the mother noted yellow discoloration of the eyes; this persisted till there presentation to Hospital. The jaundice would only subside occasionally in intensity.

At about 5 months, mother noticed abdominal distension which had also persisted till admission, it was not associated with vomiting, and there was no history of constipation.

Baby T.G was however said to have been having a good appetite all through, commonly fed on potatoes, rice and groundnut sauce, black tea and bread – not buttered, only occasionally fed on fish, beef and milk like once in 2 to 3 weeks.

Notably, the mother reported that for about 5 months prior to admission, the child had been having bouts of fever and sweating excessively at night. She had cough that had lasted about 3 weeks; No h/o contact with a known TB patient or adult with chronic cough.

No history of convulsions.

Past Medical History
This is T.G’s 3rd admission, all related to the prevailing conditions, notably when the child develops fever and cough. The previous admission was at Hoima Regional Referral Hospital located in Midwestern Uganda about 2 months ago where the parents were advised to bring the child to Mulago, Uganda’s national referral hospital for further evaluation and management. There is h/o use of oral herbal remedy to treat the child prior to admission at Hoima RRH.

No other established medical condition.

Birth History
Mother reportedly attended ANC x5, was tested for HIV – Negative and malaria which turned out positive at about 20 weeks of pregnancy, this was managed without any major events. She was not screened for Hepatitis B and Syphilis. Pregnancy was carried to term, delivered a healthy looking baby girl – T.G, from home with the aid of TBA hence baby was not weighed. She did not lose much blood; the mother and the baby were fine, she was reportedly initiated on breastfeeding within one hour and passed meconium.

Postnatally, mother reports baby passing whitish stools and this never changed, at 6 weeks the baby developed jaundice which also persisted, only fluctuating in intensity.

Growth and Development
Achieved social smile at about 3 months of age, started sitting with support at about 5 months and by 7 months she was sitting unsupported. By the time of admission, she could pick food from the plate and feed self but not by cup. T.G was reportedly a happy child smiling and chuckling with siblings but had since not been able to achieve other milestones like standing/walking.

Family – social history
T.G was the last born out of 3 siblings born to 22 year old mother and 25 year old father. The two siblings 3 and 6 years of age are healthy, and had been left under custody of the grandparents. Father lost his job 1 year ago; they solely depend on peasantry for livelihood. They had a few chickens that were all sold while trying to take care of baby Gloria. By the time of admission, T.G’s parents had no substantial source of income, even the transport to Mulago, Uganda’s National referral Hospital was solicited by church and community members.

Neither of the parents smokes cigarettes or drinks alcohol. No history of consanguinity and no family history of similar illness on either of the parents’ side but there is history of sickle cell disease on the paternal side.

Examination findings
General Exam
Sicklooking infant, wasted, no obvious dysmorphic features, silky brown hair, evenly distributed, no dermatoses, no petechial hemorrhages, moderately icteric, mild pallor, not cyanosed, no oral thrush, good dentition and oral hygiene, apyrexial (36.8°C), well hydrated, grade III digital clubbing, no leukonychia, no splinter hemorrhages, no edema.

Anthropometric Assessment
H/C: 44CM, this was normal for age
MUAC: 10cm, small for age (Normal ≥12.5cm)
Wt: 6.0Kg (Under weight)
Length: 65cm (Short for age)
Wt/Length: < -3SD

Per Abdomen:
Moderate to gross distention with visible collaterals (porto hypertension), a reducible umbilical hernia, no superficial masses or tenderness
Scm hepatomegally, hard consistency but nontender; 7cm splenomegally; no masses or tenderness at the renal angles. Dull percussion note with shifting dullness, and bowel sounds were muffled.

Respiratory System
Not in distress, RR 36b/min, good and equal air entry, no crepitations or ronchi.

CVS: Extremities warm, normal CRT, PR 114b/min, normal volume, regular, no delays, no jugular venous distention. Heart Sounds I/II heard – normal and regular, no gallop rhythm or murmur.

CNS: Unremarkable.

IMPRESSION
Failure To Thrive/Severe Acute Malnutrition – Non oedematous due to probably liver parenchymal disease to Rule out congenital biliary atresia.

Differentials
Progresive intrahepatic cholestasis
Hepatoblastoma
Liver Tuberculosis
Congenital infections like, syphilis, Hepatitis B, C or CMV
Inborn errors of metabolism like Galactosemia.

PLAN
CBC (Unremarkable save for picture of iron deficiency anaemia with HB 8.5gdl)
Hep BSAg – Negative
Mother: HIV Negative, TPHA - Nonreactive
Biochemistry: LFT/RFT (Renal panel – normal but liver enzymes elevated with conjugated hyperbilirubinemia predominant; 100.5umol/L, serum albumin – 34g/L which was normal)
Mantoux and Gene Xpert – Non reactive
Stool analysis – Not done

Abdominal Ultrasound scan with focus on hepatobiliary tree – revealed an enlarged liver with echogenic masses in parenchyma and cystic mass at base of the liver; Spleen moderately enlarged but of normal architecture.

Chest X-ray – Unremarkable (Given the high prevalence of tuberculosis, a chest X-ray was done to rule out any pulmonary involvement in case of tuberculosis).

Ultrasound guided Liver biopsy suggested by radiographer on duty at the time, however it was not done.

Progress report
Baby T.G, because of the frail state was first admitted the nutritional unit at Mulago national referral Hospital, indigenously known as Mwana Mugimu; she was started on high energy feeds for nutritional rehabilitation while collateral discussions went on between the parents, paediatric and surgical teams as we had arrived at congenital biliary atresia as the diagnosis.

The baby underwent nutritional rehabilitation for about 2 weeks however could only add about 500grams, all else was a status quo; unfortunately, a graph of weight and length was not plotted for a more objective follow assessment of the baby’s nutritional status.

Having been counseled and informed about how the delayed presentation inevitably compromises the expected outcomes with even the available treatment modalities in our setting, yet given the socioeconomic complex of the patient, liver transplantation was an impossible option to even consider, the parents allowed the team to manage the child as they deem helpful.

On November 16th, 2016, the patient underwent a laparatomy and a cystojejunostomy was done; they found extensive ascites, stained with bile, all bowel loops tinged with bile, liver was extensively cirrhotic. Identified a dilated extrahepatic cyst, and a rudimentary gall bladder. Did cystojejunostomy about 30cm from ligament of Treitz. Opened into the choledochal cyst, drained sludge and did side to side anastomosis. Unfortunately, the attending surgeons did not try to fill the biliary tree with radiology contrast to ascertain whether it was a choledochal cyst or biliary atresia and a liver biopsy was not taken at laparotomy.

Post operative: Patient was put on I.V fluids, analgesia, oxygen therapy, antibiotic therapy, with the vitals being monitored; she recovered from anaesthesia about 18hours post surgery, passed blood streaked pale stools.

On 19th November 2016, the baby was relatively stable and had resumed breastfeeding, tolerating the feeds.

There was however no substantial improvement in the ascites (abdominal distension), the jaundice did not improve and the last stools that were passed were still pale; the next day baby TG deteriorated and breathed her last on 20th November 2016.

May her soul RIP

Biliary atresia has poor prognosis especially with delayed presentation as is the norm in my setting here in Uganda. No literature exists on the prevalence and outcome of the condition however, this year 2016, 4 babies with biliary atresia were received at the national referral Hospital; all of them were delayed presentations between 6 months and one year and despite attempts to do surgery as was the case for baby TG, the outcome has been uniformly fatal. This therefore calls for more education and community involvement for early recognition and timely referral for intervention that could yield better outcomes.
Case report: 7-years old boy with BSEP deficiency

An 8 months old boy presented with swollen right thigh due to the haemorrhage. Prolonged PT-INR and PTT normalised after the vitamin K application. At the same time he had higher levels of AST (5-times the upper limit), ALT (6-times times the upper limit), normal gamma-GT, total and conjugated bilirubin (120 and 87 μmol/L respectively) and higher bile acids level. Liver ultrasound was normal. Of other signs he also had arterial hypertension (up to 160/110 mmHg) which was treated with propranolol. The presumed diagnosis of BSEP def. (PFIC 2) was confirmed at King’s College Hospital, London with immunohistochemistry. The DNA analysis was not consistent with the clinical presentation and histology results.

The boy developed severe pruritus which is partially controlled by ursodeoxycholic acid and rifampicin. He is also given lipid soluble vitamins. He is regularly followed up with abdominal ultrasound and alpha-fetoprotein for HCC.

Proposed discussion: the timing/indications for biliary diversion; the most effective follow-up.

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14-year-old girl with PFIC-2 – case report

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14-year-old girl with hepatosplenomegaly and itch was admitted to our outpatient clinic. When she was 2.5 years old celiac disease was diagnosed and hepatosplenomegaly with unknown origin was noticed. 10 years later because of itch she was diagnosed with atopic dermatitis. Moreover she was diagnosed in Endocrinology Clinic (short stature) and Metabolic Clinic. In our hepatological outpatient clinic clinical presentation (itch, hepatosplenomegaly) and laboratory tests (normal gamma-glutamyl transpeptidase (GGTP) level despite elevated bile acids) raised the suspicion of PFIC. The diagnosis was finally confirmed by genetic test (ABCB11 mutation – PFIC-2). She was treated with ursodeoxycholic acid (UDCA), but due to the severe pruritus, elevated bile acids, after 8 months, partial external biliary diversion (PEBD) was performed with good result (clinical and laboratory). Because of poor quality of life after 8 years ileal bypass was performed, but after 6 months itch and elevated bile acids occurred and she was treated with UDCA again with good result. When she was 25 years old, she got pregnant. In second trimester she developed pruritus, which gradually worsened with no response to UDCA treatment. Pruritus gradually decreased after delivery, finally resolved 6 months after delivery healthy child. After 6 years she was consulted with our clinic because of hepatic tumor. There was a high suspicion of hepatocellular carcinoma. The further fate of patient is not known.
A complicated post transplant course in patient with PFIC Type 1

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Our patient was born from normal pregnancy and delivery. She had neonatal hyperbilirubinemia. At the age of 5 months she presented with conjugated hyperbilirubinemia and diarrhea so extensive diagnostic workout was started. When she was 16 months old a diagnosis of PFIC type 1 was established.

She was treated conservatively until the age of 8 years when partial external biliary diversion was done due to severe pruritus. After that she had no complications and was well until the age of 16 years when she was admitted to our Department because of reduced drainage of bile in the stoma, laboratory signs of cholestasis and intense pruritus. Mechanical obstruction was excluded and scintigraphic findings showed impairment of liver function and signs of small bile duct obstruction. By comparison with the previous liver biopsy stage of fibrosis was lower. Due to severe pruritus and inadequate bile drainage we decided to put her on transplant list. In the next few weeks her condition improved spontaneously and bile drainage normalized. Since our patient was a teenager at that time and had issues with stoma surgeons performed internal biliary diversion.

In the next two years her clinical condition fluctuated, but slowly and progressively worsened so we decided to do a whole liver transplantation from cadaveric donor at the age of 18 years. The transplantation was uneventful, she was extubated in the operating room and first few hours in the ICU were unremarkable. 6 hours after admission she became hemodynamically unstable due to pericardial and bilateral pleural effusions which were drained. On the fourth postransplant day she developed acute graft rejection that was treated with high dose immunosuppressive therapy. In the third postransplant week doppler showed significant hepatic artery stenosis on the site of anastomosis, which was also confirmed on angiography and intravascular stent was placed. She also had an episode of abundant gastrointestinal bleeding due to duodenal ulcer. Further course of recovery was complicated by fungal pneumonia and respiratory failure that required mechanical ventilation for eight days. She developed acute renal failure and required hemodialysis for three weeks, after that her renal function slowly recovered. She also developed steroid induced hyperglycemia and was on insulin therapy for 2 months. She spent three months in ICU, and her total hospital stay was almost 5 months. Even though her postoperative course was extremely complicated, at the moment (2 years after transplantation) she is a 20 year old woman in good physical condition, on triple immunosuppressive therapy (cell cept, tacrolimus and steroids), works as a nanny and leads a dynamic and normal life.
New FXR mutation leads to intrahepatic cholestasis and liver failure

Introduction

The Farnesoid X Receptor (FXR) gene (also termed NR1H4) is a nuclear receptor gene involved in bile production regulation. It is a ligand-activated transcription factor that plays an essential role in bile acids (BA) homeostasis through regulation of genes involved in BA synthesis, conjugation and export and in the enterohepatic circulation. It has also been shown to be involved in metabolic pathways and to regulate innate immunity processes and plays an anti-inflammatory role in the liver.

Only recently mutations in the FXR gene have been found to cause progressive familial intrahepatic cholestasis, in a report of 4 children with FXR mutations and cholestasis published earlier this year.

Case report

The patient was the fifth child of consanguineous parents of Arab origin. He presented with early onset jaundice following an uncomplicated pregnancy and delivery. His growth and development were normal. He had no other symptoms. Laboratory investigation revealed elevated liver enzymes and cholestasis, elevated ammonia and coagulopathy and normal GGT. Basic workup for neonatal cholestasis causes yielded no results.

In liver tissue, markedly distorted architecture was seen, with portal tracts that were expanded by fibrosis and cholangiolar proliferation. Native bile ducts were not reduced in number. In the parenchyma, cholestasis, feathery and ballooning degeneration of hepatocytes, acinar transformation of hepatocytes, and bile plugging were seen. Iron deposition was minimal and PAS-diastase did not reveal cytoplasmic globules.

The patient was started on oral ursodeoxycholic acid. He has been breastfed with complementary pregestimil bottle-feeding and supplemented with A, D, E and K vitamins and gaining weight nicely. However, at the age of 8 months, he developed fulminant hepatic failure and passed away.

The parents were healthy, as were 3 of their 4 older daughters. The forth developed neonatal cholestasis and died of liver failure at 7 months of age.

The patient’s DNA was analyzed by whole exom sequencing. A mutation in the FXR gene was found, which has not been reported before. Cytosine deletion on position 100 934 551 on chromosome 12 caused a change in the framework of the protein starting with amino acid proline in position 355 and causing termination in position 377. No mutations in other cholestasis related genes have been found. Both parents and 2 of the 3 sisters were carriers of the mutation.

As compared to the three previously described mutations, which were more upstream in the DNA binding domain or zinc fingers regions, the current mutation is in the ligand binding region, much more downstream in the gene sequence. This case demonstrates that impairment of the ligand binding function can lead to major dysfunction and fatal outcome, no less then mutations in the regulatory parts of the protein.
Charged multivesicular protein 5, a newly identified bile salt transport pump (BSEP)-interacting protein, involves the membrane targeting of BSEP

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Background: Bile salt transport pump (BSEP) is the pivotal molecule mediating the bile salt transport from hepatocytes into the bile canaliculi. Progressive familial intrahepatic cholestasis type 2 patients with BSEP mutations were found to have abnormal expression or membrane targeting of BSEP.

Aim: To elucidate the interacting proteins of BSEP and the roles on BSEP-subcellular trafficking.

Methods: We used the human BSEP fragment as the bait to apply yeast two-hybrid screening in human fetal liver cDNA library. The novel interacting protein uncovered was confirmed by the biochemical assay and immunofluorescence staining. The knockdown of the interacting candidate was further analyzed in the in vitro assay for elucidating its roles on the trafficking and function of BSEP.

Results: Charged multivesicular protein 5 (CHMP5) is a newly identified BSEP-interacting protein, which interacts to the first ATP-binding cassette of BSEP. Using immunofluorescence staining, CHMP5 was found to be co-localized with the cytoplasmic BSEP instead of membranous BSEP in fetal, neonatal, and adult human livers. As knockdown of CHMP5 by RNA interference, CHMP5 does not affect the protein amount but the membrane targeting of BSEP in Hep G2 cells. In CHMP5 knockdown cells, the membrane targeting of BSEP was hampered; and the bile salts secretion was decreased.

Conclusion: CHMP5 is a newly identified BSEP interacting protein, which regulates the membrane targeting of BSEP.
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