Genetics and the liver

David Cassiman, MD, PhD
Gastroenterology-Hepatology and Metabolic Center
University Hospitals Leuven

Young man, 25 years

Childhood: at 6 wks jaundice, acholic stools and dark urine; hepatomegaly.

Laparoscopic cholangiography: normal extrahepatic biliary tree, but intrahepatic atresia of bile ducts

Liver path: ductopenia and ductal plate malformation – Alagille syndrome?

No butterfly vertebrae, no posterior embryotoxon, no abnormalities on cardiac US

Family history: no consanguinity, no liver disease, great aunt in maternal lineage died of renal insufficiency after years of dialysis. 3 siblings without medical problems.

➔ Tentative diagnosis PFIC1 or PFIC2 (normal gGT cholestasis) but no genetic confirmation

Biliary atresia

OMIM: Biliary atresia is likely multifactorial in etiology. A proposed mechanism includes genetic predisposition to the disease with immune dysregulation and environmental factors, such as a virus or toxin, playing variable roles. Genetic factors are believed to contribute to susceptibility to the disease (Leyva-Vega et al., 2010).

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Am J Med Genet A. 2010 April ; 152A(4): 886–895. doi:10.1002/ajmg.a.33332.

Genomic Alterations in Biliary Atresia Suggests Region of Potential Disease Susceptibility in 2q37.3

Melissa Leyva-Vega[1], **Jennifer Gerfen**[2], **Brian D. Thiel**[2], **Dorota Jurkiewicz**[3], **Elizabeth B. Rand**[1], **Joanna Pawlowska**[4], **Diana Kaminska**[4], **Pierre Russo**[5], **Xiaowu Gai**[6], **Ian D. Krantz**[2], **Binita M. Kamath**[7], **Hakon Hakonarson**[8], **Barbara A. Haber**[1], and **Nancy B. Spinner**[2]

Physical exam 2022:

120/60 mmHg, 80/min

1.71 m, 55kg, eutrophic

Leverrand voelbaar 3cm ORR, Li lob vergroot percutoir, milt vergroot maar rand niet voelbaar.

Geen stigmata van chronisch leverlijden verder.

Gastro 3-2017: no varices.

Cardiac US 3-2017: normal

FIBROSCAN 13-03-2017: 11.6 kPa METAVIR F3

FIBROSCAN 11-04-2022: 14.6 kPa METAVIR F4 (cirrhosis)

Liver US 6-11-2022:

Cirrosis with collaterals. Spleen 15 cm.

BMD in 2016: mild osteopenia

Current meds:

Ursochol 300 6/d: stopped by patient

Rifampicine 150 mg per day: stopped by patient

Liver gene panel UCL 2022!

CLDN1 homozygote for c.280G>A, p.(Ala94Thr) (rs531006128), not reported in LOVD or ClinVar

5/7 software tools predict it’s a pathogenic variant (class 5).

Concerne un nucleotide peu conservé et un acide aminé moyennement conservé

N'est pas rapportée dans les populations contróles (gnomAD)

L'écart physico-chimique entre l'alanine et la threonine est peu important

Absence de mutation ponctuelle et absence de variation du nombre de copies dans les gènes ABCB4, ABCB11, ATP8B1, NR1H4, TJP2.

Absence de mutation ponctuelle et absence de variation du nombre de copies dans les autres gènes analysés : AKR1D1, AMACR, BAAT, BCS1L, CC2D2A, CLDN1, CYP27A1, CYP7B1, DCDC2, DGUOK, HNF1B, HSD3B7, INVS, JAG1, MKS1, MPV17, NOTCH2, NPC1, NPC2, NPHP1, NPHP3, NPHP4, PKHD1, PNPLA3, POLG, SLC25A13, SMPD1, TALDO, TMC4, TMEM216, TM6SF2, TRMU, UGT1A1, VIPAS39 et VPS33B.

Conclusion

Non-syndromic bile duct paucity, probably NISCH (Claudin1 mutations).

Cirrhosis and portal hypertension, but asymptomatic.

Alk Phos <2x ULN, transaminases remain mildly elevated.

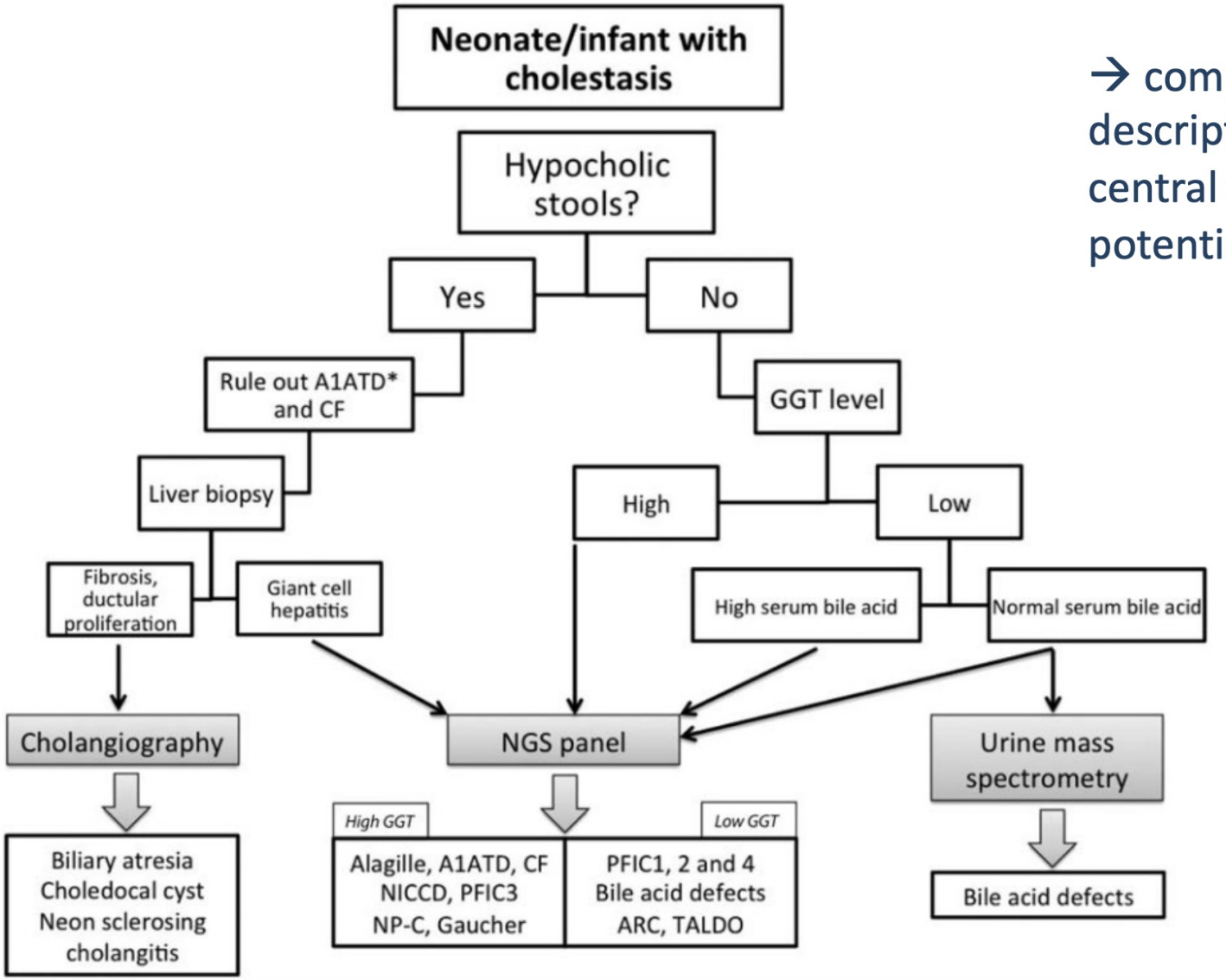
Platelets decreased for the first time (hypersplenism in the context of portal hypertension?).

Follow-up:

Vaccinations (flu, COVID, Pneumococci), HAV and HBV OK

US screening for liver lesions every 6 months

Gastro screening for varices when platelets drop < 110 and Fibroscan > 25 kPa…



→ comprehensive phenotype description of the patient is central to harnessing the maximal potential of genomic data

FIG. 2. Algorithm adopted in Bergamo for the diagnostic workup of cholestatic infants. *In infants with acholic stools, A1AT is tested in serum before Kasai portoenterostomy.

Rare liver diseases

ELSEVIER

Molecular Genetics and Metabolism

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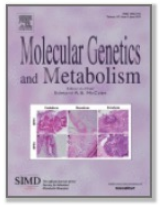


Review article

Clinical and biochemical footprints of inherited metabolic diseases. II. Metabolic liver diseases

Carlos R. Ferreira [a], David Cassiman [b], Nenad Blau [c, d]

ONLINE ONLY ARTICLES

Myelodysplasia and liver disease extend the spectrum of RTEL1 related telomeropathies

Shirleny R. Cardoso, Alicia C.M. Ellison, Amanda J. Walne, David Cassiman, Manoj Raghavan, Bhuvan Kishore, Philip Ancliff, Carmen Rodríguez-Vigil, Bieke Dobbels, Ana Rio-Machin, Ahad F.H. Al Seraihi, Nikolas Pontikos, Hemanth Tummala, Tom Vulliamy, Inderjeet Dokal

Vol. 102 No. 8 (2017): August, 2017 https://doi.org/10.3324/haematol.2017.167056

ORIGINAL ARTICLES: METABOLIC LIVER DISEASE

Mitochondrial hepatopathy in adults

a case series and review of the literature

Cloots, Kristien[a]; Verbeek, Jef[a]; Orlent, Hans[b]; Meersseman, Wouter[a]; Cassiman, David[a]

Author Information

European Journal of Gastroenterology & Hepatology 25(8):p 892-898, August 2013. | ***DOI:*** 10.1097/MEG.0b013e32835ee629

HNF1B deficiency causes ciliary defects in human cholangiocytes

Philip Roelandt [1], Aline Antoniou, Louis Libbrecht, Werner Van Steenbergen, Wim Laleman, Chris Verslype, Schalk Van der Merwe, Frederik Nevens, Rita De Vos, Evelyne Fischer, Marco Pontoglio, Frédéric Lemaigre, David Cassiman

Affiliations + expand

PMID: 22706971 DOI: 10.1002/hep.25876

JIMD
JOURNAL OF INHERITED METABOLIC DISEASE
SSIEM

Letter to the Editor

NTCP deficiency and persistently raised bile salts: an adult case

Filip Van Herpe, Hans R. Waterham, Christopher J. Adams, Marcel Mannens, Hennie Bikker, Frédéric M. Vaz, David Cassiman

nature communications

Article | Open Access | Published: 19 November 2022

PPARγ lipodystrophy mutants reveal intermolecular interactions required for enhancer activation

Maria Stahl Madsen, Marjoleine F. Broekema, Martin Rønn Madsen, Arjen Koppen, Anouska Borgman, Cathrin Gräwe, Elisabeth G. K. Thomsen, Denise Westland, Mariette E. G. Kranendonk, Marian Groot Koerkamp, Nicole Hamers, Alexandre M. J. J. Bonvin, José M. Ramos Pittol, Kedar Nath Natarajan, Sander Kersten, Frank C. P. Holstege, Houshang Monajemi, Saskia W. C. van Mil, Michiel Vermeulen, Birthe B. Kragelund, David Cassiman, Susanne Mandrup ✉ & Eric Kalkhoven ✉

Female, 65y

4/2014: left vocal chord paralysis → nodus left thyroid lobe →FNAC: follicular neoplasia - R/ total thyroidectomy

4/2014: Raised liver tests during admission → D/ NASH cirrhosis Child A, and status post-HBV

06/2015: hypertrophic cardiomyopathy (AHT) – gene panel HCMP 92 genes negative

02/2019: raised CK's, axonal sensorimotor polyneuropathy, vacuolar myopathy

Extended history-taking

In childhood: hepatosplenomegaly and short stature. Admission with liver biopsy negative. Her abdominal distension only regressed after the age of 12.

Family history:

No apparent consanguinity.

- Father died of lung cancer in old age. Mother died of cirrhosis (alcoholic?).
- No siblings, no unexplained mortality in the family.
- 1 son 46y: she had no problems during pregnancy or childbirth.

What diagnosis do you prefer?

1. Bad luck
2. HCMP and “NASH” cirrhosis: lamin A/C?
3. HCMP and myopathy: Danon disease (lamp2) with coincidental cirrhosis due to NASH ànd HBV
4. Some other metabolic/genetic disease

Gene panel neuromuscular diseases

D/ glycogenosis type 3 (GSD3a; compound heterozygote variants in AGL, amyloid-1,6-glucosidase, debrancher):

- hypertrophic CMP,
- cirrhosis,
- myopathy

NO hypoglycemias, NO lactic acidosis when fasting, YES mixed hyperlipidemia, NO hyperuricemia.

R/ slow carbs 4-5x/d OR ketogenic diet (effect on HCMP?)

Spectrum of liver diseases and genetics

- Liver steatosis (NAFLD, MAFLD, NASH, lean NASH)
- Hepato- and/or splenomegaly
- Cirrhosis (”cryptogenic”)
- Liver cancer (A1AT, porphyria), liver adenomatosis
- Acute liver failure (with febrile syndrome: NBAS etc)
- Portal vein thrombosis (Jak2 acquired mutation)
- Cholestasis (loooong list) and jaundice
- Bile stones
- Non-cirrhotic portal hypertension (X-chromosomal abnormalities, CVID, telomerase defects)
- Deficiencies of fat-soluble vitamins
- Hyperammonemia
- Pharmacogenomics and drug-induced liver injury
- Auto-immune liver disease
- Susceptibility genes for liver disease (PNPLA3, TM6SF2, MBOAT7, CYP2E1, complement factor V, HFE, A1AT)

Cirrhosis

1. Glycogenosis (III, IV, IXg)
2. Wilson
3. Erythropoietic Protoporphyria (EPP)
4. Lipodystrophies (pparG, lamin A/C)
5. CDG (low ceruloplasmin!)
6. Bile acid synthesis defects
7. …

Liver steatosis

Leading article

NASH may be trash

David Cassiman,[1,2] Jaak Jaeken[2]

The liver is a stupid organ. It has only addition, the first distinction (alcoholic vs

develop NAFLD/NASH, but also type 1 diabetics have been known to develop NAFLD/NASH. In addition, NAFLD/NASH is supposedly associated with the metabolic syndrome, but—certainly when the definition of this syndrome is systematically broadened to encompass

Gut. 2008 Feb;57(2):141-4.

Amino-acid disorders:

- Hepatorenal tyrosinemia type I
- Homocystinuria

Bile acid synthesis defects

Carbohydrate disorders:

- Galactosemia
- **Hereditary fructose intolerance**
- Glycogenoses (type I, III,, IV, VI, VIII, Fanconi-Bickel, IX)

Disorders of glycosylation (C.D.G.)

Lipid and fatty acid disorders:

- A- or hypobetalipoproteinemia
- Alpha- and beta-oxidation defects
- Dorfman-Chanarin syndrome

Metal disorders:

- Wilson disease

Mitochondrial disorders

Peroxisomal disorders

Hepato- and/or splenomegaly

1. Gaucher disease
2. Acid sphingomyelinase deficiency (Niemann-Pick A/B)
3. Lipid accumulation disorders (LAL-D, Tangier, abeta, …)
4. Niemann-Pick C
5. Mucopolysaccharidoses
6. Glycogenoses
7. …

Acute liver failure

1. Wilson
2. Mitochondrial (Pol G defect receiving valproate)
3. Hereditary Fructose Intolerance
4. Hyperammonemia: UCD, OA
5. With or following febrile syndrome: NBAS, LARS1, RINT1
6. …

Adenomatosis/HCC

- Wilson (HCC ànd CC)
- Glycogenoses
- Tyrosinemia type I
- Acute Hepatic Porphyria! (HCC and CC – noncirrhotic!)
- Urea cycle defects
- Mitochondrial hepatopathy
- …

Research Article
Genetic and Metabolic Diseases

JOURNAL OF HEPATOLOGY

Clinical utility of genomic analysis in adults with idiopathic liver disease

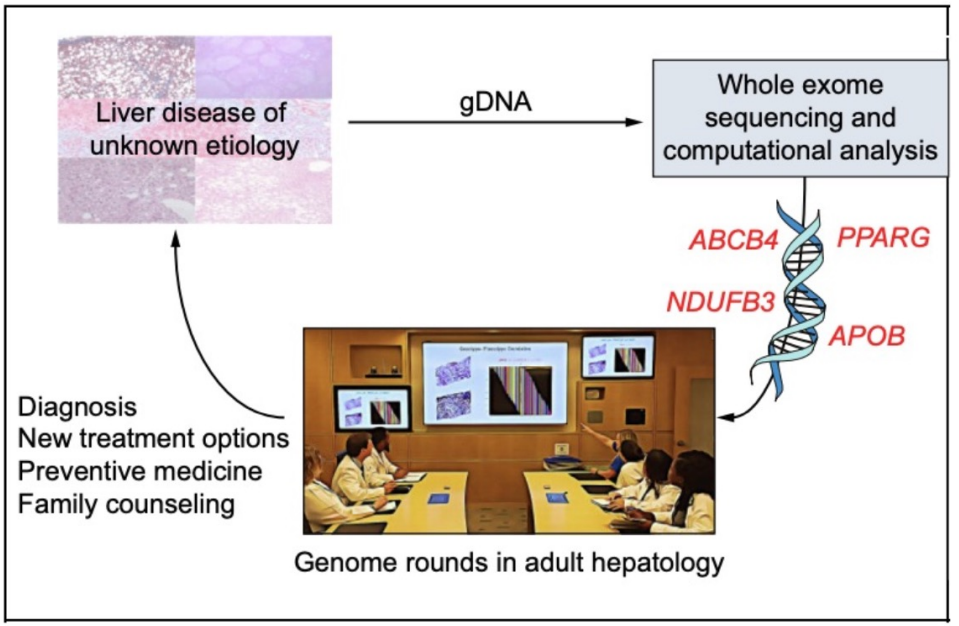
Aaron Hakim[1], Xuchen Zhang[2], Angela DeLisle[1], Elif A. Oral[3], Daniel Dykas[4], Kaela Drzewiecki[1], David N. Assis[1], Marina Silveira[1], Jennifer Batisti[1], Dhanpat Jain[1,2], Allen Bale[4], Pramod K. Mistry[1,5,#], Silvia Vilarinho[1,2,*,#]

[1]*Department of Internal Medicine, Section of Digestive Diseases, Yale School of Medicine, New Haven, CT, USA;* [2]*Department of Pathology, Yale School of Medicine, New Haven, CT, USA;* [3]*Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, MI, USA;* [4]*Department of Genetics, Yale School of Medicine, New Haven, CT, USA;* [5]*Department of Pediatrics and of Cellular & Molecular Physiology, Yale School of Medicine, New Haven, CT, USA*

Journal of Hepatology **2019** vol. 70 | 1214–1221

- 30% cirrhoses et 14% des patients en attente de transplantation hépatique souffrent d'une pathologie hépatique d'étiologie inconnue (PMIDs 21647651, 28293093).

Graphical abstract



Highlights

- Whole exome sequencing led to a diagnosis in 5/19 cases of unexplained liver disease.
- These 5 cases represented 4 monogenic disorders diagnosed in adulthood.
- Genomic analysis informed the treatment and management of liver disease.

= +- 25%

74 | APPROACH TO THE PATIENT WITH HEPATO-GASTROENTEROLOGICAL OR ABDOMINAL SIGNS AND SYMPTOMS

DAVID CASSIMAN AND CARLA E. M. HOLLAK