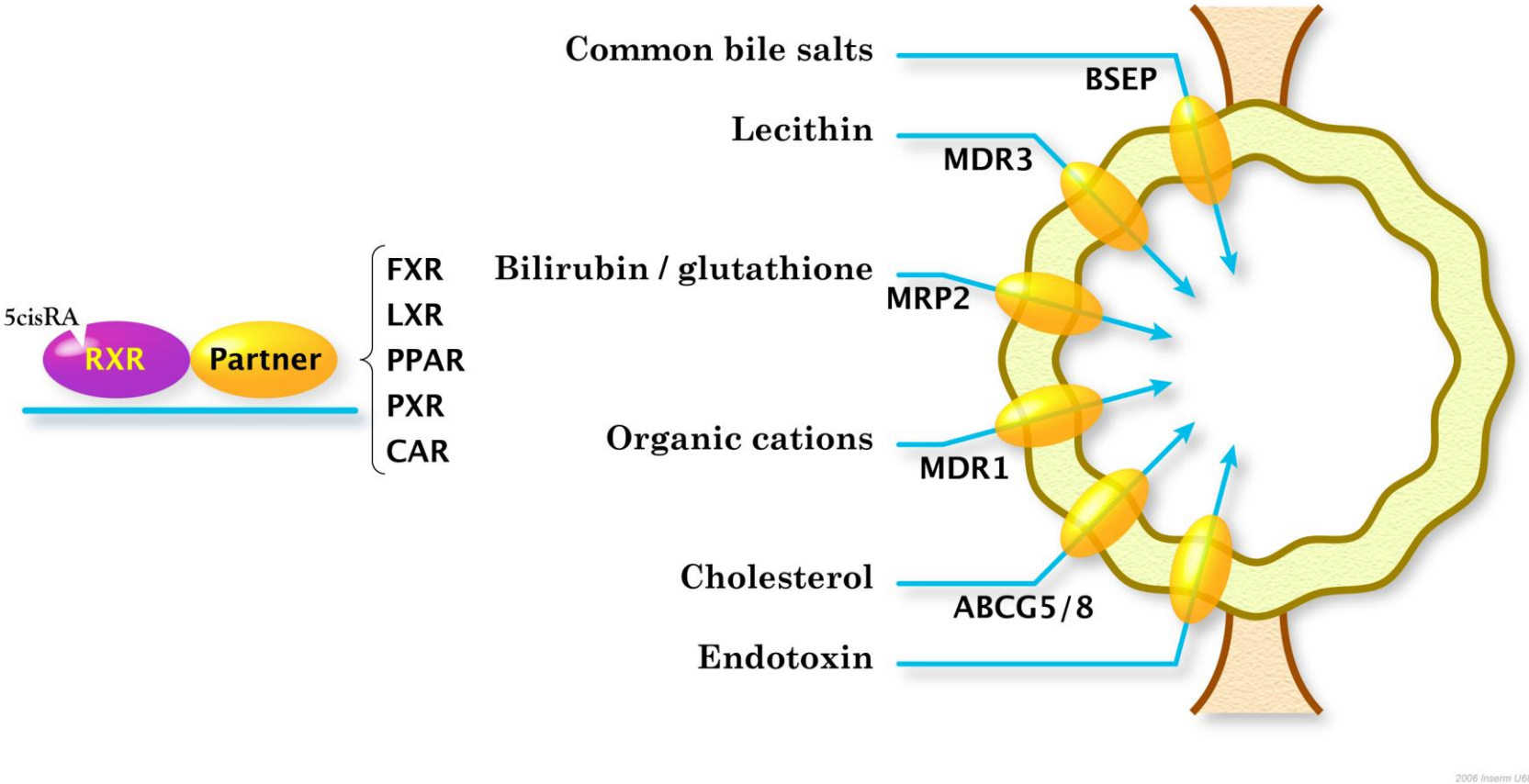
LPAC et Hépatolithiase

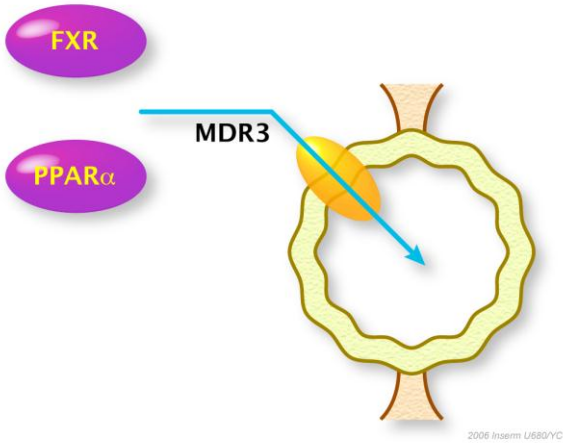
Paris, 10 Mai 2012

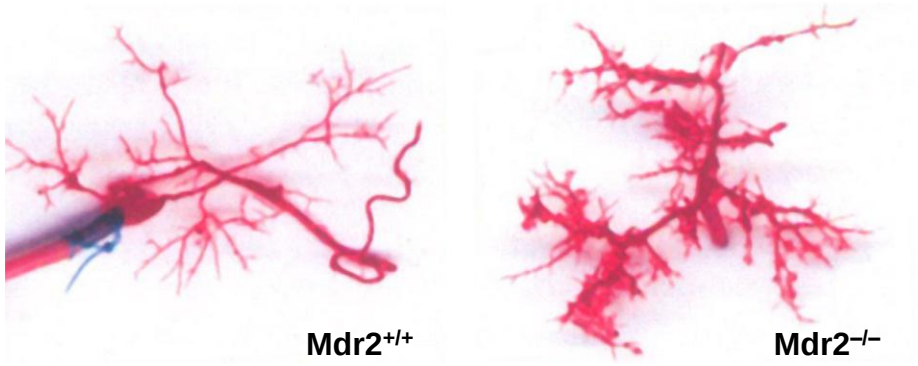
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS saint antoine UPMC PARIS UNIVERSITAS Faculté de médecine Pierre et Marie CURIE Circulation, metabolism, nutrition Inserm French Institute of Health and Medical Research


5cisRA
RXR
Partner
FXR
LXR
PPAR
PXR
CAR
Common bile salts
BSEP
Lecithin
MDR3
Bilirubin / glutathione
MRP2
Organic cations
MDR1
Cholesterol
ABCG5/8
Endotoxin
2006 Inserm U680/YC

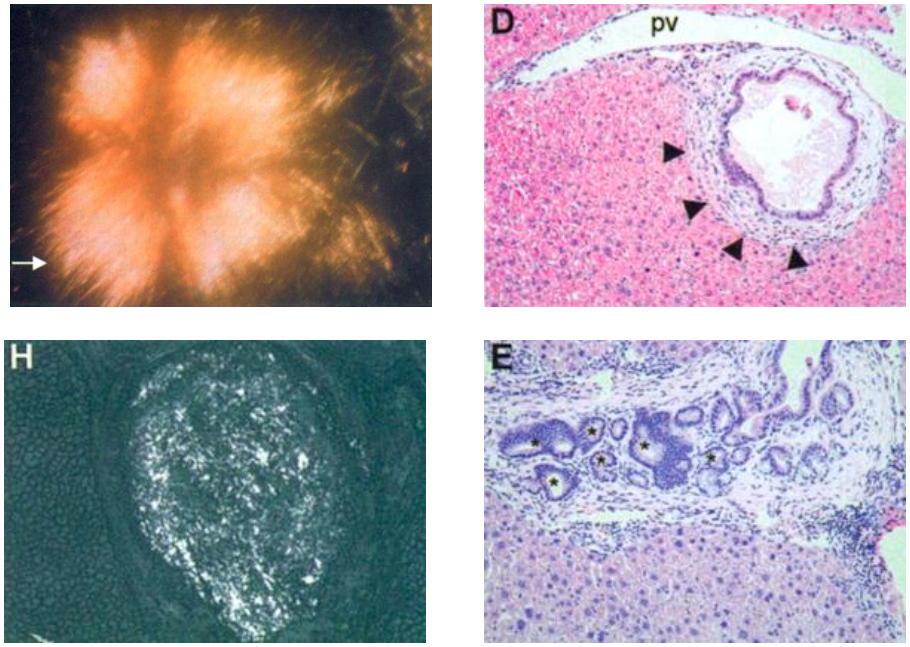
MDR3 : Historique

- **1988 : clonage et séquençage du gène**
- **1993 : premier modèle de souris ko (absence de phospholipides dans la bile + inflammation biliaire)**
- **1996 : absence d'expression hépatique de la protéine au cours de PFIC3**
- **2001 : les mutations hétérozygotes du gène sont associées au syndrôme LPAC et à la cholestase gravidique**
- **2004 : la souris mdr2 –/– développe une cholangite sclérosante et une lithiase biliaire intrahépatique**





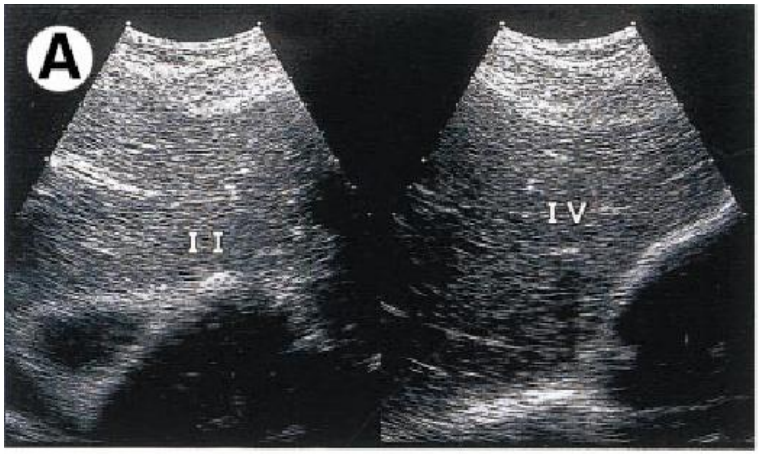
Fickert et al Gastroenterology 2002



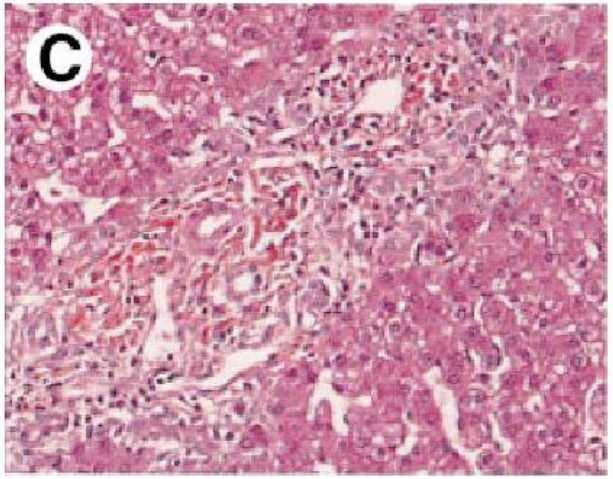
Lammert et al Hepatology 2004

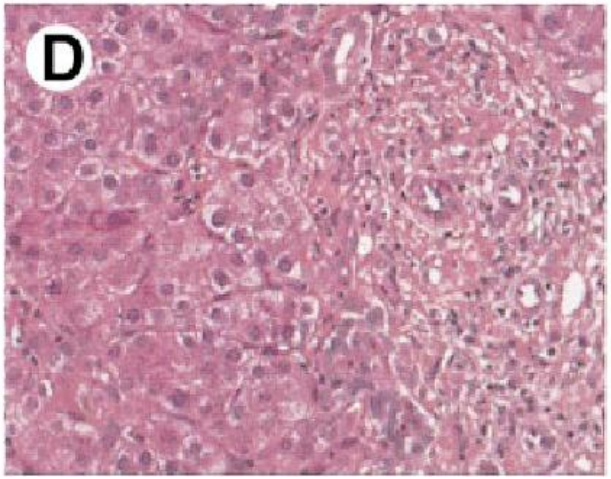
:s	Age	Sex	Age at diagnosis (*yr*)	Features at presentation	Familial history	Follow-up
	35	F	28	Cholestasis and biliary pain during pregnancy with stillborn fetus Cholecystectomy Recurrence after cholecystectomy	Parents (1a and 1b) free of symptom	Free of symptom and norm liver enzymes under UDC during a 2nd pregnancy
	41	F	25	Cholestasis and biliary pain during pregnancy; premature baby Cholecystectomy Recurrence after cholecystectomy	Husband (2a) free of symptom, son (case 3) cholesterol cholelithiasis	Cholestasis during the 2nc pregnancy Free of symptom and norm liver enzymes under UDC
	26	M	24	Cholestasis and biliary pain Cholecystectomy Recurrence after cholecystectomy	Brother (17 years old) (3a) free of symptom	Free of symptom and norm liver enzymes under UDC
	34	F	22	Cholestasis and biliary pain after starting oral contraception and during pregnancy; premature baby Cholecystectomy Recurrence after cholecystectomy	Father gallbladder gallstones at the age of 30	Cholestasis after starting progesterone treatment view to in vitro fertilizatic Free of symptom and norm liver enzymes under UDC
	55	F	15	Cholestasis and biliary pain Cholecystectomy Recurrence after cholecystectomy	Mother gallbladder gallstones at the age of 27, son and daughter (29 years old) free of symptom (5a 5b)	Cholestasis and biliary pai Free of symptom and norm liver enzymes under UDC
	60	M	55	Cholestasis and biliary pain Cholecystectomy Recurrence after cholecystectomy	Two daughters (28 and 33 years old) without experience of pregnancy and free of symptom	Free of symptom and norm liver enzymes under UDC

ursodeoxycholic acid treatment


A
II
IV


B


C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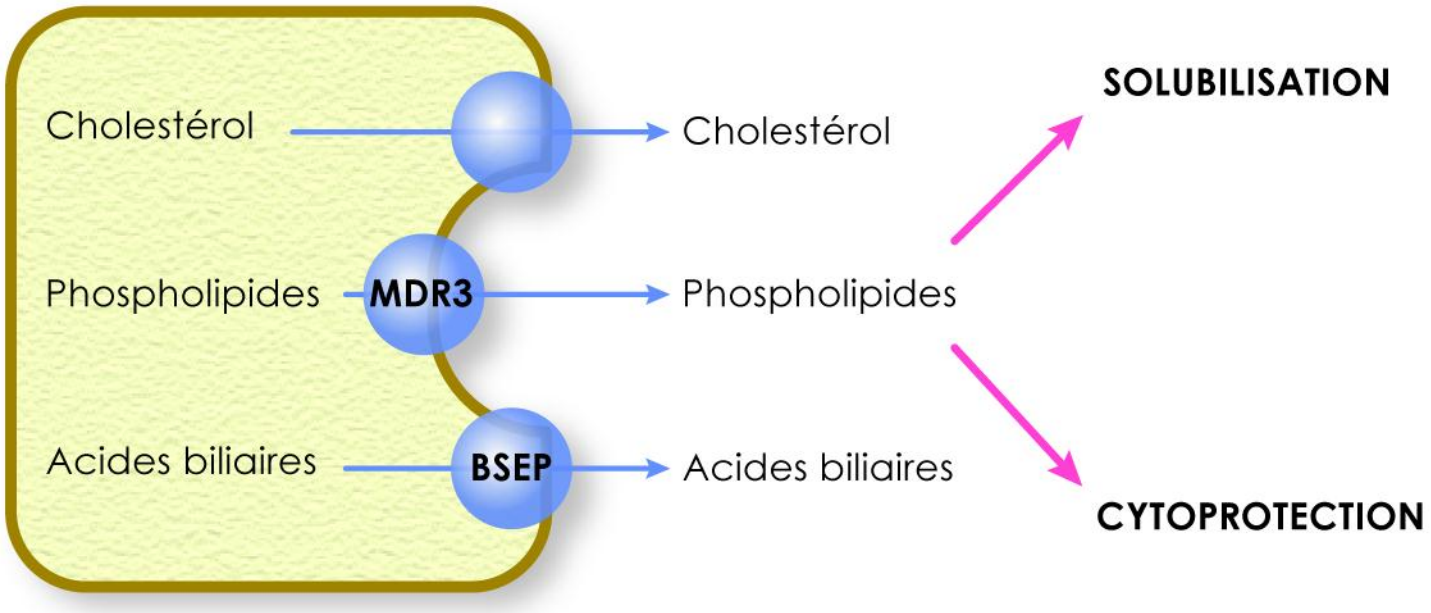
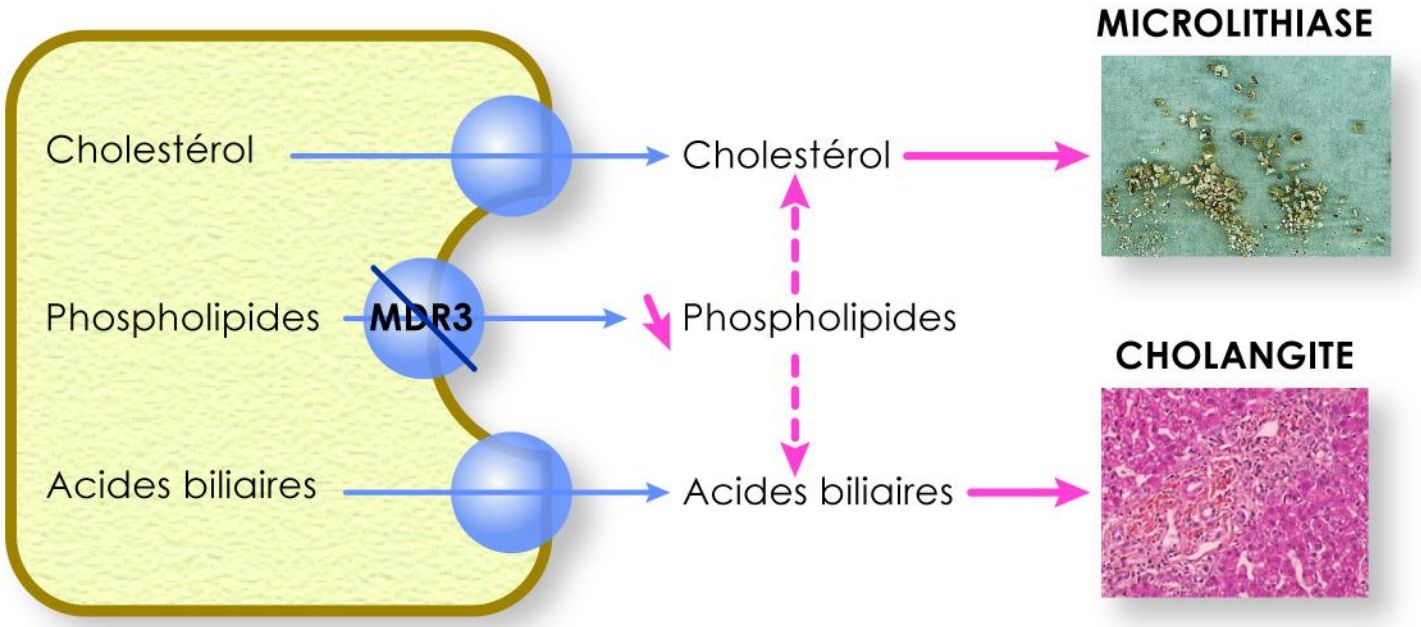
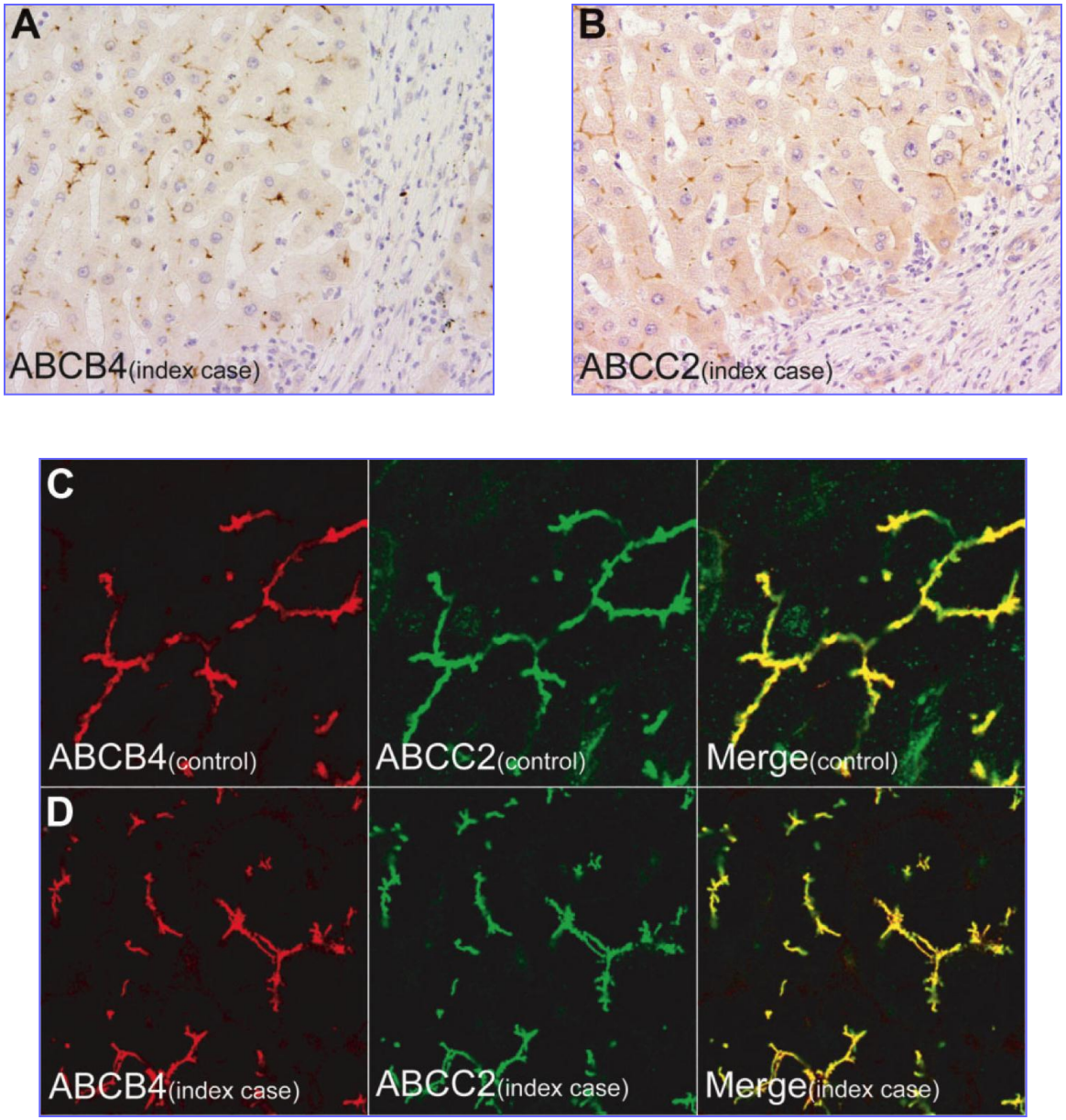
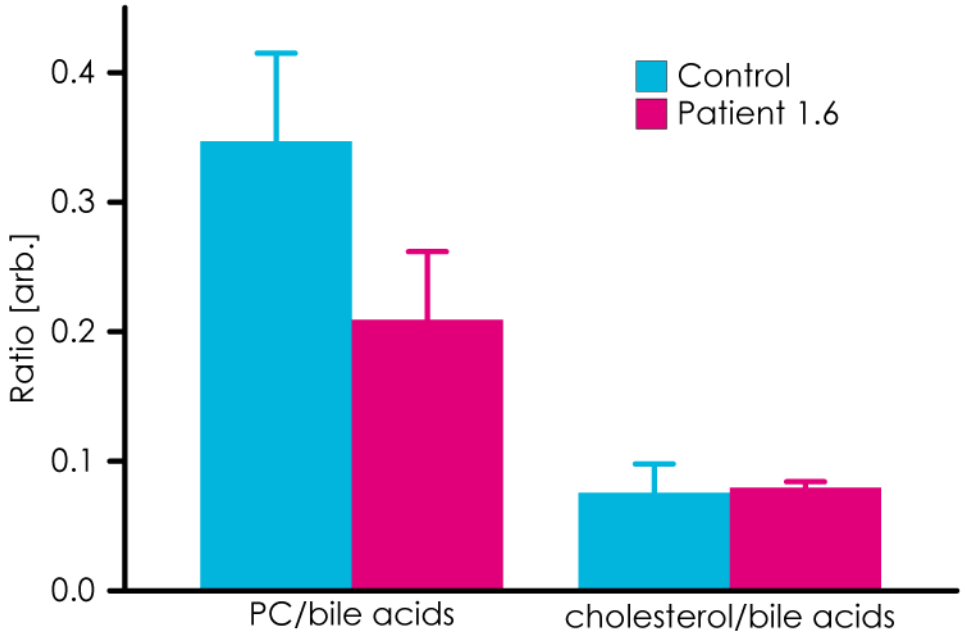




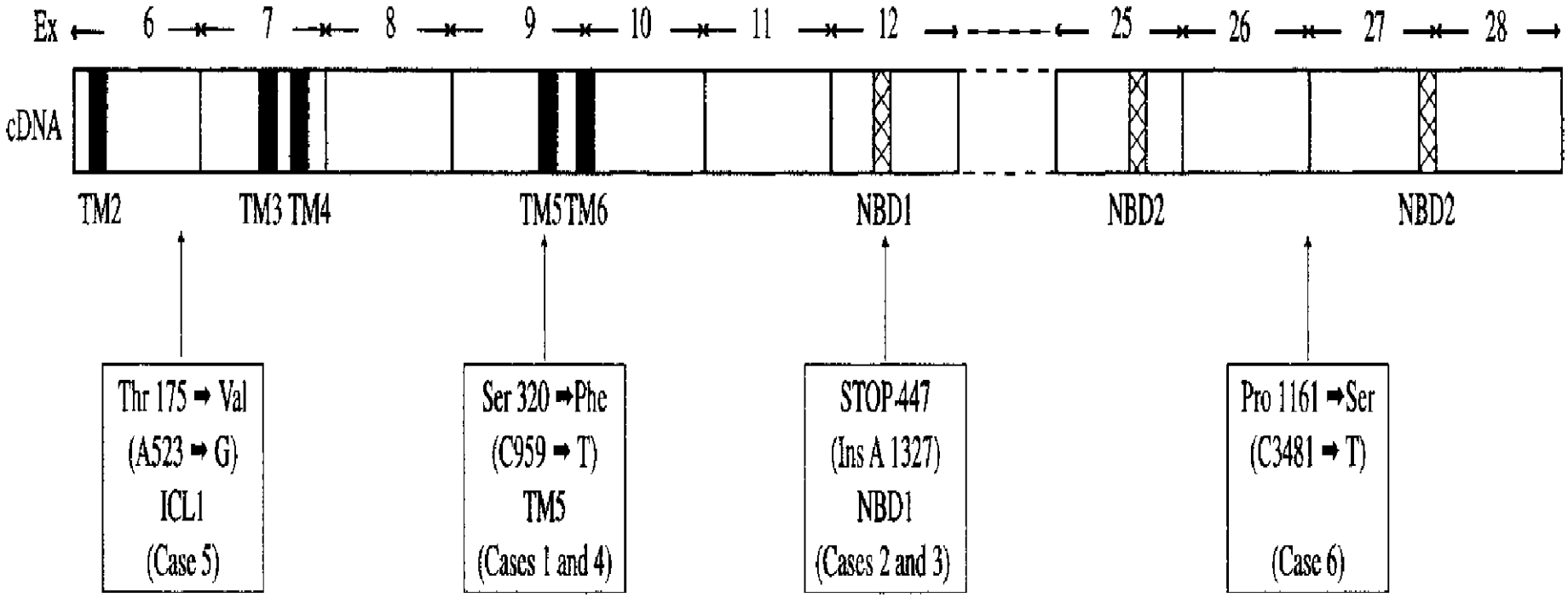


Gotthard et al. Hepatology 2008



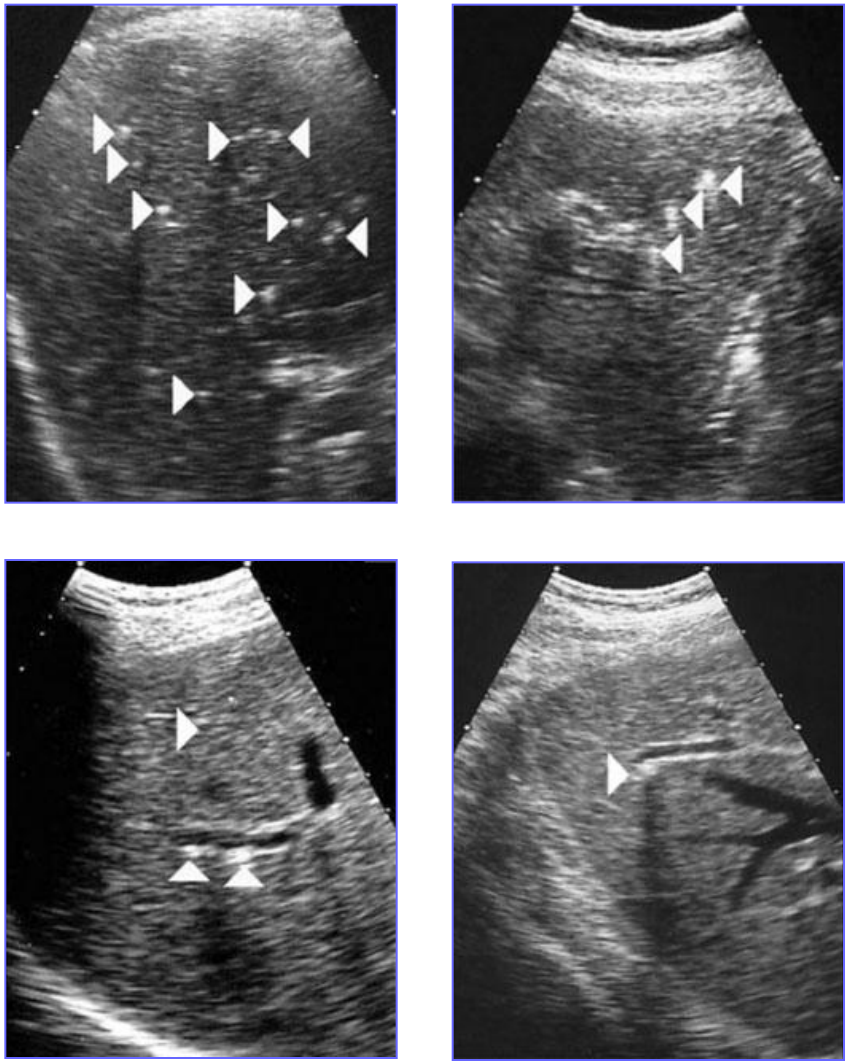
PC and Cholesterol content relative to bile acids

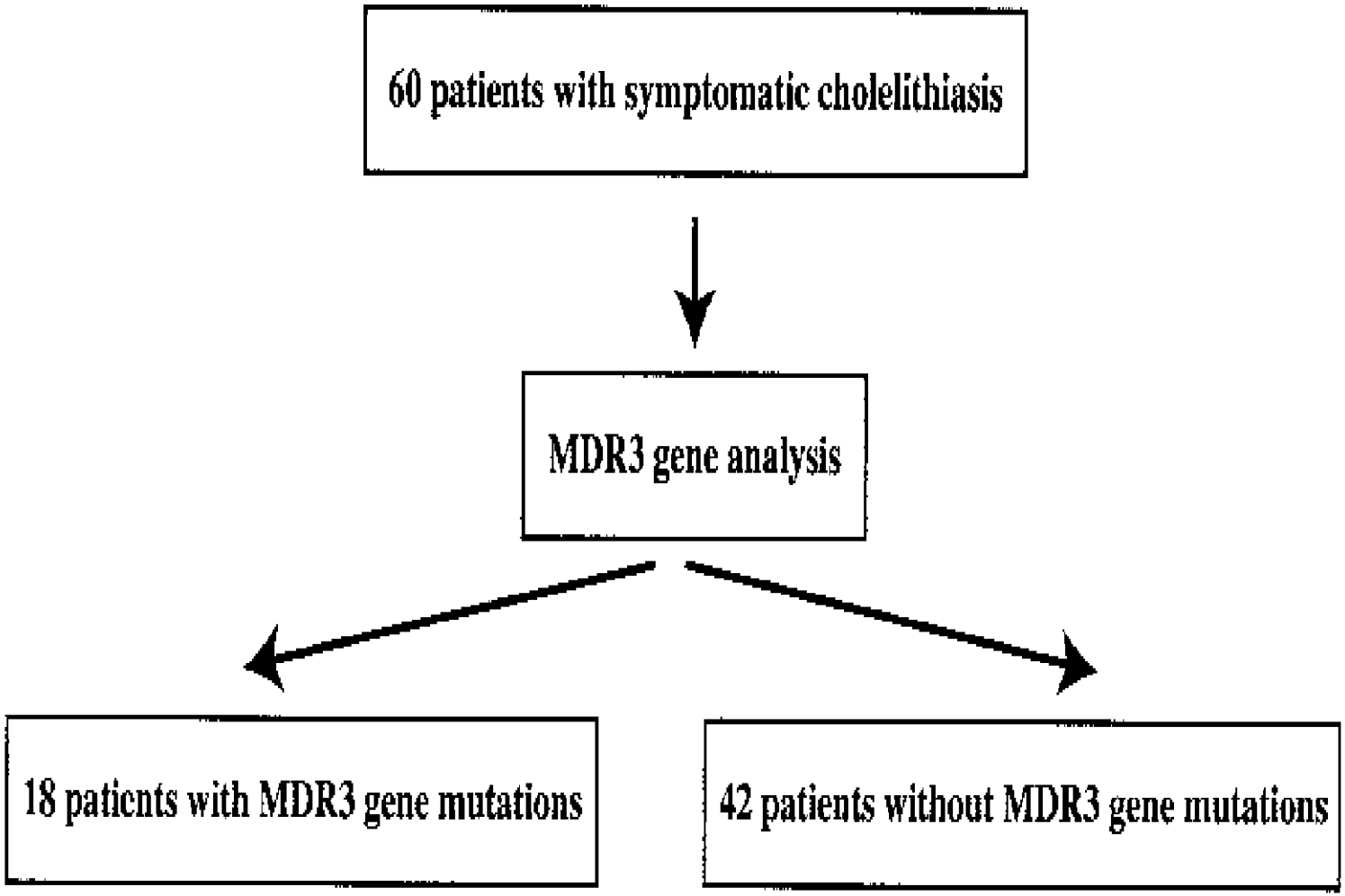
Nature et localisations des mutations identifiées



Description du syndrome LPAC
(*Low Phospholipid Associated Cholelithiasis*)

- Symptômes biliaires avant 40 ans.
- Au moins un épisode de colique hépatique ou d'angiocholite ou de pancréatite aiguë.
- Cholestase chronique modérée.
- Récidive des symptômes après cholécystectomie.
- Matériel échogène dans les voies biliaires intrahépatiques.
- Apparition des symptômes au décours d'une grossesse.
- Efficacité de l'AUDC sur les symptômes et leur récidive.

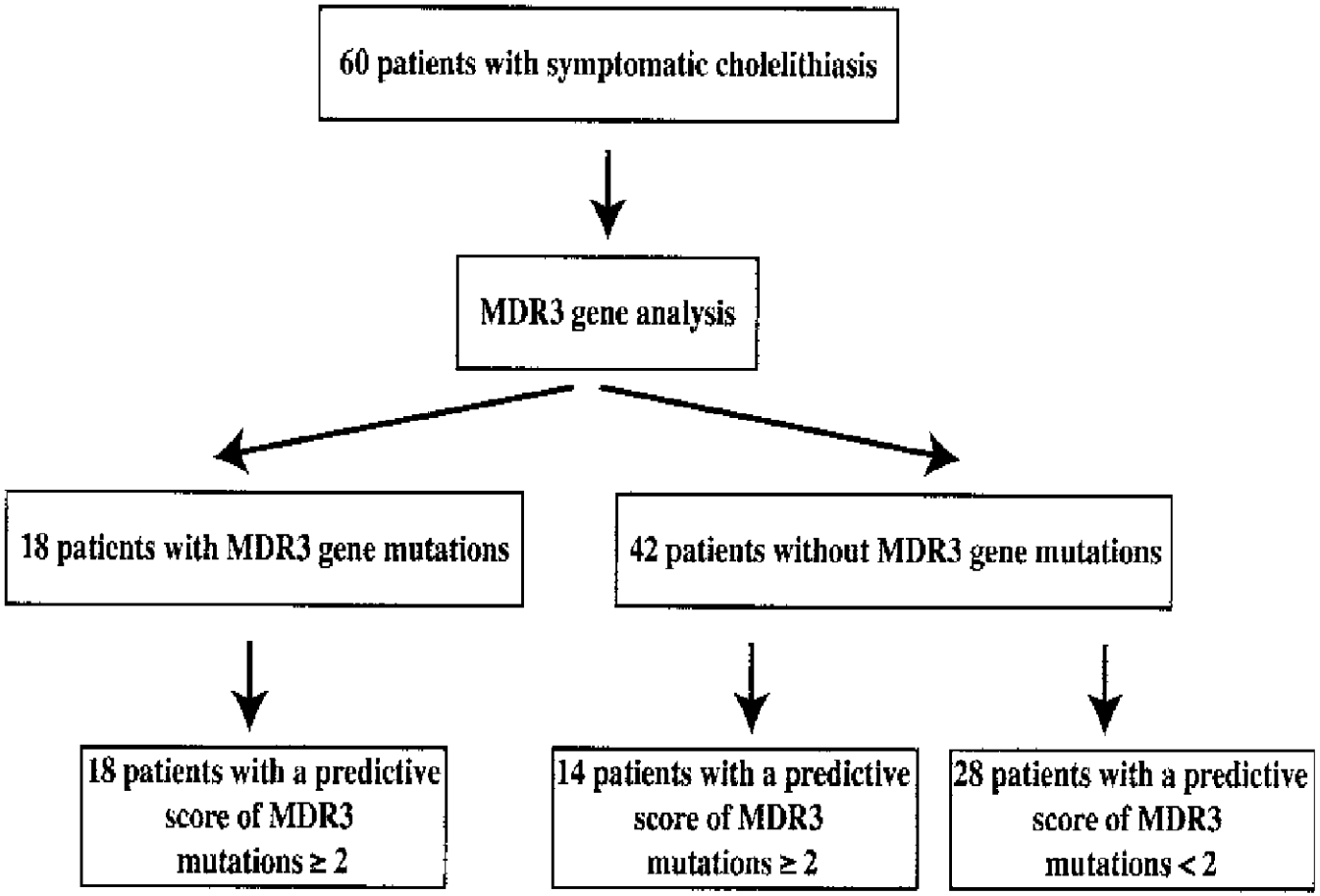


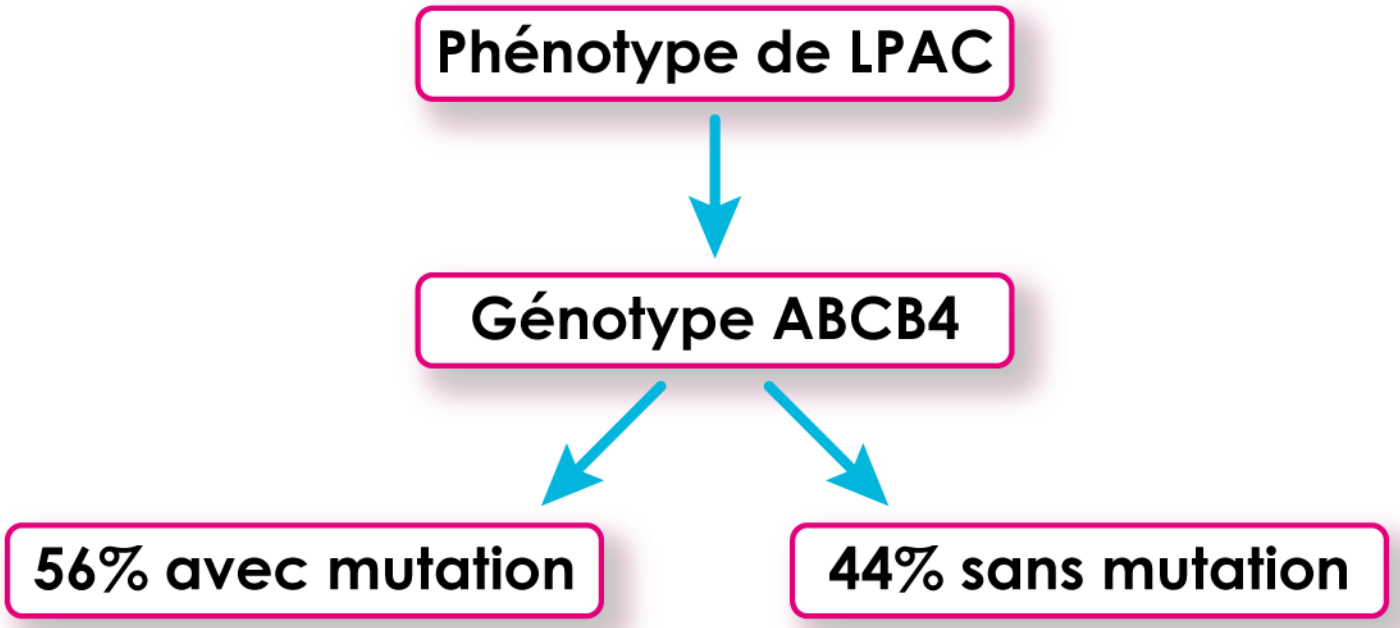

60 patients with symptomatic cholelithiasis
MDR3 gene analysis
18 patients with MDR3 gene mutations
42 patients without MDR3 gene mutations

Odds Ratios for the presence of ABCB4 gene mutations in patient with LPAC

Clinical criterion	OR	p
Familial history of cholelithiasis	5,4	0,01
Increased serum GGT activity	1,1	1
History of ICP	4,9	0,02
Intrahepatic hyperechoic material	12,4	0,0005
Recurrence after cholecystectomy	18,9	< 0,0001
Age < 40 at the onset of symptoms	7,8	0,008
Gender (M *vs* F)	0,8	1

Gastroenterology, 2003


60 patients with symptomatic cholelithiasis
MDR3 gene analysis
18 patients with MDR3 gene mutations
42 patients without MDR3 gene mutations
18 patients with a predictive score of MDR3 mutations ≥ 2
14 patients with a predictive score of MDR3 mutations ≥ 2
28 patients with a predictive score of MDR3 mutations < 2

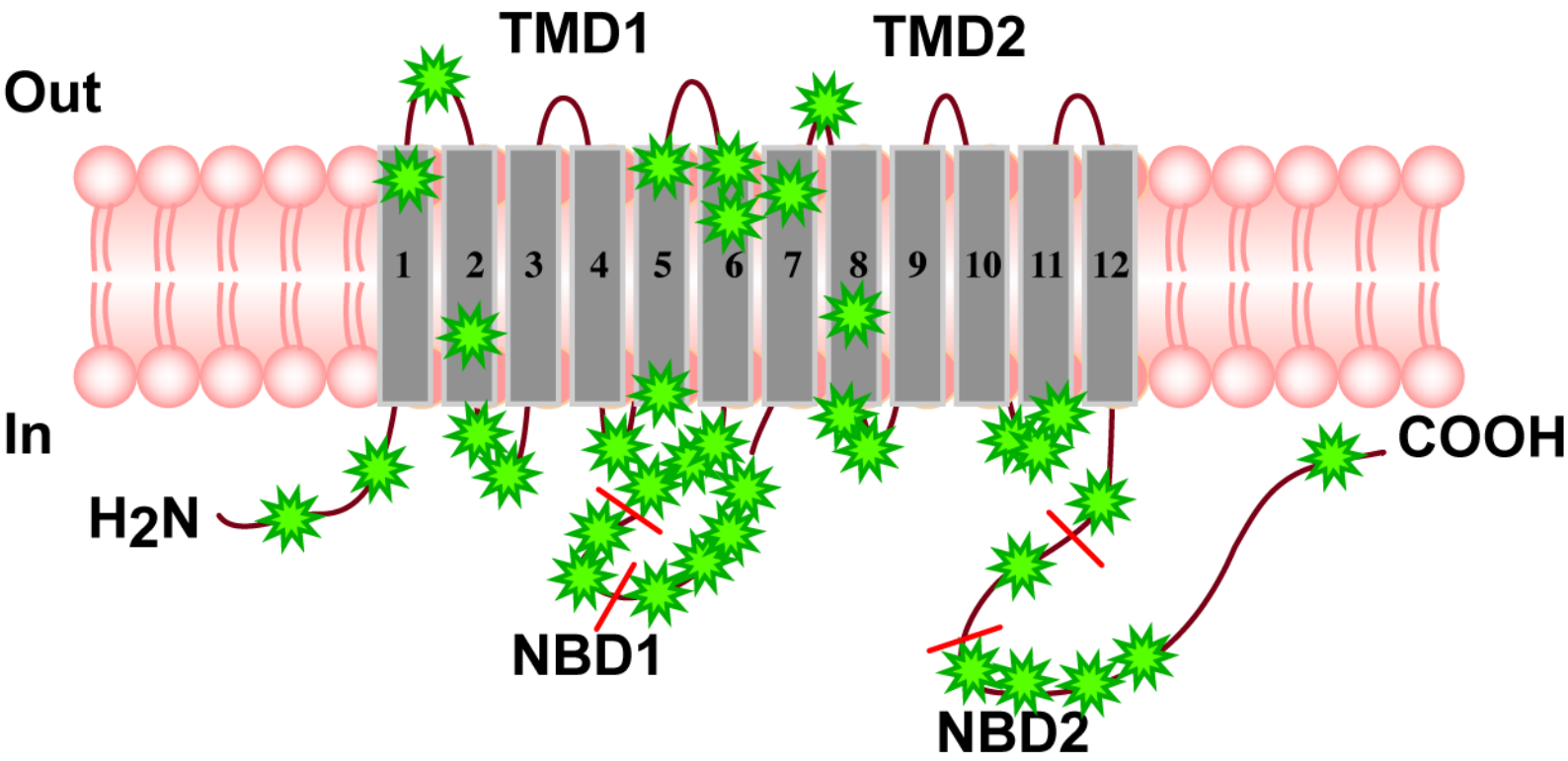


Rosmorduc et al. Gastroenterology, 2003

Caractéristiques cliniques des 156 patients avec le syndrome LPAC

	avec mutation n = 79	sans mutation n = 77	
Type de mutation	Non sens 25 % Faux sens 75 %	—	
Age de survenue des symtômes (ans)	32 ± 12	32 ± 11	(ns)
Sex ratio (% femmes)	70 %	63 %	(ns)
Complications biliaires :	57 %	64 %	
- aiguës	39 %	51 %	(ns)
- chroniques	18 %	13 %	
Grossesses (n)	44	19	
- Cholestase gravidique	52 %	42 %	(ns)
- Complication fœtal	14 %	21 %	

Localisation des mutations du gène ABCB4

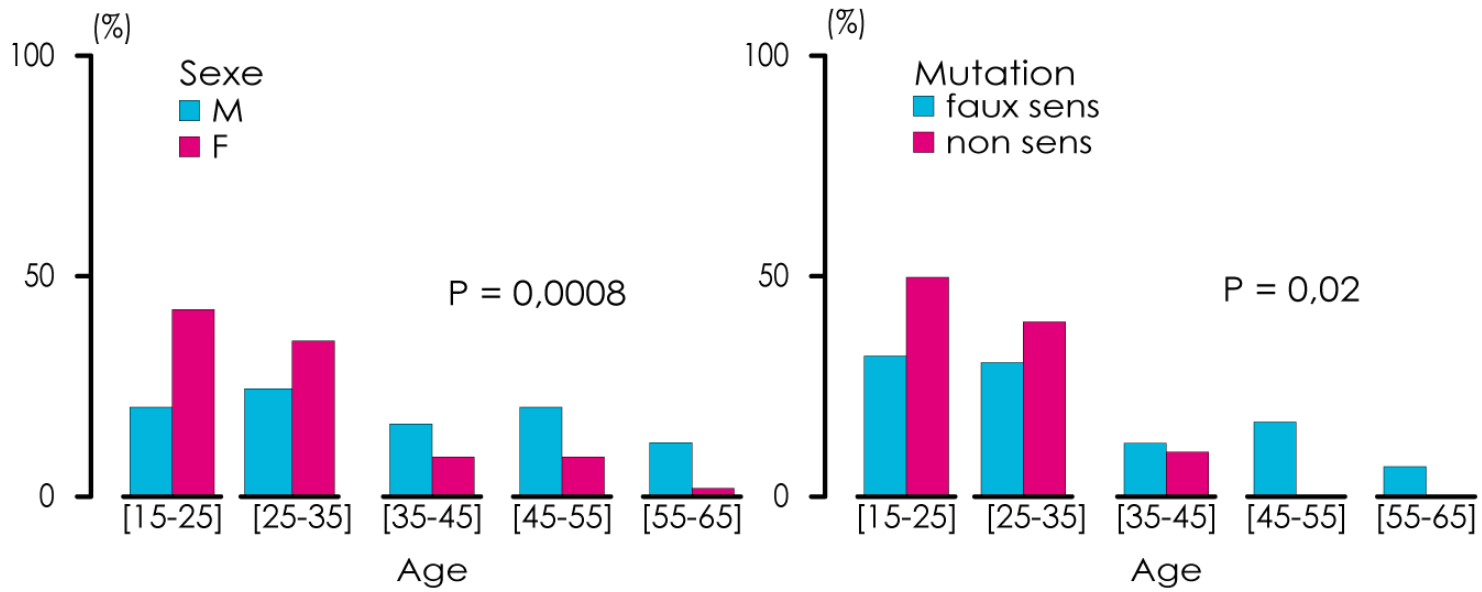


Localisation des mutations du gène ABCB4

Hétérozygotes	**73**
Hétérozygotes composites	2
Homozygotes	4
– Faux sens	4
– Non sens	0

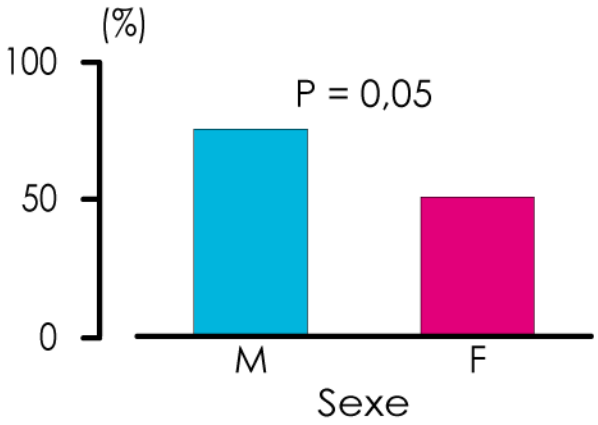
Mutation non sens	**25,0 %**
N terminal	3,5 %
1ère boucle IC	8,3 %
2ème boucle IC	1,2 %
3ème boucle IC	**28,0 %**
4ème boucle IC	3,5 %
5ème boucle IC	4,8 %
TM 1, 2, 5, 7, 8	15,5 %
1ère boucle EC	3,5 %
4ème boucle EC	1,2 %
6ème boucle EC	1,2 %

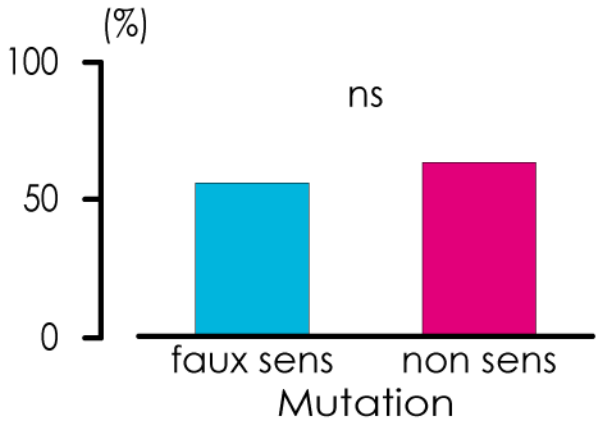
Age de survenue des douleurs biliaires en fonction du type de mutation et du sexe

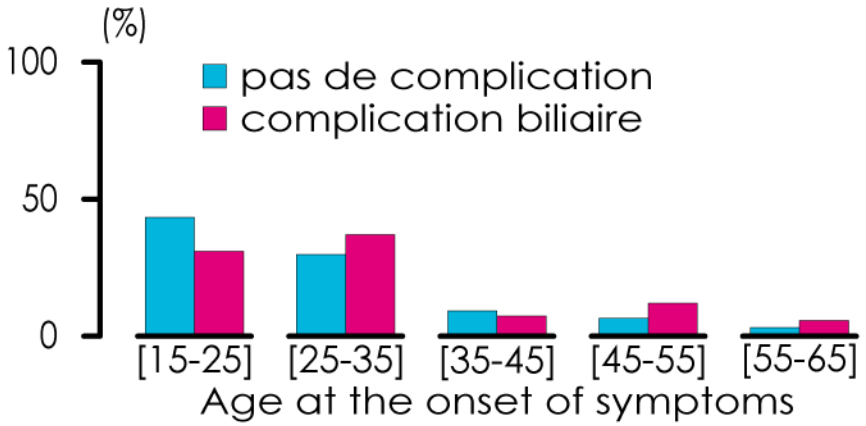


	Age moyen aux symptômes	
Homme et mutation faux sens	40 ± 13 ans	
Homme et mutation non sens	30 ± 13 ans	P = 0,001
Femme et mutation faux sens	31 ± 12 ans	
Femme et mutation non sens	26 ± 6 ans	

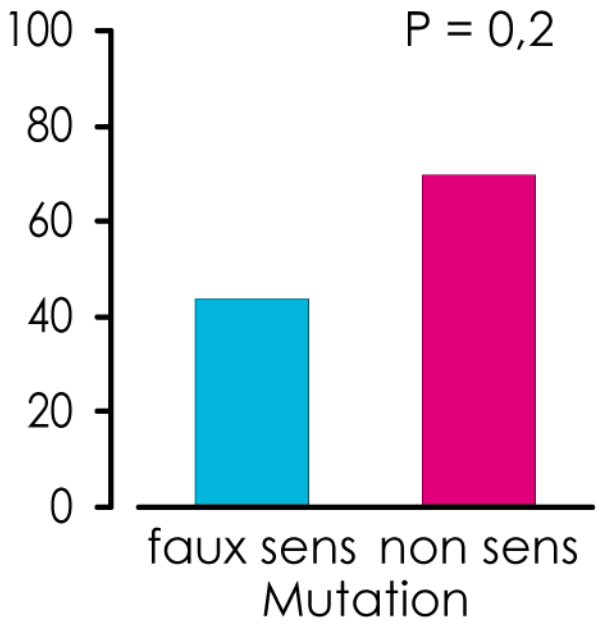
Complications biliaires en fonction du sexe, du type de mutation et de l'âge de survenue des symptômes



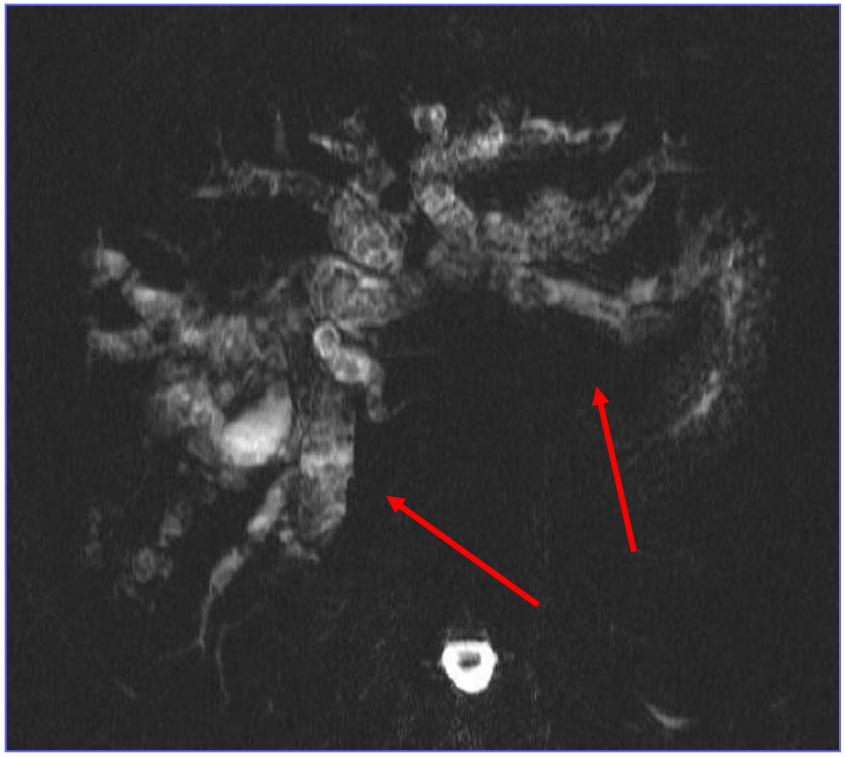




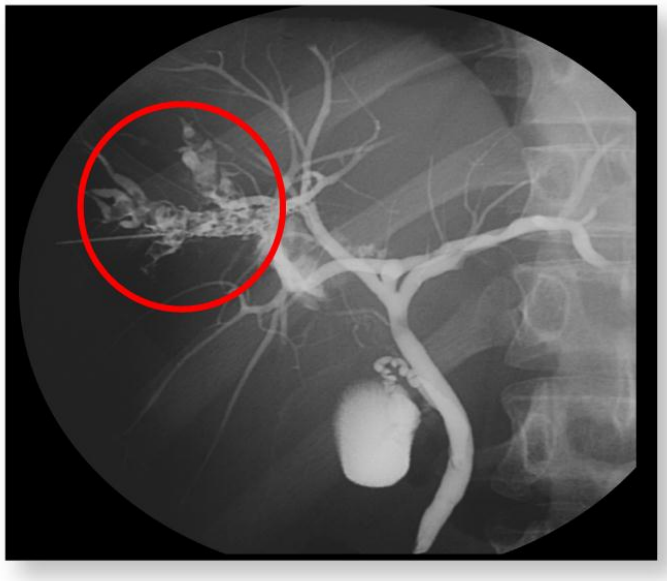
Survenue d'une cholestase gravidique en fonction du type de mutation

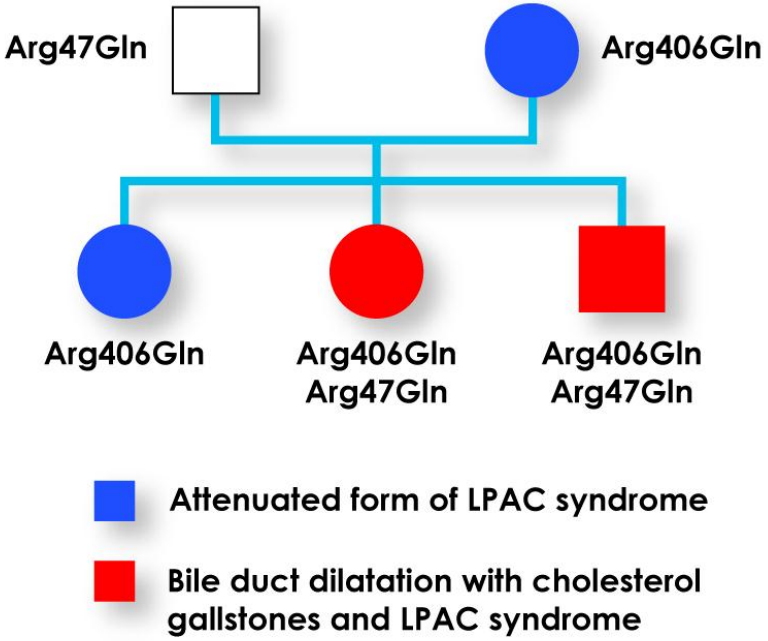


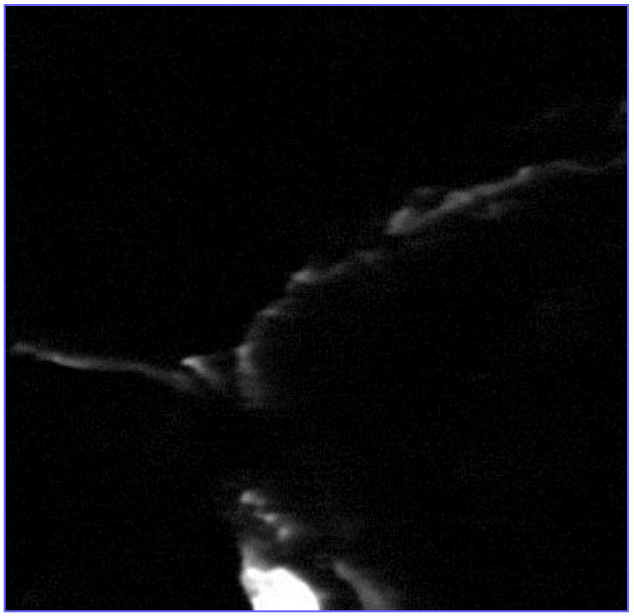
Dilatation non kystique des voies biliaires au cours du syndrome LPAC

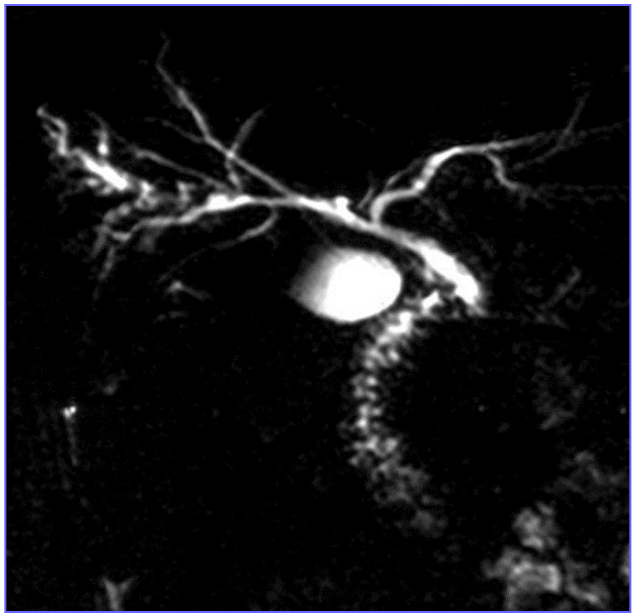


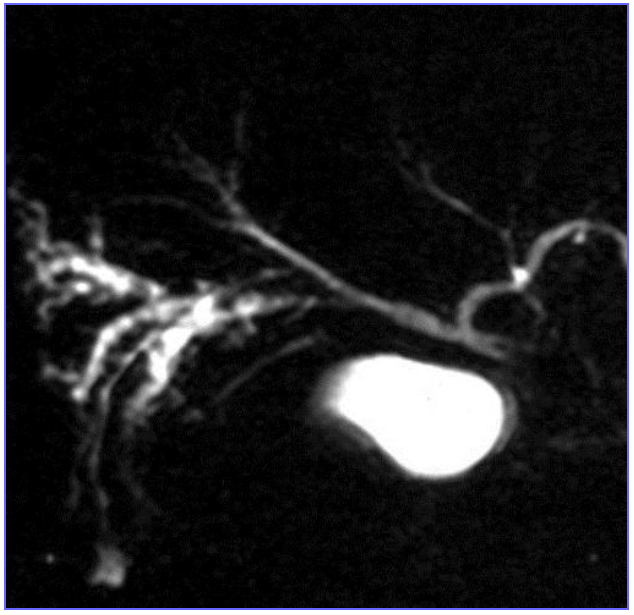
Dilatation non kystique segmentaire au cours du syndrome LPAC

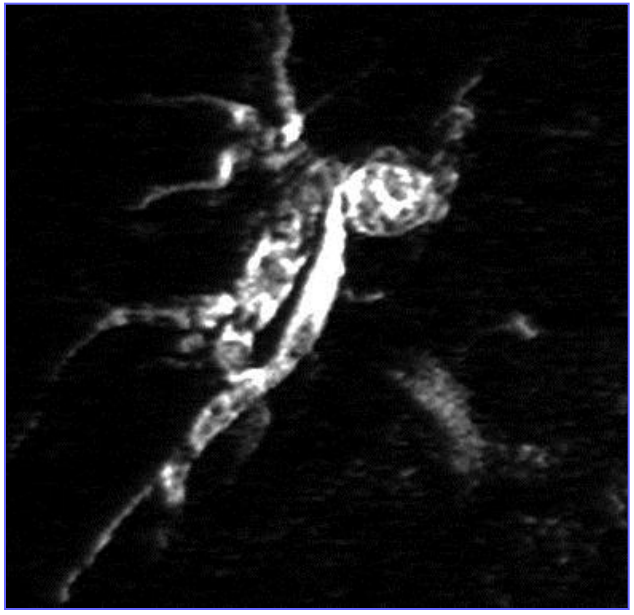


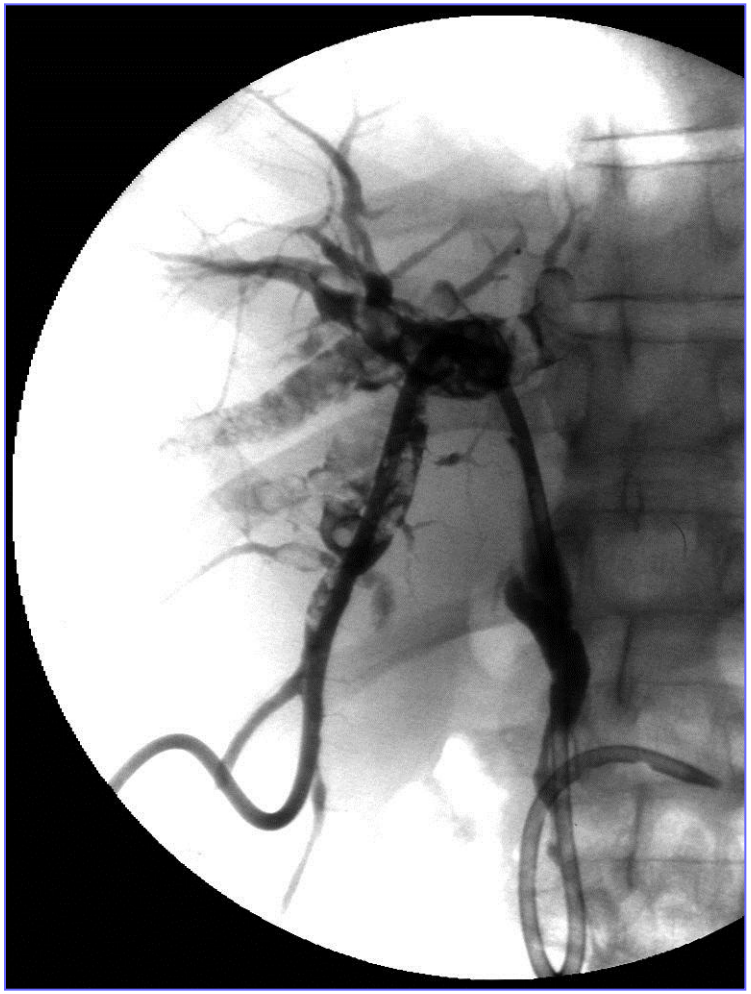


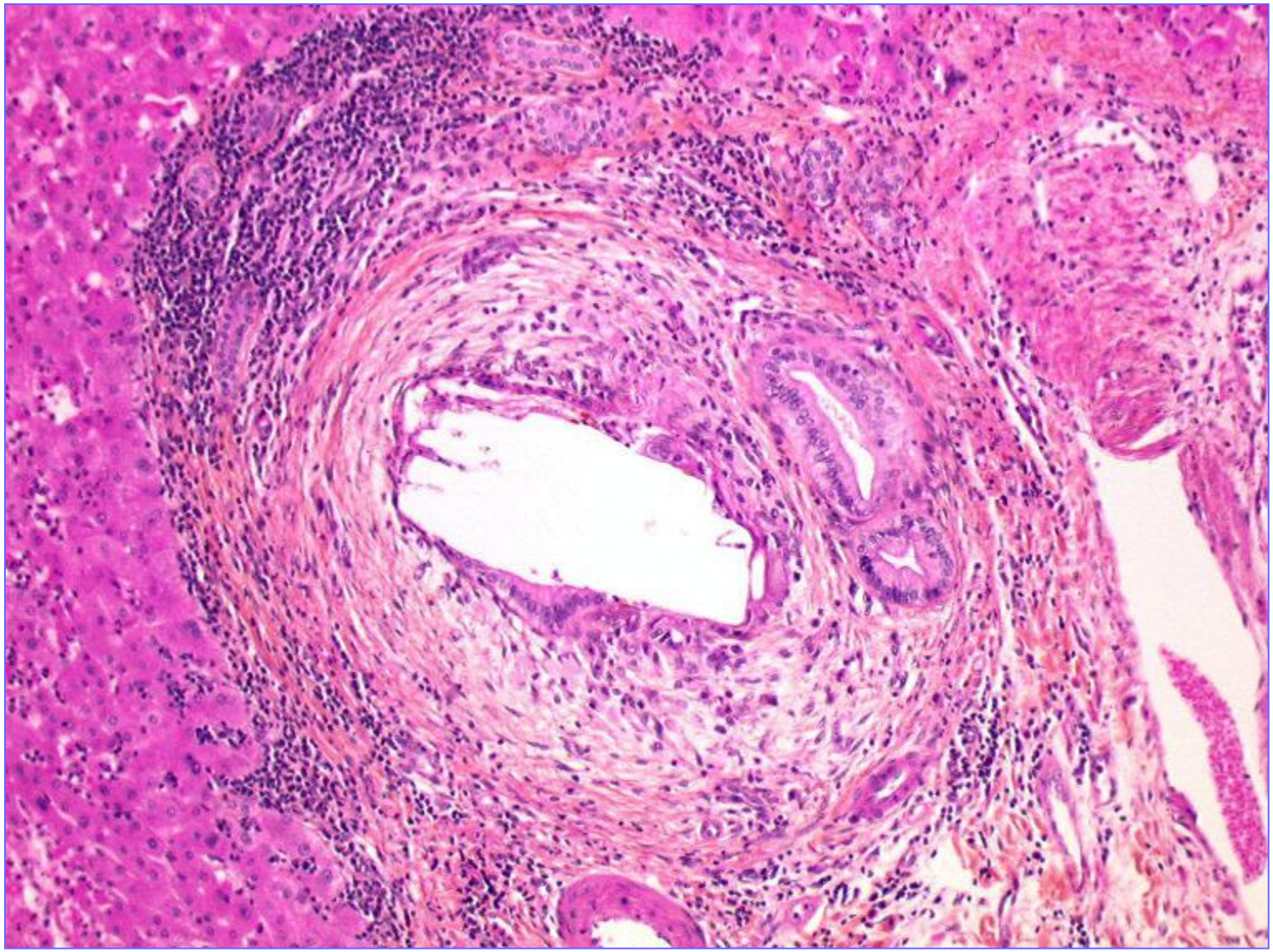


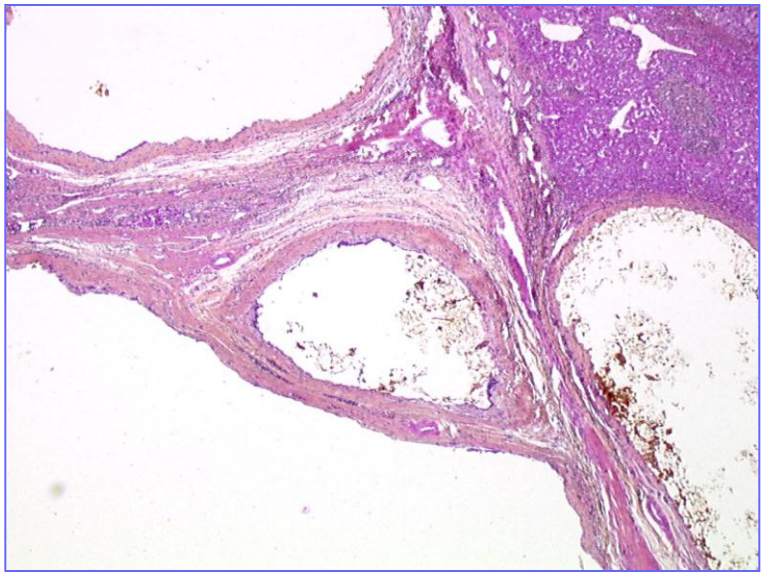


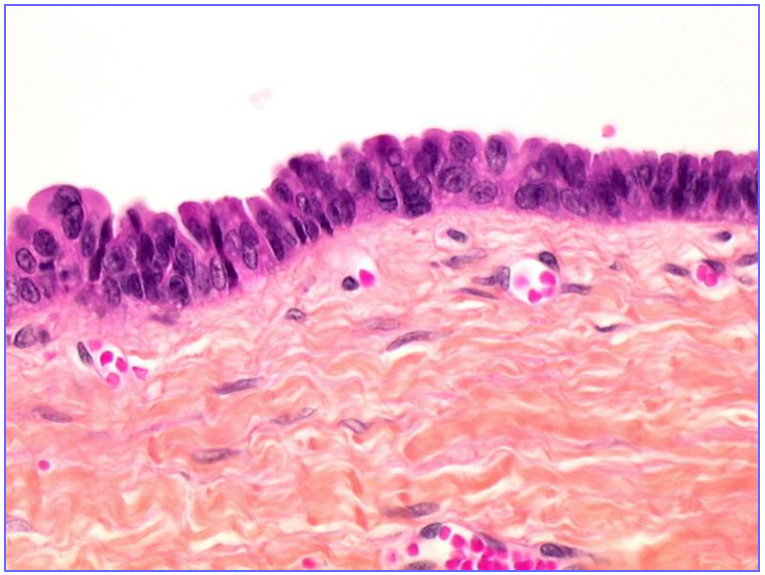


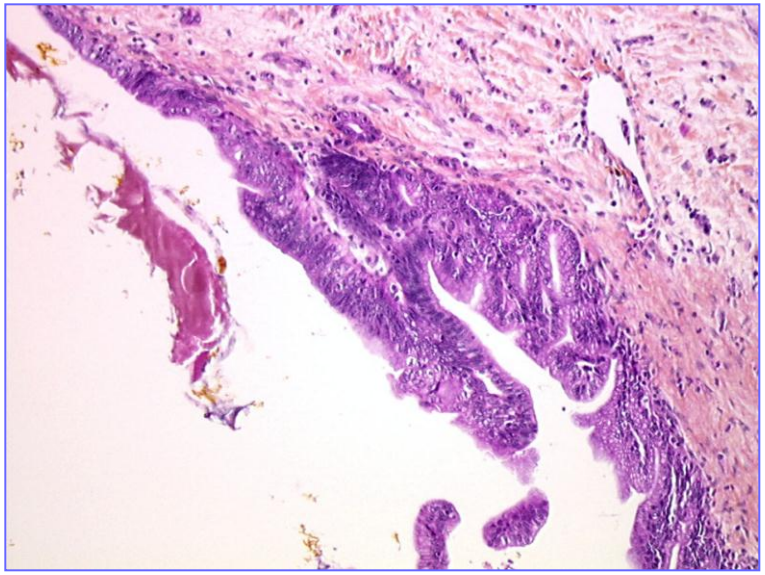


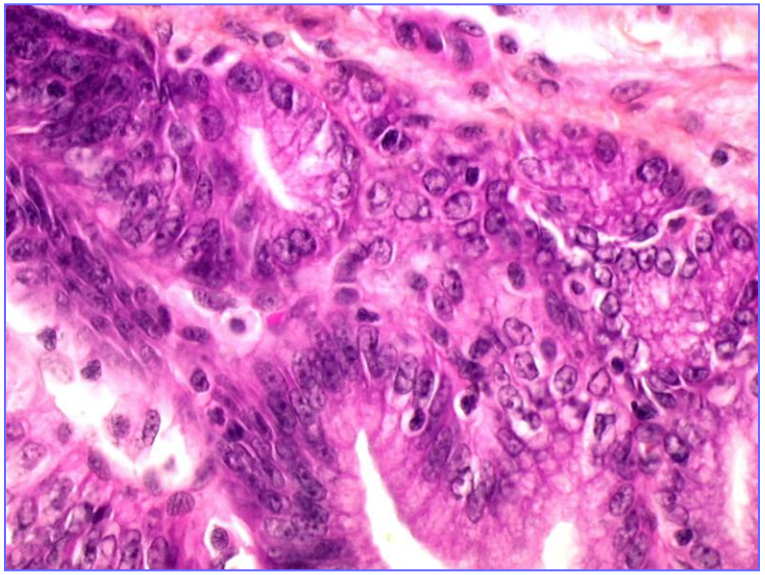


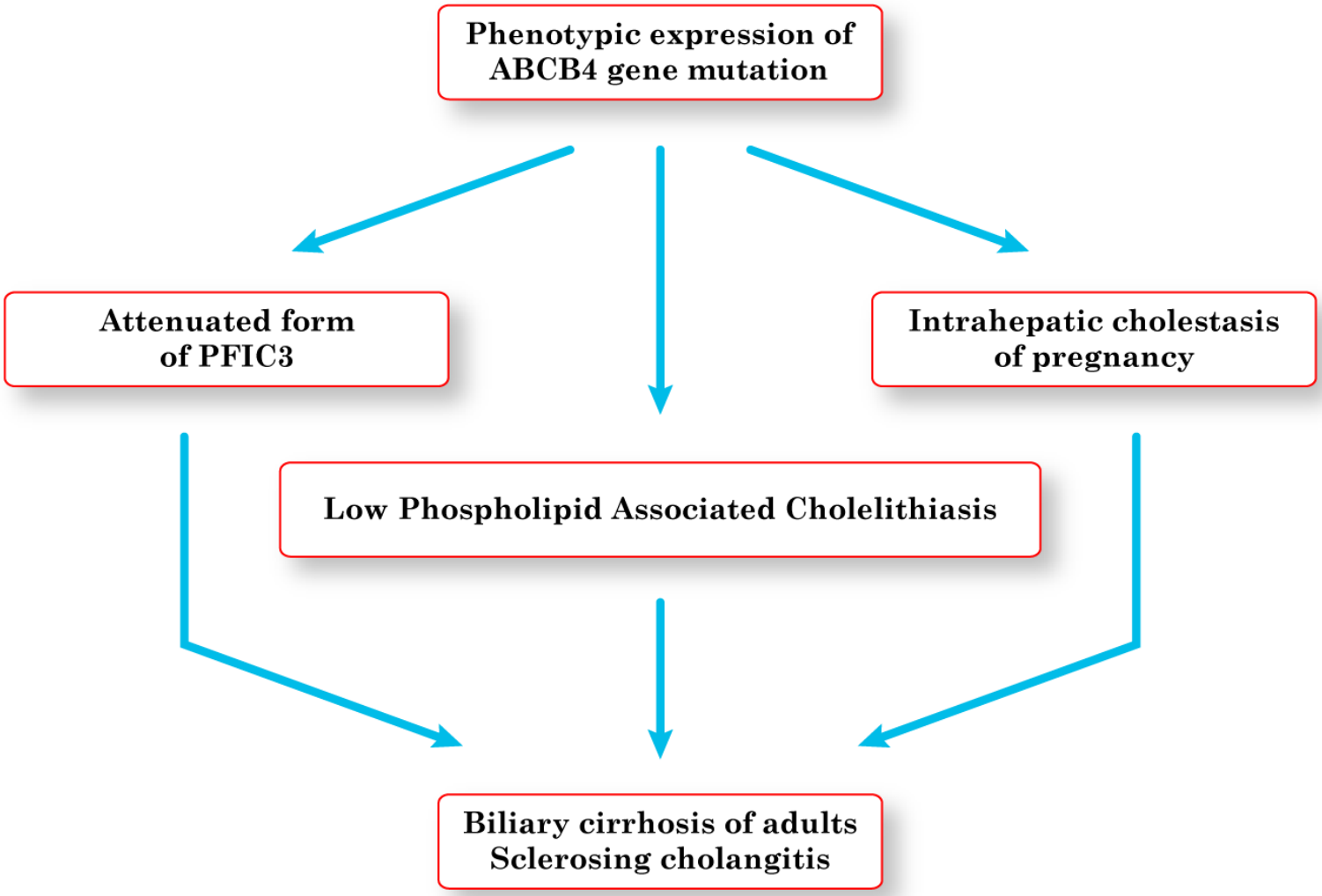






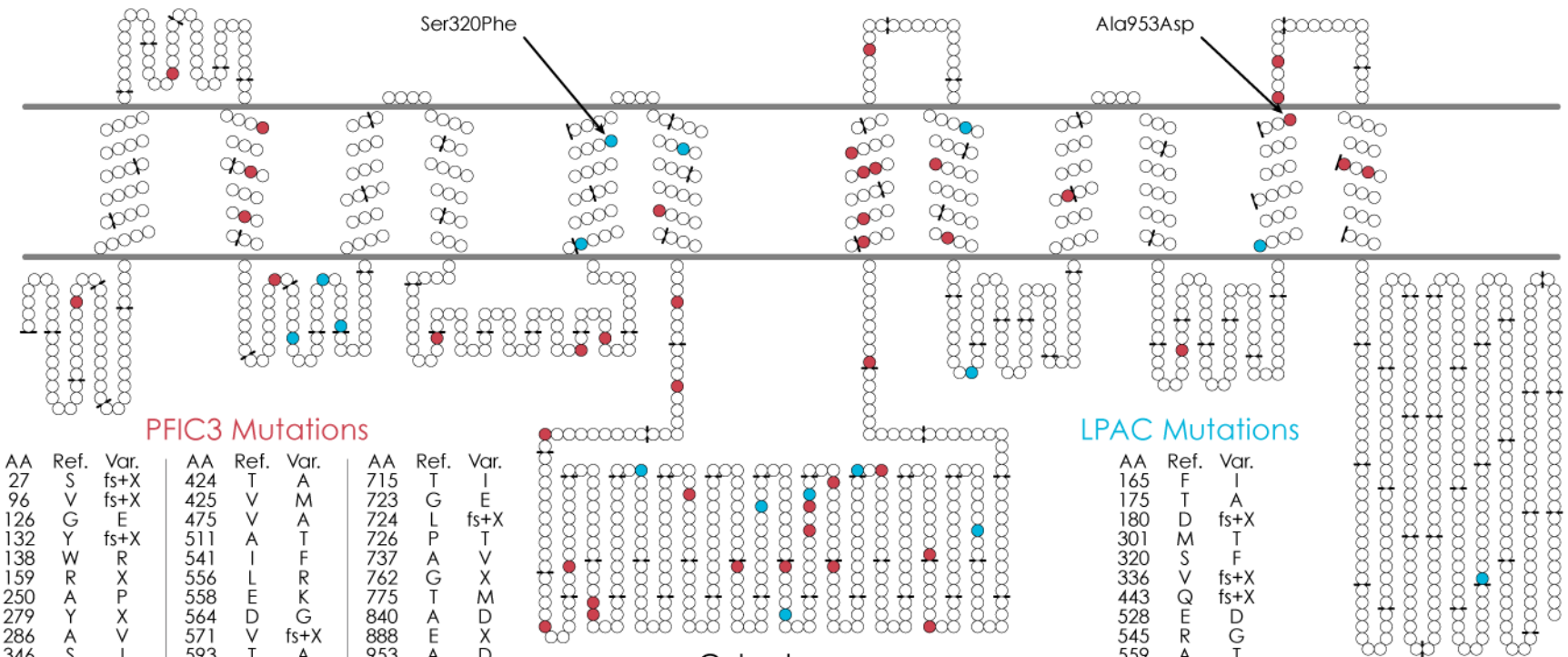





Phenotypic expression of ABCB4 gene mutation
Attenuated form of PFIC3
Intrahepatic cholestasis of pregnancy
Low Phospholipid Associated Cholelithiasis
Biliary cirrhosis of adults Sclerosing cholangitis

Overlapping features of Progressive Familial Intrahepatic Cholestasis 3 and Low Phospholipid-Associated Cholelithiasis in two adult siblings with *ABCB4* heterozygous compound status.

Patrick Chamouard, Véronique Barbu, Dominique Wendum, Chantal Housset, Olivier Rosmorduc, Raoul Poupon



PFIC3 Mutations

AA	Ref.	Var.
27	S	fs+X
96	V	fs+X
126	G	E
132	Y	fs+X
138	W	R
159	R	X
250	A	P
279	Y	X
286	A	V
346	S	I
357	F	L
364	A	V
379	S	fs+X
395	E	G
403	Y	H

AA	Ref.	Var.
424	T	A
425	V	M
475	V	A
511	A	T
541	I	F
556	L	R
558	E	K
564	D	G
571	V	fs+X
593	T	A
630	M	V
636	Q	X
701	L	P
711	F	S

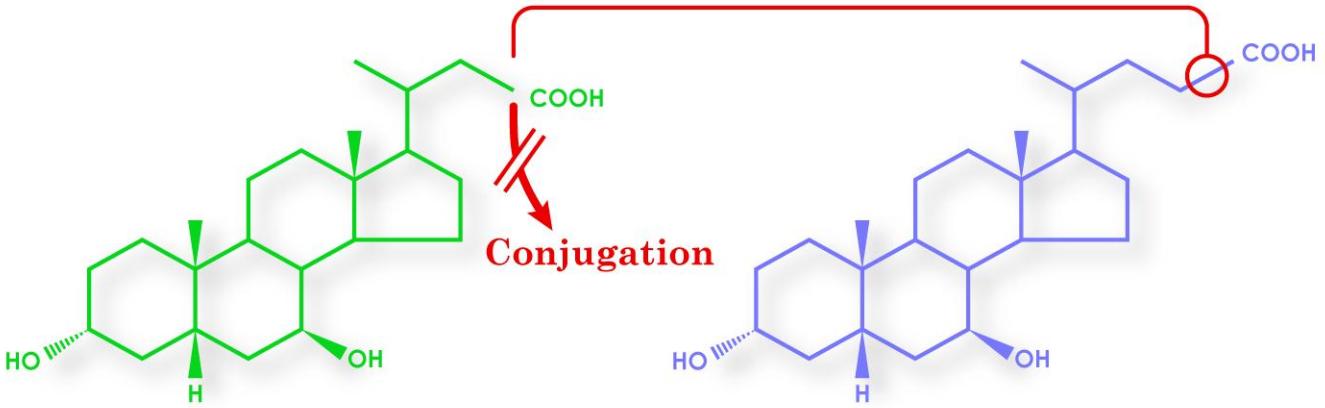
AA	Ref.	Var.
715	T	I
723	G	E
724	L	fs+X
726	P	T
737	A	V
762	G	X
775	T	M
840	A	D
888	E	X
953	A	D
954	G	S
957	R	X
981	V	fs+X
983	G	S

LPAC Mutations

AA	Ref.	Var.
165	F	I
175	T	A
180	D	fs+X
301	M	T
320	S	F
336	V	fs+X
443	Q	fs+X
528	E	D
545	R	G
559	A	T
591	L	Q
658	W	X
756	L	fs+X
788	R	E
934	A	T
1161	P	S

Nor-ursodeoxycholic acid (norUDCA)

- **Side chain-shortened homologue of UDCA**

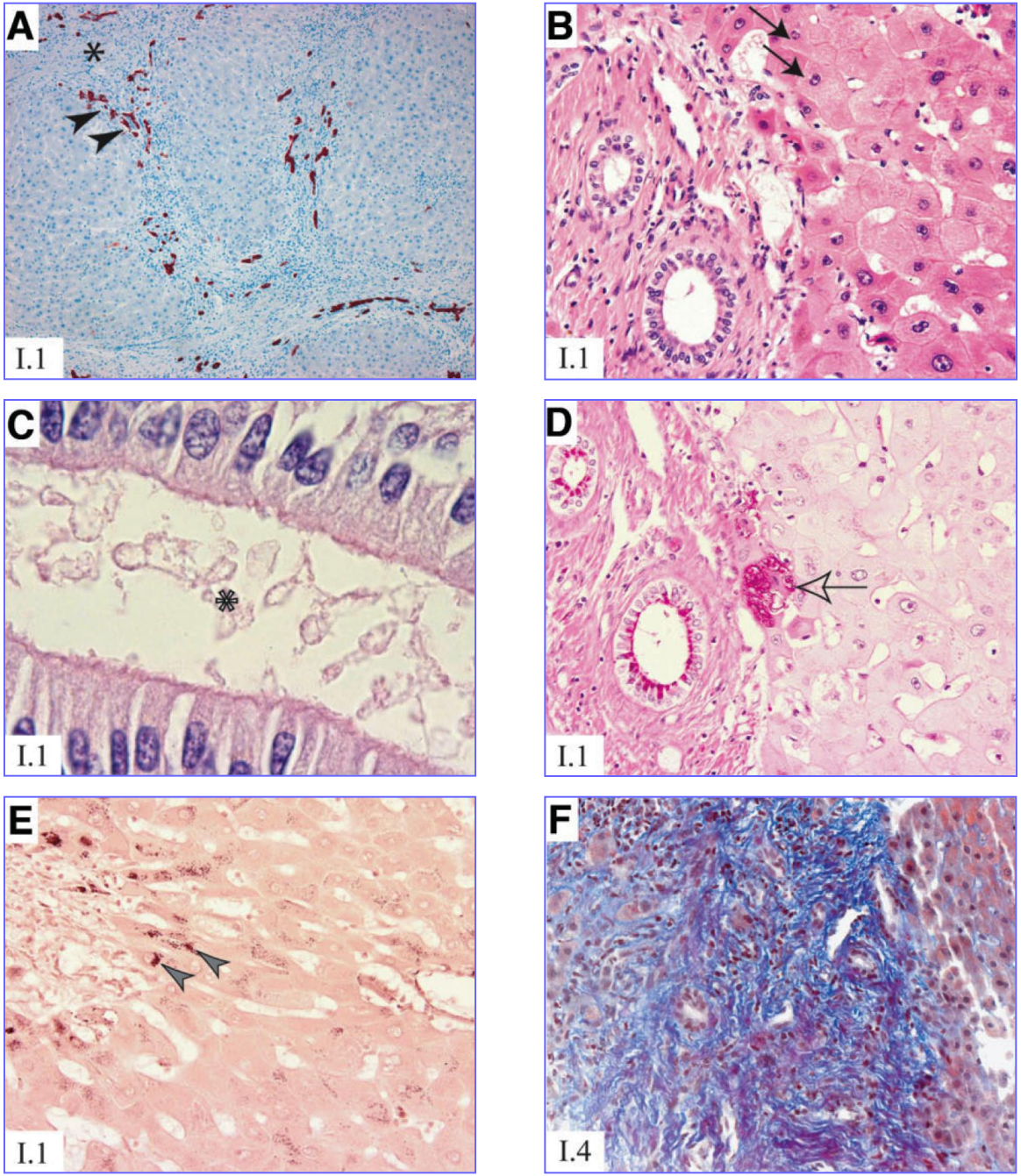


- **More hydrophilic and conjugation resistant**
- **Cholehepatic shunting, HCO_3-rich choleresis**
- **Reverses sclerosing cholangitis in mdr2-/- mice**

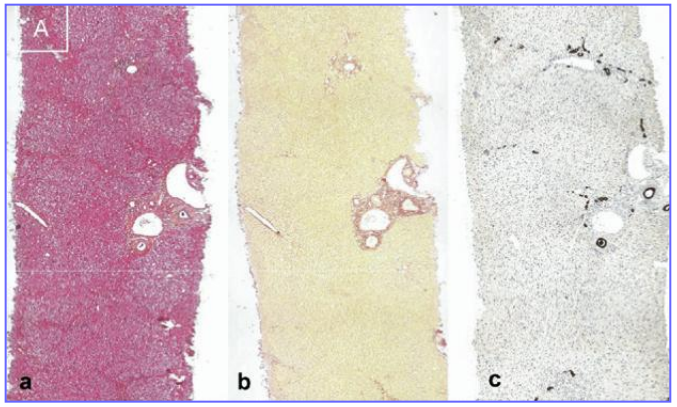
Yoon et al. Gastroenterology 1986; Hofmann et al. Hepatology 2005; Fickert et al. Gastroenterology 2006

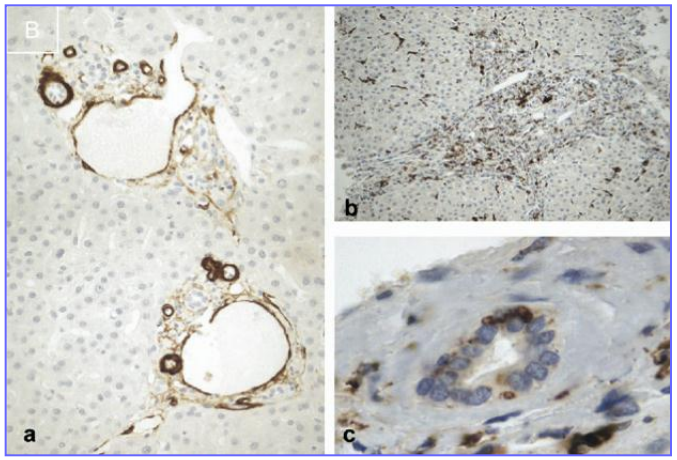
Syndrômes cholestatiques associés aux mutations du gène MDR3

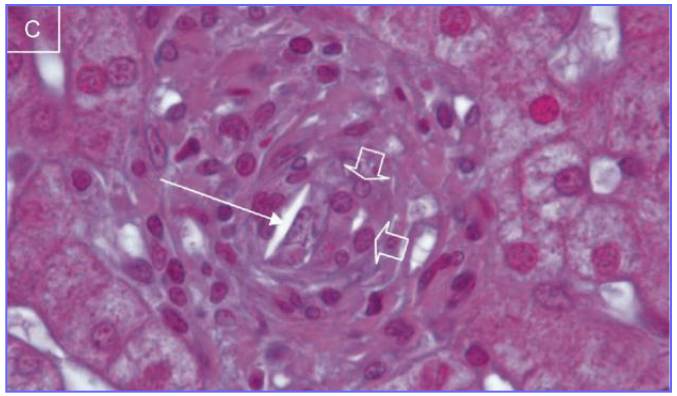
- **Associations certaines**
  - **PFIC3**
  - **Cholestase, ductopénie, fibrose et cirrhose biliaires de l'adulte**
  - **Cholestase gravidique (à GGT élévées)**
  - **Syndrôme LPAC (sans ou avec dilatation segmentaire des voies biliaires intrahépatiques)**
- **Associations probables ou possibles**
  - **Hépatolithiase orientale**
  - **Cholestase médicamenteuse**
  - **Cholestase de la nutrition parentérale**
  - **Cholestase et cholangiopathie du sepsis**
  - **Cholangiopathie post-transplantation**
  - **CBP, CSP**

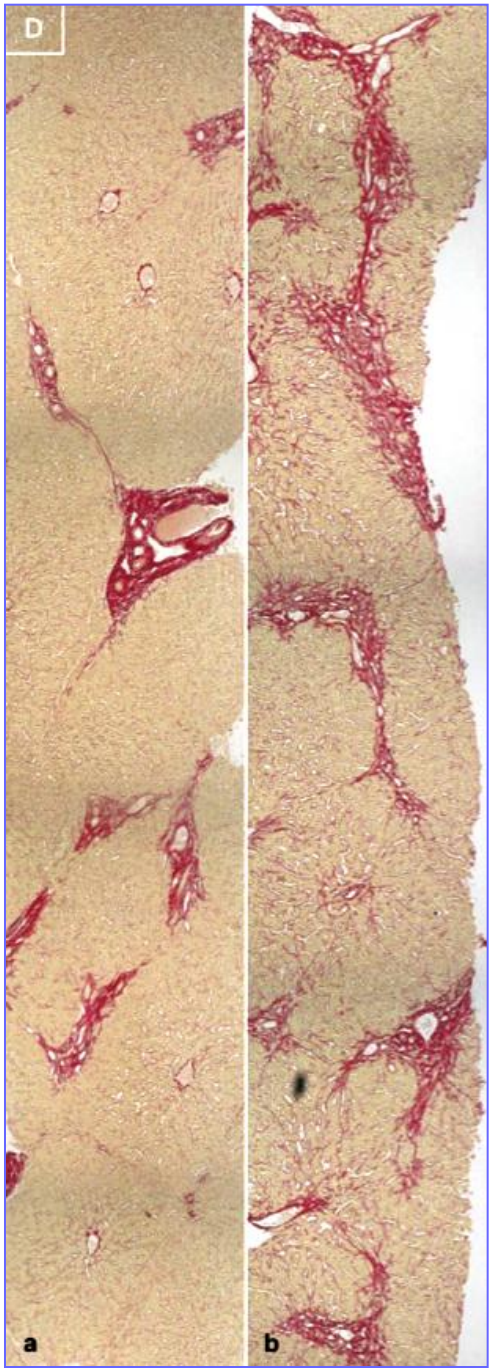


Gotthard et al. Hepatology 2008









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