Low-phospholipid-associated cholelithiasis syndrome: Prevalence, clinical features, and comorbidities

Catherine Dong, Bertrand Condat, Magalie Picon-Coste, Yves Chretien, Pascal Potier, Béatrice Noblinski, Lionel Arrivé, Marie-Pierre Hauuy, Véronique Barbu, Anware Maftouh, Farid Gaouar, Karima Ben Belkacem, Chantal Housset, Raoul Poupon, David Zandite-s, Olivier Chazouilleres, Christophe Corpechot

Table of contents

Table S1. Multiple regression a-lysis of clinical features associated with LPAC diagnosis when evidence for common bile duct lithiasis was limited to imaging features.

Clinical features	**FDR LogWorth (95% confidence interval)**		
	All cases (n=308)	**Cases with typical imaging features (n=272)**	**Cases with typical imaging features and *ABCB4* variant (n=106)**
Imaging evidence of intrahepatic micro or macro-lithiasis	55.0 (54.1 – 55.8)	–	–
Recurrence of symptoms after cholecystectomy	15.7 (15.2 – 16.3)	27.5 (26.6 – 28.5)	11.8 (11.1 – 12.4)
Age at first symptoms before 40	2.5 (2.3 – 2.8)	15.9 (15.3 – 16.6)	10.8 (10.3 – 11.3)
Imaging evidence of CBD lithiasis	3.4 (3.1 – 3.6)	5.4 (5.0 – 5.8)	3.5 (3.2 – 3.8)
No history of obesity or overweight	NS	6.0 (5.5 – 6.4)	4.5 (4.1 – 4.9)
No history of acute cholecystitis	1.7 (1.5 – 1.9)	8.3 (7.8 – 8.7)	4.3 (3.9 – 4.6)

FDR: false discovery rate. CBD: common bile duct. NS: not significant at the 0.05 level. The FDR LogWorth is a quantitative measure of how strong is the association between diagnosis and clinical features in multiple logistic regression a-lysis. It is defined as -log10(FDR p-value). A value that exceeds 2 is significant at the 0.01 level.

Table S2. Non-exhaustive list of the main *ABCB4* variants observed in the LPAC cases of this study.

Variant	Location	Allele Frequency (GnomAD 2.1)	Amino-acid change	Nature of variation	Status	Mutpred2 score	Mutation taster	Reference	Predicted consequences	Number of times found
79A>G	Exon 2	NA	Ser27Gly	Missense	HTZ	0.065		[1]	Pathogenic	1
101C>T	Exon 3	0.053%	Thr34Met	Missense	HTZ	0.023	Polymorphism	[2]	VUS	1
139C>T	Exon 4	NA	Arg47*	Nonsense	HTZ	-			Pathogenic	1
140G>A	Exon 4	0.0088%	Arg47Gln	Missense	HTZ	0.545		[3]	VUS	4
202G>A	Exon 4	0.00040%	Gly68Arg	Missense	HTZ	0.840			Pathogenic	1
217C>G	Exon 4	0.073%	Leu73Val	Missense	HTZ	0.302	Disease causing	[4]	Pathogenic	1
344G>T	Exon 5	NA	Arg115Ile	Missense	HTZ	-			VUS	1
475C>T	Exon 6	0.0018%	Arg159*	Nonsense	HTZ	0.340			Pathogenic	2
523A>G	Exon 6	1.15%	Thr175Ala	Missense	HTZ	0.383	Disease causing	[5, 6]	Conflicting	3
524C>T	Exon 6	0.023%	Thr175Met	Missense	HTZ	0.340	Disease causing	[7]	VUS	1
578G>A	Exon 7	NA	Gly193Glu	Missense	HTZ	0.695			VUS	1
609dup	Exon 7	NA	Ala204Cysfs*39	Frameshift	HTZ	-			Pathogenic	1
959C>T	Exon 9	0.016%	Ser320Phe	Missense	HTZ	0.830			Pathogenic	2
1015dup	Exon 10	0.075%	Ser339Phefs*17	Frameshift	HTZ	-			Pathogenic	1
1130T>C	Exon 11	0.00040%	Ile377Thr	Missense	HTZ	0.669			VUS	1
1217G>A	Exon 11	0.00080%	Arg406Gln	Missense	HTZ	0.468	Disease causing	[8]	VUS	1
1295_1301del	Exon 12	NA	Cys433Argfs*7	Frameshift	HTZ	-			Pathogenic	1
1327C>G	Exon 12	NA	Gln443Glu	Missense	HTZ	0.701			VUS	1
1420delG	Exon 13	NA	Val474Trpfs*2	Frameshift	HTZ	-			Pathogenic	1
1553delT	Exon 13	NA	Leu518Tyrfs*16	Frameshift	HTZ	-			Pathogenic	1
1576G>T	Exon 14	NA	Val526Phe	Missense	HTZ	0.838			VUS	1
1633C>T	Exon 14	0.00080%	Arg545Cys	Missense	HTZ	0.903			Pathogenic	1
1646G>A	Exon 14	0.0036%	Arg549His	Missense	HTZ	0.406	Disease causing	[9]	Pathogenic	1
1675C>A	Exon 14	NA	Ala559Thr	Missense	HTZ	0.826			VUS	1
1712del	Exon 14	NA	Val571Aspfs*16	Frameshift	HTZ	-			Pathogenic	1
1744C>T	Exon 15	0.0032%	Arg582Trp	Missense	HTZ	0.761			VUS	1
1769G>A	Exon 15	0.45%	Arg590Gln	Missense	HTZ	0.885			Pathogenic	4
1772T>A	Exon 15	0.00040%	Leu591Gln	Missense	HMZ	0.938			Pathogenic	1
1973G>A	Exon 16	NA	Trp658*	Nonsense	HTZ	-			Pathogenic	1
1981C>T	Exon 16	0.0014%	Arg661Cys	Missense	HTZ	0.063	Polymorphism		VUS	1

2078delC	Exon 17	0.00040%	Pro693Hisfs*6	Frameshift	HTZ	-			Pathogenic	1
2363G>A	Exon 19	0.82%	Arg788Gln	Missense	HTZ	0.779			VUS	1
2363G>A	Exon 19	0.82%	Arg788Gln	Missense	HMZ	0.779			VUS	1
2406G>A	Exon 20	NA	Trp802*	Nonsense	HTZ	-			Pathogenic	2
2661dup	Exon 21	NA	Glu888Argfs*17	Frameshift	HTZ	-			Pathogenic	1
2800G>A	Exon 23	0.12%	Ala934Thr	Missense	HTZ	0.567			VUS	4
2869C>T	Exon 23	NA	Arg957*	Nonsense	HTZ	-			Pathogenic	1
2953G>T	Exon 24	0.00040%	Val985Leu	Missense	HTZ	0.184	Disease causing	[10]	VUS	1
3279+1G>A	Intron 25	0.00040%	N/A	Splice	HTZ	-			VUS	1
3511_3512delAA	Exon 27	0.00040%	Lys1171Glyfs*29	Frameshift	HTZ	-			Pathogenic	1
3828T>C	Exon 28	NA	*1280Arg ext*20	No-stop	HTZ	-			VUS	1

NA, not available. N/A, non-applicable. HTZ, heterozygous. HMZ, homozygous. VUS, variant of uncertain significance. Mutpred2 score > 0.5: likely pathogenic or pathogenic. Mutation taster and/or reference suggesting pathogenicity: only given when Mutpred2 score < 0.5. Note: in total, *ABCB4* gene variants were detected in 122 (45%) of the 269 LPAC patients with a genotyping test available (87% of the whole cohort).

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