Biochemical and Biophysical Research Communications 396 (2010) 58–62

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

The genetic background of gallstone formation: An update

Hanns-Ulrich Marschall [a,*], Despina Katsika [a], Mats Rudling [b], Curt Einarsson [a]

[a] Department of Gastroenterology and Hepatology, Karolinska Institutet, Karolinska University Hospital at Huddinge, S-141 86 Stockholm, Sweden
[b] Department of Endocrinology, Metabolism, and Diabetes, Karolinska Institutet, Karolinska University Hospital at Huddinge, S-141 86 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 13 February 2010

Keywords:
Gallstones
ATP binding cassette transporter
Swedish Twin Registry
Lithogenic genes
Association study

ABSTRACT

Gallstone disease is one of the most prevalent gastrointestinal diseases with a substantial burden to health care systems that is expected to increase in ageing populations at risk. This review summarizes recent data on the genetic background of cholesterol gallstones and the role of biliary lipid composition. Three previously unknown non-synonymous mutations in the *ABCB4* gene encoding the hepatobiliary phospholipid-flippase MDR3 are presented.

1. Introduction

Gallstone disease is one of the most common gastrointestinal diseases. Worldwide prevalence rates scatter between 5% and 20% but may be as high as 70% in female American Indians. Major risk factors for the development of cholesterol gallstones are female gender, parity, a family history for gallstone disease, and of globally increasing importance, factors attributed with the metabolic syndrome (obesity, dyslipidemia, insulin resistance). Thus, gallstone disease is a multifactorial disease based on a complex interaction of environmental and genetic factors [1–3].

More than 90% of gallstones consist mainly of cholesterol and are formed within the gallbladder. Cholesterol hypersaturation of bile is a prerequisite for the formation of such stones. Bile mainly consists of water (90% by weight) and three lipid species: cholesterol (4 mol per cent of lipids), phospholipids (24%) and bile salts (72%). For each of these components, specific ATP-binding-cassette (ABC) transport proteins are expressed at the canalicular membrane domain of hepatocytes; ABCB4, in humans also known as multidrug resistant p-glycoprotein MDR3, acts as a "flippase" that translocates phospholipids from the inner to the outer leaflet of the membrane, ABCB11, also known as the bile salt export pump BSEP, is the main bile salt transporter, and cholesterol is transported by ABCG5 and ABCG8 that form obligate heterodimers [3]. Cholesterol gallstone formation may be enhanced by decreased gallbladder motility or protein factors such as mucin [2,3]. It is still unclear whether bacteria, including *Helicobacter* species, have a pathogenetic role in cholesterol gallstone formation [4]. However, biliary tract infections are connected to the formation of brown pigment stones, consisting of cholesterol stones in a pigment matrix. The rare black pigment stones consist mainly of calcium bilirubinate [3]. This review aims to update on the genetic background of gallstone disease and to discuss factors contributing to biliary cholesterol hypersaturation.

2. Genetics of cholesterol gallstone disease

Our large study in Swedish twins provided conclusive evidence for the role of genetic factors for the development of symptomatic gallstone disease [5]. Based on data from 43,141 twin pairs born between 1900 and 1958, concordance rates were significantly higher in monozygotic compared to dizygotic twins, and we calculated that genetic effects accounted for 25% (95% CI, 9–40%) of the phenotypic variation among twins [5]. A similar heritability (29 ± 14%) of symptomatic gallstone disease was found in a study of 358 families in Wisconsin [6]. Shared and unique environmental effects accounted for 13% (95% CI, 1–25%) and 62% (95% CI, 56–68%), respectively, of the phenotypic variation among the Swedish twins [5]. In fact, due to shared environmental effects, body mass index was confirmed as a major risk factor for symptomatic gallstone disease in Swedish twins by comparison with the whole population but without differences as to zygosity [7].

A large number of candidate gallstone genes have been identified in studies in inbred mouse strains using the quantitative trait loci analysis and a mouse map was developed describing the chromosomal organization of candidate gene loci [8]. Twenty-three candidate *lith* genes have been identified that are closely related to the regulation of synthesis, uptake and excretion of hepatobiliary lipids [8]. Among these, the genes encoding the hepatocanalicu-

* Corresponding author. Fax: +46 8 58582335.
E-mail address: hanns-ulrich.marschall@ki.se (H.-U. Marschall).

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doi:10.1016/j.bbrc.2010.02.143

lar cholesterol hemitransporters ABCG5/8 were found [9]. Disruption of *ABCG5/8* in mice leads to an increase in the fractional absorption of dietary plant sterols, which is associated with an increase of plasma sitosterol, and extremely low biliary cholesterol concentration, as compared to wild-type controls [10].

In humans, a genome-wide linkage analysis of Mexican American families first identified a gallstone susceptibility locus on chromosome 1p10, but also on chromosomes 2p, 3q, 4p, 8p, 9p, 10p, and 16q, overlapping with mouse *Lith* loci [11]. The genome-wide association study of gallstone patients from Germany and Chile [12] and a linkage study in affected sib pairs from Germany and Romania [13] then identified the D19H variant of *ABCG8*, located on chromosome 2, as a susceptibility factor for human gallstone disease. Odds ratios for heterozygous and homozygous 19H carriers were 2.2 (95% CI, 1.8–2.6) and 7 (95% CI, 0.9–158.6), respectively [12,13], and 8–11% of total gallstone risk can be attributed to this variant [12,13]. Of note, the human *ABCG5/ABCG8* locus is homologous to the mouse susceptibility locus *Lith* 9 [9]. The D19H variant was replicated as a susceptibility factor for gallstone diseases in China, where D19H increased the gallstone risk in patients younger than 50 years of age (OR, 12.4; 95% CI, 1.7–90) [14]. In Chinese gallstone populations, also other non-synonymous polymorphisms, Q604E on the *ABCG5* gene [14], and T400 K on the *ABCG8* gene [15] were associated with increased risk (OR, 6.4; CI, 1.3–30.7 [14] and 2.3; CI, 1.12–4.76 [15], respectively) but only in male patients older than 50 years of age. We recently confirmed D19H as a risk factor for symptomatic gallstone disease (OR, 2.5; CI, 1.3–4.8) in 341 Swedish twins where 20.8% of gallstone cases carried at least one D19H allele as compared to 9.4% in stone-free controls [16]. We also found a trend ($p = 0.052$) for a positive association with the Q604E variant of the *ABCG5* gene in this particular Swedish population (OR, 1.5; CI, 1.00–2.16) [16].

American and European carriers of the D19H variant were found to have decreased intestinal cholesterol absorption and increased hepatic synthesis of cholesterol [17,18], leading to lower total and LDL-cholesterol [18]. Lower total cholesterol and triglyceride levels were also found in another study in Caucasian gallstone siblings, in this case both for carriers of the *ABCG5* Q604E or *ABCG8* D19H variants [19]. Consistent with upregulated cholesterol synthesis, D19H carriers had a significantly more effective reduction of LDL-cholesterol during treatment with statins, which might be of clinical relevance [20]. Of note, in non-obese Chinese gallstone patients, ABCG5/G8 expression in the liver increased significantly and correlated with the percentage of biliary cholesterol and cholesterol saturation index [21]. They also seemed to have an increased rate of cholesterol absorption in the small intestine [22]. Taken together, these findings support the assumption that D19H increases the ABCG5/G8 mediated transfer of cholesterol into bile, which conversely results in biliary cholesterol hypersaturation. However, a recent study in healthy non-obese Chinese provided discordant data, i.e., a significant association of D19H gene polymorphism with elevated total and LDL-cholesterol [23], which might be attributed to different ethnic background and dietary habits.

In a specific and rare subgroup of patients with cholelithiasis a single mutation was found in the gene that encodes the phospholipid-flippase ABCB4 [24,25]. Rosmorduc et al. found point mutations in *ABCB4* in 18 out of 32 patients in "low phospholipid-associated cholelithiasis" or LPAC [24], a syndrome characterized by cholesterol gallstone disease before the age of 40 with both gallbladder stones, intrahepatic sludge and microlithiasis, and recurrent biliary symptoms after cholecystectomy. The responsible defect, low biliary phospholipid secretion, was confirmed in *Mdr2*$^{-/-}$ mice that spontaneously develop cholecystolithiasis [26]. Mutations in *ABCG4* are connected to a number of hepatobiliary diseases spanning from neonatal cholestasis to cirrhosis of childhood [27] and in particular, to intrahepatic cholestasis of pregnancy (ICP), where 12 different genetic variants and four splicing mutations in *ABCB4* have been reported so far (reviewed in [28]). A recent study has also described an *ABCB4* haplotype, which is associated with the "severe" ICP phenotype of serum bile acids >40 μmol/L [29] that conversely is significantly associated with cholesterol gallstone disease [30]. We found a previously unknown *ABCB4* compound heterozygosity (c.2108T>G and c.2800G>A) in a 45-year-old African woman with mild cholestasis, cholecystolithias and intrahepatic gallstones that under her third pregnancy developed severe ICP demanding section in week 33 (unpublished observation). We also recently identified a co-inheritance of a novel *ABCB4* mutation (c.2960C>T) and the *ABCG8* D19H variant in a Swedish monozygotic twin pair where both sisters suffered from juvenile onset gallstone disease, oral contraceptive and pregnancy aggravated cholestatic liver disease, and progressive liver fibrosis [31]. Nevertheless, mutations in *ABCB4* seem to be a rare cause for cholesterol gallstone disease. A recent Norwegian study found less than 2% of young adults to be heterozygous for functionally relevant *ABCB4* mutations [32].

Mutations in the bile salt export pump BSEP seem to be even less frequently associated with symptomatic gallstone disease. Mutations in *ABCB11* were observed in 7 of 11 Dutch patients with cholelithiasis and BRIC2 (benign recurrent intrahepatic cholestasis type 2) [33]. A recent study in sib pairs with gallstones could not find a link between lithogenic dyslipidemia, gallstone risk and four common variants of *ABCB4* and the A444V variant of *ABCB11* [34], although the latter is a significant risk locus for ICP [35].

Expression of ABC transporters is under control of ligand-activated nuclear receptors (NR). *ABCB4* and *ABCB11* are induced by the farnesoid X receptor (FXR; official gene symbol *NR1H4*) whereas *ABCG5* and *ABCG8* are target genes of the liver X receptor (LXR) (reviewed in [36]). FXR is a bile acid sensor but recently FXR was found to be target of other NRs (and presumably glucose as well) and in addition to regulate hepatic bile acid synthesis, uptake and excretion genes, also to impact on numerous genes involved in turnover of cholesterol and triglycerides, and glucose homeostasis (reviewed in [37]). Bile acid–mediated activation of FXR was also shown in the ileum where FXR induces the synthesis and secretion of FGF19, which subsequently represses bile acid synthesis [38] by binding to a cell surface receptor composed of the FGF receptor 4 (FGFR4), a tyrosine kinase, and β-klotho, a single pass transmembrane protein.

A possible reduction of plasma FGF19 may be present in lean subjects with gallstone disease [39]. Although a theoretically attractive possibility, it is unclear whether variation in the FGF19 gene is important for gallstone precipitation. However, activation of the FGFR4/β-klotho complex by FGF19 activates phosphorylation cascades that culminate in the transcriptional repression of *CYP7A1*, the gene encoding cholesterol 7α-hydroxylase, the rate-limiting enzyme in bile acid synthesis (summarized in [40]). Thus, it is not surprising that gene variants that ultimately reduce bile acid synthesis and thus their levels, in Americans and Chinese, variants of *CYP7A1* [41,42], and in Mexicans, of *NR1H4* [43], were found to be associated with cholesterol gallstone disease. Supporting the close association to gallstone disease, *NR1H4* variants were also found in ICP [44].

Recently, the A105G variant of the *SLC10A2* gene encoding the apical sodium-dependent bile acid transporter (ASBT) was identified as a risk genotype for gallstone disease (OR, 2.04; CI, 1.19–3.55), which is the first positive genetic association with a protein involved in bile acid transport [45]. Diminished intestinal bile acid uptake may be of pathogenetic importance.

In smaller studies, other polymorphisms of genes were found to be associated with cholesterol gallstone disease, with striking ethnic differences, e.g., between Asian (China, Japan) and European

Table 1
Human cholesterol gallstone (*LITH*) genes that have been identified and updated in 2010.[d]

Genes	Gene symbols	Databases		Inheritance pattern (countries where reported)			Gene variants	Potential mechanisms
		OMIM[a,b]	Genecards[c]	Rare monogenic	Familial oligogenic	Common polygenic		
ATP binding cassette transporter B4	*ABCB4*	171060 and 600803	GC07M 086676	(−)	(+)	(−)	Multiple	Biliary phospholipid secretion ↓
ATP binding cassette transporter B11	*ABCB11*	603201	GC02M 169604	(+)	(−)	(−)	Multiple	Biliary bile salt secretion ↓
ATP binding cassette transporters G5/G8	*ABCG8*	605459/ 605460 and 611465	GC02P 043951/ GC02P 043977	(−)	(−)	(+) (Germany Sorbs, Chile, China, Sweden) (China)	*ABCG8* p.D19H (*rs11887534*) p.T400K (*rs4148217*)	Biliary cholesterol secretion ↑
	ABCG5			(−)	(−)	(+) (China)	*ABCG5* p.Q604E (*rs6720173*)	
β_3 Adrenergic receptor	*ARDB3*	109691	GC08M 037939	(−)	(−)	(+) (Germany)	p.R64W (*rs4944*)	Gallbladder hypomotility
Apolipoprotein A1	*APOA1*	107680	GC11M 116211	(−)	(−)	(+) (China, India)	−75G>A, RFLP	Biliary cholesterol secretion ↑ secondary to reverse cholesterol transport ↑
Apolipoprotein B	*APOB*	107730	GC02M 021135	(+)	(−)	(+) (China, Poland)	c.2488C>T, c.4154G>A	Biliary cholesterol secretion ↑ secondary to hepatic VLDL synthesis ↓ and intestinal cholesterol absorption ↑
Apolipoprotein C1	*APOC1*	107710	GC19P 050109	(−)	(−)	(+) (India)	RFLP	APOC1 ↑ remnant-like particle cholesterol ↑
Androgen receptor	*AR*	313700	GC0XP 066680	(−)	(−)	(+) (Greece)	c.172$(CAG)_n$	
Cholecystokinin 1 receptor	*CCK1R*	118444	GC04M 026159	(+)	(−)	(+) (India)	RFLP	Gallbladder and small intestinal hypomotility
Cholesterol ester transfer protein	*CETP*	118470	GC16P 055553	(−)	(−)	(+) (Finland)	RFLP	Hepatic cholesterol uptake ↑ from HDL catabolism ↑
Cytochrome P450 7A1	*CYP7A1*	118470	GC08M 059565	(+)	(−)	(+) (China)	Promoter SNP-204A>C	Bile salt synthesis ↓
Estrogen receptor 2	*ESR2*	601663	GC14M 063621	(−)	(−)	(+) (Greece)	c.1092+3607$(CA)_n$	Cholesterol synthesis ↑
Low-density lipoprotein receptor related protein (LRP) associated protein 1	*LRPAP1*	104225	GC04M 003551	(−)	(−)	(+) (India)	Intron 5 insertion/deletion (*rs11267919*)	Hepatic cholesterol uptake ↑ from chylomicron remnants via LRP ↑
Sodium-dependent bile acid transporter	*SLC10A2*	601295	GC13M 102494	(−)	(−)	(+) (Germany)	c.378-105A>G (*rs9514089*)	Intestinal bile acid uptake ↓

[a] *Abbreviations used:* OMIM, on-line Mendelian inheritance in man; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism.
[b] http://www.ncbi.nlm.nih.gov/entrez.
[c] http://www.genecards.org.
[d] Reproduced with modifications and with permission from F. Lammert, T. Sauerbruch, Pathogenesis of gallstone formation: updated inventory of human lithogenic genes, in: M.C. Carey, P. Dité, A. Gabryelewicz, V. Keim, J. Mössner (Eds.), Future Perspectives in Gastroenterology (Falk Symposium 161), Springer, Dordrecht. 2008, pp. 99–107.

populations (Finland, The Netherlands). These included a number of genes encoding cholesterol transporting and metabolizing proteins, i.e., apolipoproteins A1, B and C1 (*APOA1* [46], *APOB* [42,47–49], *APOC1* [50]), cholesteryl ester transport protein (*CETP* [51]), low-density lipoprotein receptor related protein (LRP) associated protein 1 (*LRPAP1* [52]), as well as steroid hormone receptors such as β_3 adrenergic receptor (*ARDB3*) [53], androgen receptor (*AR*) [54] and estrogen receptor 2 (*ESR2*) [54], as shown in Table 1 (modified and extended from [55] and [56], with permission by F. Lammert).

3. Black pigment stones

Black pigment stones are found in patients with hemolytic anemia and Crohn's disease due to increased biliary excretion of unconjugated bilirubin [3]. The Gilbert syndrome-associated functional TATA box TA repeat variant *UGT1A1*28* was found to increase susceptibility to pigment stone formation both in patients with hemolytic anemia [57] and cystic fibrosis [58], but also in an otherwise healthy Greek population with Gilbert syndrome [59]. However, although a very high association between total serum bilirubin levels and *UGT1A1* variants was found in a recent genome-wide association meta-analysis including 9.464 individuals from Framingham, Rotterdam and Iceland, top SNPs in *UGT1A1* were not associated with gallbladder or gallstone disease [60].

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