Genetic factors in cholesterol gallstone disease

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ABSTRACT

Most common diseases are strongly influenced by inheritance, but, to date, relatively few genes have been identified that are responsible for the familial clustering of these diseases. In the great majority of cases, no Mendelian inherited trait can be demonstrated. With the exception of cholesterol gallstones associated with low phospholipid level, induced by mutations in the gene of the multidrug resistant protein (MDR3/ABCB4), and of the mutations in the gene of cholesterol 7 alpha hydroxilase (CYP7A1), recently identified, no single genetic mutation or polymorphism has been found in association with cholesterol gallstone disease in humans.

This happens because common diseases, such as cholesterol gallstone disease, are complex disorders, where multiple genes and environmental factors collaborate to their development. Cholesterol gallstone disease is characterized by a genetic predisposition to lithogenesis, involving multiple genes and gene-gene interactions plus interaction with a “lithogenic” environment. The combination of these factors leads to gallstone formation if a threshold of susceptibility is reached, since each susceptibility allele only confers a modest increase in risk.

There are six major classes of candidate genes which, by encoding hepatobiliary lipid regulators and transporters, could contribute to bile supersaturation in cholesterol and the formation of gallstones. These have been identified in experimental model. The quantitative trait locus (QTL) mapping is a powerful genetic technique for the identification of genes determining complex traits. Subsequently mapping studies can be undertaken in humans for identification of orthologous LITH genes, because of the exceptional man-mouse chromosome homology.

Keywords: genetics, cholesterol gallstones, lithogenic genes, risk factors, QTL mapping

INTRODUCTION

Prevalence of cholesterol gallstone disease is rising in the industrialized countries in Europe and North America. More than 20 million people in the United States have gallstones (1). Given the higher incidence at advanced ages, the longer life expectancy of the population and the high costs of cholecystectomy, gallstone disease represents a significant burden for these societies. The annual costs of gallstone disease in the United States are higher than 6.5 billion USD (2). In Romania, necroptic (3) and sonographic (4) studies have shown a prevalence of 11-12% of gallstone disease, with an estimated 2.3 million gallstone carriers, and an increasing trend in the last decades (5).

Sustained efforts are presently directed to elucidate the etiology of this common disease, with the goal of preventing gallstone formation. Ethnicity and family history are among the major risk factors for cholesterol lithogenesis. Furthermore, monozygotic twins are much more likely to be concordant for gallstones than dizygotic twins. Gallstone susceptibility might be caused by a genetic predisposition involving multiple genes and gene-gene interactions plus interaction with a “lithogenic” environment including diet, obesity, weight loss, multiple pregnancies etc. The combination of these factors leads to gallstone formation if a threshold of susceptibility is reached, since each susceptibility allele only confers a modest increase in risk (6, 7).
PATHOGENESIS OF CHOLESTEROL GALLSTONE DISEASE

A brief description of the current information regarding cholesterol gallstone pathogenesis is necessary in order to analyze the role of environment and of genetics in the development of the disease.

Three types of abnormalities have been classically considered to be responsible for cholesterol gallstone formation (Table I). The primary and major abnormality consists of bile supersaturation in cholesterol, which is determined by changes in the proportion of the three major lipids in bile: cholesterol, bile acids and phospholipids.

The hepatic cholesterol pool results from de novo synthesised cholesterol (key enzyme: HMGCoA reductase), or from plasma lipoprotein particles, especially HDL. Most of the cholesterol derives from the diet, only about 20% results from de novo synthesis. Cholesterol is esterified in the liver (key enzyme: ACAT) and is incorporated in VLDL, or it is excreted as free cholesterol in the bile. In the liver, cholesterol is also converted into bile acids, cholesterol 7a hydroxylase (CYP7A1) being the rate limiting enzyme for bile acid biosynthesis. An increased biliary cholesterol saturation might result from an increased de novo synthesis, an increased uptake from plasma lipoproteins, a decreased conversion into bile acids or a decreased cholesterol esterification.

Additional abnormalities favoring cholesterol gallstone formation are enhanced nucleation of cholesterol crystals, mucus hypersecretion and gallbladder hypomotility. Enhanced nucleation and mucus hypersecretion favor crystal formation, and gallbladder stasis allows crystals to grow and aggregate, forming stones. When bile is highly supersaturated in cholesterol, gallbladder motility or nucleation might not be too much altered, but in case of a slightly supersaturated bile, hypomotility and enhanced nucleation should be the dominant abnormality.

A fourth abnormality (Table I) leading to lithogenesis has been recently added: intestinal hypomotility. The small intestine represents the site of absorption and reabsorption of dietary cholesterol, and also plays an important regulatory role in the enterohepatic circulation of bile salts. Slow intestinal transit allows bile salts to remain longer in the intestine, exposed to the action of bacteria, and thus favors their transformation into dehydroxylated and more hydrophobic bile salts (acid deoxycholate). Deoxycholate inhibits synthesis of the bile acids in the liver, increasing cholesterol excretion into bile.

Genes controlling synthesis of transporters and enzymes involved in the secretion of biliary lipids are the major natural candidates to influence lithogenesis. Genes involved in the control of gallbladder motility or mucus secretion represent a second large group of candidate genes (8).

ENVIRONMENTAL RISK FACTORS

Besides the unmodifiable risk factors for cholesterol lithogenesis (female gender, increasing age and genetic susceptibility), there are numerous well documented environmental risk factors for gallstones (summarized in (6, 9) (Table 2).

The main risk factors for cholesterol gallstones, namely obesity, hypertriglyceridaemia, type 2 diabetes mellitus, atherogenic diet and physical inactivity are also major risk factors for the metabolic syndrome. Most of the other risk factors are similar. Therefore, cholesterol gall-
stone disease could be considered as a component of the metabolic syndrome (10).

**EVIDENCE FOR THE GENETIC BACKGROUND**

Most common diseases are strongly influenced by inheritance, but, to date, relatively few genes have been identified that are responsible for the familial clustering of these diseases. This happens because common diseases are almost all complex disorders, where multiple genes and environmental factors collaborate to their development. Cholesterol gallstone disease is such a complex disease, characterized by a genetic (polygenic) predisposition to lithogenesis.

**Ethnic and racial differences in prevalence**

Necropsy and population studies have shown differences in worldwide gallstone prevalence, which can not be completely explained by environmental factors. There are African and Asian populations with very low prevalence (<5%), European and American populations with intermediate prevalence (10-30%) and populations of Native American ancestry (Pima Indians in Arizona, Mapuche Indians in Chile) with extremely high prevalence of cholesterol gallstones (30-70%). The ethnic subpopulations living in the same country (United States, Chile), but having different heritage of Amerindian admixture (1, 11, 12), significantly differ in gallstone prevalence. That these high differences in prevalence exist between ethnic groups sharing the same environment can be explained only by a genetic predisposition to gallstone formation.

**Familial clustering**

The family history is a very robust tool for identifying genetic susceptibility. Family histories can be divided into levels of risk. *Low risk* family histories are those with few affected members, often with only the proband or index case affected. This could be evidence of a single gene recessive disorder, but more likely represents a sporadic non-genetic occurrence of disease in an adult. *High risk* families are those with multiple generations affected in a pattern that is consistent with a single gene disorder, such as some of the cancer syndromes. These families usually are recognized by the various components of the inherited syndrome occurring in family members. The biggest group of families is that of moderate risk, and gallstone disease belongs to this group. A disease will be found in more than one individual in these families, but the pattern of expression is incomplete and does not follow strict Mendelian rules of inheritance. These are the most difficult to understand but represent the greatest opportunity for genetic studies, and this is where the powerful new technologies driven by the Human Genome Project will have the greatest impact.

An increased prevalence of gallstones was found in siblings and among the relatives of gallstone carriers as compared with families of controls (ratio 3:1) (13-15). The greater the number of affected relatives, the greater the risk of gallstones occurring at younger ages, reflecting a stronger polygenic predisposition.

**Twin studies**

A higher saturation of the bile and a greater correlation of the cholic and deoxycholic acid contents were found in the monozygotic as compared with dizygotic twins, as well as a 40% concordance rate for gallstones in monozygotic as compared with 0% in dizygotic twins (16). A very recent study performed on 43,141 twin pairs in Sweden (17) has indicated a significantly higher gallstone presence in monozygotic versus dizygotic twins (concordance rate 12% versus 6%) confirming the role of the genetic influence (25%), and also stressing the environmental influence: shared (13%) or individual environmental influence (62%). Genetic influence was also found in the phenotype of the disease (symptomatic or asymptomatic) (18-20). The genetic heritability derived from these studies was 0.29± 0.14 (19) and 0.44 ± 0.18 (21) for symptomatic stones, similar to that found in obesity or type 2 diabetes mellitus.

| Hepatic lipid regulatory enzymes   |
| Hepatic lipoprotein receptors and related proteins |
| Hepatic and intestinal intracellular lipid transporters |
| Hepatic and intestinal membrane lipid transporters |
| Hepatic lipid regulatory transcription factors |
| Cholecystokinin, CCK receptors, and gallbladder mucins |

**TABLE 3.** The candidate genes for cholesterol gallstones encode
CANDIDATE GENES FOR CHOLESTEROL LITHOGENESIS

There are six major classes of candidate genes which could contribute to bile supra-saturation in cholesterol and the formation of gallstones (22) (Table 3).

Hepatic lipid regulatory enzymes

The candidate genes encoding the de novo synthesis of cholesterol, the bile acid synthesis and cholesterol esterification in the liver are: 3 hydroxy-3-methylglutaryl-coenzyme A (HMGCoA), cholesterol 7a hydroxylase, sterol 27-hydroxylase, and sterol O-acyltransferase 2 (formerly Acat 2). The genes encoding these enzymes have been already mapped to the mouse chromosomes (Table 4).

Hepatic lipoprotein receptors and related proteins

The receptors for the HDL lipoproteins (scavenger receptor 1), for the LDL particles (APOB/E receptor) or chylomicron remnants (hepatic lipase) allow plasma lipids to be taken up in the liver. Other genes involved in the extrahepatic metabolism of lipoproteins could be considered as LITH candidate genes, such as lecithin-cholesterol acyltransferase 1 (LCAT), hepatic lipase (LIP), phospholipid transfer protein (PLTP), and scavenger receptor 1 (SRB1) (Table 4).

<table>
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<td>HMG-CoA reductase</td>
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<td>Sterol O-acyltransferase 2</td>
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<td>12q13.3-q15</td>
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<td>12</td>
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TABEL 4. Chromosomal location of candidate gallstone genes in mice and humans (modified after (6, 22))
terol acyl transferase (Table 4). Polymorphisms of the human APOE gene (23-25) and of the human gene encoding the cholesteryl ester transfer protein (CEP), which transfers cholesteryl esters between lipoproteins (26) have been found to be associated with cholesterol lithogenesis.

Hepatic and intestinal intracellular lipid transporters

The intracellular transport of biliary lipids is realized by specific transporters, such as the sterol carrier protein 2 (SCP2), the Niemann-Pick type C1 (its mutation leads to the Niemann-Pick type C1 disease) or the phospholipid and bile salt carriers. Location of their genes has been identified on the mouse chromosomes (Table 4). The SCP2 gene was overexpressed in patients with cholesterol gallstones, indicating that SCP2 may be an important cause of cholesterol gallstones.

Hepatic and intestinal membrane lipid transporters

This is the class of transporters most intensely researched in cholestasis, as well as in biliary lithogenesis, because bile formation and secretion critically depends on their activity. The transporters of the biliary lipids from the hepatocyte to the bile against their concentration gradients in the bile (the export pumps) belong to the ATP-binding cassette (ABC) family of membrane transporters. The bile salt export pump (BSEP, ABCB11) transports monovalent bile salts into bile. Mutations in ABCB11 cause the progressive familial intrahepatic cholestasis type 2 (PFIC type 2). The canalicular multi-specific organic anion transporter (multidrug resistance-related protein 2) (ABCC2, MRP2) favors excretion of organic anions including bilirubin. Mutations in ABCC2 were found in the patients with Dubin Johnson syndrome. The phosphaditidylcholine “flipase” (multiple drug resistance protein) (ABC8/MDR3) promotes transport of phospholipids into bile. Mutations in ABCB4 cause the progressive familial intrahepatic cholestasis type 3 (PFIC type 3) and have also been found in association with cholesterol gallstones (27-29). Point mutations in the gene controlling the ileal (apical) Na/bile salt transporter (SLC10A2) lead to bile salt malabsorption and might favor pigment lithogenesis.

Recently two genes, ABCG5 and ABCG8, have been identified, encoding sterolin-1 and sterolin-2, respectively, mutations of which cause the human disease sitosterolemia (30-34). The ABCG5 and ABCG8 transporters have a role in the intestinal absorption and biliary excretion of the neutral sterols (34, 35). Experiments in mice confirmed that ABCG5 and ABCG8 are the major hepatobiliary transporters for cholesterol, that they protect against dietary sterol accumulation in the body and that stimulation of cholesterol excretion by LXR (liver X receptor) agonists requires ABCG5 and ABCG8 (30, 33-37).

Hepatic lipid regulatory transcription factors

The sterol regulatory element binding transcription factors (SREBF) 1 and 2 up-regulate the transcription of Hmgcr and Ldrl.

The nuclear hormone receptors are a superfamily of cellular receptors that regulate gene transcription. In general, these proteins are activated upon binding ligands, namely small hydrophobic molecules like bile salts and steroid hormones. Dimers of the retinoid receptor that binds retinoic acid (RXR) and a ligand specific counterpart bind to a responsive element in the promoter region of a gene and thereby regulate transcription. BSEP expression is controlled by the nuclear receptor pair RXR/FXR, in which FXR is the farnesoid X receptor, which has high affinity for bile salts. Binding of bile salts to FAR in the dimer RXR/FXR induces transcription of the BSEP gene, leading to enhanced protein levels and increased bile salt secretion. FXR might also represent a candidate gene for biliary cholesterol lithogenesis (38, 39).

Cholecystokinin, CCK receptors, and gallbladder mucins

Cholecystokinin is the major regulator of gallbladder postprandial emptying, after binding to the CCKAR receptor. Gallbladder stasis favors gallstone formation. Cck and Ccak have been mapped to mouse chromosomes and are presently under intensive research (Table 4). Effects of polymorphisms of MUC genes on biliary lithogenesis are also under investigation, as mucin hypersecretion favors crystal formation and aggregation in the gallbladder lumen, but no polymorphisms could be correlated to gallstone formation yet.
IDENTIFICATION OF LITH GENES

Association studies

Most association studies have focused on a common genetic variation. Common genetic variants (or polymorphisms) are those for which two or more alleles which exist in 1% or more of the population at large. The association studies are performed by comparing the incidence of a particular polymorphism in affected patients with the incidence of disease in a carefully matched control group. Because common variants are present at high frequency, they can be discovered in any modest sized group of individuals. In the case of complex disease, there is the risk of a false positive (by chance) association. Many associations are therefore not consistently reproduced, so it is very important to have large samples of individuals tested in replicative studies (40).

Association of gallstone formation with some gene polymorphisms in humans has been reported. Certain polymorphisms of the apolipoprotein E genes were correlated with cholesterol gallstone formation. APOE locus in humans was found to be a risk factor for cholesterol gallstone formation. APOE is inherited as three different allelic variants (E2, E3 and E4). The E4 genotype is associated with a higher incidence of gallstones, a higher cholesterol content of stones and also a higher recurrence rate after extracorporeal shock-wave lithotripsy (23-25). The E2 genotype protects against gallstone formation. The effect of E4 genotype could be explained by an increased hepatic uptake of chylomicron remnants. Polymorphisms of APOB and APOA1 and CETP (gene of the cholesteryl ester transfer protein) are presently under investigation, some studies indicating a possible association with cholesterol gallstone disease (26).

In complex diseases, haplotype analysis might offer more information than analysis of the individual polymorphisms. A haplotype is a specific set of alleles present on a single chromosome. The reconstruction of haplotypes from genotype data in a population (by Bayesian method) increases the statistical power of an association study by doubling the sample size and simplifying the data structure (41). This type of analysis has also been used to investigate the genetics of gallstone disease. Through screening of the ABCG5 and ABCG8 genes for mutations in the sitosterolemia patients, polymorphisms in both genes have been reported (30, 42, 43) and some ABCG5/ABCG8 polymorphisms have already been reported to contribute to the genetic variation in plasma lipid levels and in cholesterol saturation of the bile (44-46).

Linkage analysis

Linkage analysis has proved extremely valuable in mapping single gene disorders, but it is much more difficult to use in multifactorial, polygenic disorders, perhaps in part because of a limited power to detect the effect of common alleles with modest effect on disease. Only a reduced number of studies linking genomic regions to gallstone disease have been performed in humans.

An alternative approach would be to identify the cholesterol gallstone susceptibility loci in suitable animal models. This is obtained by mating inbred strains of mice highly susceptible to developing gallstones with inbred strains of mice resistant (with very low susceptibility) to the disease. The F1 offspring are then “backcrossly” mated with the high risk parental strain. By studying the cosegregation of polymorphic markers at multiple loci with the disease, susceptibility regions can be identified. The quantitative trait locus (QTL) mapping is a powerful genetic technique for the identification of genes determining complex traits. Subsequently mapping studies can be undertaken in humans for identification of orthologous LITH genes because of the exceptional man-mouse chromosome homology (Table 4) (22, 47-49).

MONOGENIC GALLSTONE DISEASE IN HUMANS

Gallstone disease is a complex disease. In the great majority of cases no Mendelian inherited trait can be demonstrated. With the exception of cholesterol gallstone disease associated with low phospholipid level, induced by mutations in the gene of the multidrug resistant protein (MDR3/ABCB4), recently reported by Rosmorduc (27), Jaquemin (28) and Shoda (29, 50), and of the mutations in the gene of cholesterol 7 a hydroxilase (CYP7A1) reported by Pullinger (51), no single genetic mutation or polymorphism has been found in association with cholesterol gallstone disease in humans. The mutations in ABCB4 (MDR3) are associated with a particular type of cholelithiasis, characterized by intrahepatic sludge, cholesterol gall-
stones and mild cholestasis (increased aGT)(27, 28, 50).

Some unique genetic defects have also been found in association with pigment stones, such as changes in the CCK receptor (CCKAR)(52-54), mutations in the cystic fibrosis gene (CFTR/ABCC7) (55) or in the gene controlling the ileal transporter of bile acids (IBAT/SLC10A2) (56, 57).

**GALLSTONE (LITH) GENES IDENTIFIED IN MICE**

Until now, at least 20 Lith genes have been identified in the experimental model, the best characterized being Lith1 and Lith2 (Fig. 1. The murine gallstone map). The congenic strains of mice for Lith1 and Lith2 develop cholesterol gallstones when fed a lithogenic diet. Abcb11, the gene encoding BSEP on the canalicular membrane of the hepatocyte co-localizes with Lith1. The congenic strains of mice for Lith2 have an increased secretion of organic anions because of overexpression of MRP2, encoded by Abcc2, which co-localizes with Lith2. The gene which encodes the basolateral transport of organic cations Slc22a1 co-localizes with Lith3 on mouse chromosome 17 (58). Recently, new QTLs have been identified (by linkage analysis) in mice and named Lith 4, Lith 5, Lith 10, Lith 6, Lith (7, 22, 59). The genes encoding Abcg5-Abcg8 co-localize with Lith 9 and are located on chromosome 2 (60). The putative list of Lith genes remains open. The relevance of the Lith genes for human cholelithiasis is under intense research, by means of linkage analysis and association studies in symptomatic and asymptomatic carriers of gallstones.
CONCLUSION

The individual predisposition to cholesterol gallstone disease in the presence of environmental risk factors could be determined by a complex genetic basis. It is probable that a significant proportion of individuals have a genetic predisposition to develop cholesterol gallstones. It is also possible that other individuals have susceptibility alleles for developing obesity and type 2 diabetes mellitus, diseases with a high risk of cholesterol gallstone formation.

By evaluating gene polymorphisms or haplotypes, individual prognostic factors might be identified in subjects with “healthy” phenotypes. Screening of the LITH genes in obese patients or in patients with other metabolic diseases could become important especially when the associated diseases have an increased surgical risk. Elucidation of the molecular genetics of cholesterol gallstone disease might also offer new possibilities of gallstone prevention or therapy.

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susceptibility to cholesterol cholelithiasis. *J Clin Invest* 2004; 114:521-528