Genetics of Gallstone Disease

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Gallstones - a Common Disease

- Gallstone prevalence in Europe and America: 10 - 20%

- > 170,000 and 700,000 cholecystectomies per year in Germany and the United States, respectively

- Mortality of cholecystectomies in ASA I-III patients: 0.4%
  BQS *Germany* (2006)

- Costs (United States): $6.5 billion / year
Gallstones: Classification

- **Cholesterol stones**
  - Black pigment stones: 10%
  - Bilirubin polymers: 10%
  - Calcium bilirubinate: 20%

- **Cholesterol**
  - Gallbladder (and bile ducts): 70%

- **Gallbladder (and bile ducts)**
  - Infected bile ducts: 20%
Cholesterol Gallstones: Pathophysiology

- Biliary cholesterol hypersecretion
- Gallbladder hypomotility
- Slow intestinal transit
- Increased deoxycholate levels

Inbred Mouse Model: *Lith* Genes

*Paigen*-diet
(15% fat, 1% cholesterol, 0.5% cholic acid)

**Susceptible**
- C57L
- C57BL/6
- SWR

**Resistant**
- AKR
- 129
- A/J

Inbred mouse strains
= homozygous for all alleles

⇒ Gallstone (*Lith*) genes determine the formation of cholesterol gallstones in mice

Lammert et al. *Gastroenterology* (2001)
Mouse Model: Enterohepatic *Helicobacter*

C57L inbred mouse strain +/- enterohepatic *Helicobacter* spp.

Gallstone prevalence:  
Infected 40 - 80%  
Uninfected (SPF) 10 - 20%

Maurer, Carey et al. *Gastroenterology* (2005)
Mouse Models: Three Causative Factors

- Genetic factors (Lith genes)
- Dietary factors (e.g. cholesterol, cholic acid)
- Enterohepatic infections / inflammatory responses
Epidemiological Studies: At-risk Populations

USA
- Amerindian
- Caucasian
- African-American

Chile
- Amerindian
- Mapuche
- Hispanics
- Maori


Twin Study: Gallstones - a Genetic Disease

Swedish Twin Registry
Karolinska Institutet

Monozygotic twins N = 11073
Dizygotic twins N = 18183

Concordance rate (%)

< 65 ≥ 65 < 65 ≥ 65 years

Structural Equation Modelling

Genetic factors
"LITH genes" (25%)

Unique environmental factors (62%)
Common environmental factors (13%)

Katsika et al.
Hepatology (2005)

Lammert & Sauerbruch
Genetics of Gallstone Disease

Genetic factors

Environmental factors

Monogenic / oligogenic cholelithiasis

Polygenic (common) cholelithiasis

ABCB4
CFTR
UGT1A1
CCKAR
CYP7A1
...

LITH genes

Diet
Obesity
Insulin resistance
Multiparity
...

Monogenic Cholelithiasis: \( ABCB4 \) Deficiency

**Low Phospholipid Associated Cholelithiasis (LPAC)**
**Gallbladder Disease Locus 1 (\( GBD1 \))**

- Mutations of the phospholipid transporter \( ABCB4 \)
- Age at onset of symptoms < 40 years
- Cholesterol gallbladder stones and intrahepatic sludge or microlithiasis (OR 6.1)
- Recurrence of biliary symptoms after cholecystectomy (OR 8.5)
- Positive family history
- Mild chronic cholestasis
- Association with intrahepatic cholestasis of pregnancy

Oligogenic Cholelithiasis: Cystic Fibrosis (CF)

UDP glucuronosyltransferase

*UGT1A1*

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TATA box

A(TA)$_6$TAA wild-type

A(TA)$_7$TAA Gilbert polymorphism

Genotype | Bilirubin (mg/dl)
---------|-------------------
(TA)$_6$(TA)$_6$ | 0.35 ± 0.03
(TA)$_6$(TA)$_7$ | 0.54 ± 0.05$^*$
(TA)$_7$(TA)$_7$ | 0.72 ± 0.08$^*$

Polygenic Cholelithiasis: SAFDGS Genome Scan

- San Antonio Family Diabetes/Gallbladder Study (SAFDGS)
- Cohort: 715 individuals from 39 families
- Phenotyping: ultrasound-based (cholecystectomy, gallstones)
- Genotyping: 10-cM scan of autosomal chromosomes (382 microsatellites)
- Variance components analysis
- Metabolic syndrome risk score as covariate

Polygenic Cholelithiasis: SAFDGS Genome Scan

Personalized risk profiling:
- Genetic factors (ABCB4, ABCB11, UGT1A1 ...)
- Environmental factors (enterohepatic bacteria ...)

**Speculation: Future Developments**

- **Defined low-risk groups**
  - Primary prevention without drugs
    - Weight reduction, sports, diet modification
    - or non-surgical therapy ?

- **Defined high-risk groups**
  - Screening & early therapy
    - Prevention with drugs
      - (nor)UDCA, FXR agonists ?, antibiotics ?
  - or prophylactic cholecystectomy ?

Primary prevention without drugs

Weight reduction, sports, diet modification

or non-surgical therapy ?

Screening & early therapy
Prevention with drugs

(nor)UDCA, FXR agonists ?, antibiotics ?

or prophylactic cholecystectomy ?