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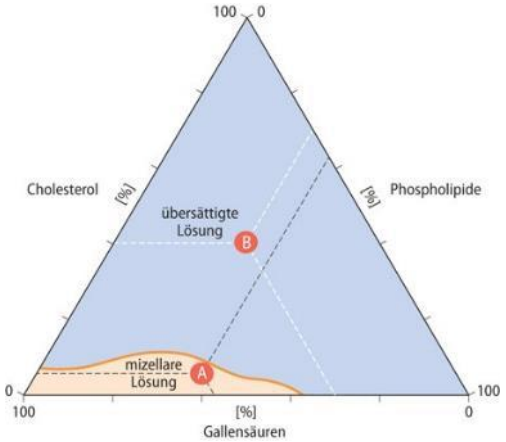
A genome-wide association scan identifies the hepatic cholesterol transporter ABCG8 as a susceptibility factor for human gallstone disease

Buch et al., Nature Genetics 2007

Bible Class, Milestone Paper, 19.03.2025, Sebastian Schappert

Introduction

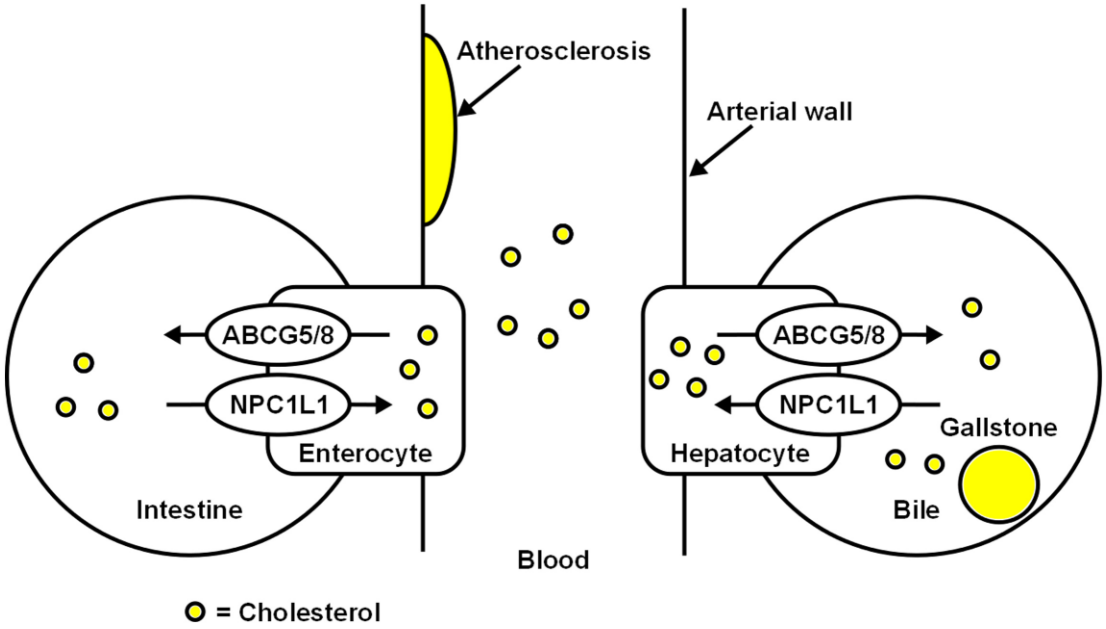
- Gallstones are a common disease, affecting 10–20% of people in Western countries.
- Cause: Cholesterol oversaturation in bile → Crystallization → Gallstone formation.
- Besides environmental factors, genetics plays a significant role.
- **Study objective**: Identify genetic risk factors for gallstone disease.



What was known?

- Family studies suggested a strong **genetic predisposition** for gallstones.
- The ABCG8 gene encodes a transport protein responsible for **cholesterol secretion** into bile.
- Animal studies showed that mutations in ABCG8 affect cholesterol excretion.
- However, no direct genetic evidence in humans was available before this study.

What was known?



Methods

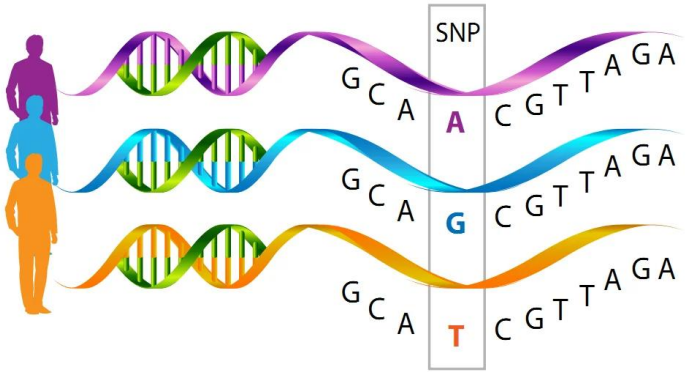
Study Design – Genome-Wide Association Study (GWAS)

- **GWAS approach**: Screening for **genetic variations (SNPs)** associated with gallstones.
- **Analysis of >500,000 SNPs** across the entire genome.
- **Comparison** of genetic differences between patients and controls.

Methods

What Is an SNP (Single Nucleotide Polymorphism)?

- A small genetic variation in a DNA sequence.
- Can influence **protein function or disease risk**.
- Study goal: Identify SNPs **significantly associated** with gallstones.



Methods

Initial GWAS Panel:

- **Participants**: 280 gallstone patients and 360 gallstone-free controls from Germany.
- **Genotyping**: Utilized the GeneChip Human Mapping 500K Array Set from Affymetrix, which assesses over 500,000 SNPs across the genome.

Follow-Up Analysis:

- **Selection of SNPs**: based on the initial GWAS, **238 SNPs** showing the most significant associations were selected for further analysis.
- **Replication Cohort**: independent cohort, 1,105 symptomatic gallstone patients and 873 controls, to validate the findings.

Results

Initial GWAS Findings:

- **Significant SNPs:** initial scan identified several SNPs with potential associations to gallstone disease, **rs11887534 in the ABCG8** gene exhibited one of the strongest associations.

Replication and Combined Analysis:

- **Replication Results:** In the follow-up cohort, SNP rs11887534 consistently showed a significant association with gallstone disease.
- **Combined Analysis:** When combining data from both the initial and replication cohorts:
  - **Odds Ratio (OR):** Carriers of the minor allele of rs11887534 had an **OR of 2.2** for developing gallstone disease
  - **P-Value:** The association was **highly significant** with a p-value of 1.4×10^{-14}

Results

Functional Implications:

- **ABCG8 Gene:** Encodes protein involved in the secretion of cholesterol into bile.
- **SNP rs11887534:** Results in an amino acid change (D19H) in the ABCG8 protein, altering its function.
- **Mechanism:** The D19H variant → Increased cholesterol secretion → Bile oversaturation → Gallstone formation.
- Genetic predisposition explains why some people develop gallstones despite a similar diet

Impact and Implication

- First **direct genetic evidence** linking ABCG8 to gallstones.
- Findings helped to better understand gallstone **pathophysiology**.
- Long-term applications:
  - **Genetic testing** to identify high-risk individuals.
  - **Targeted prevention** strategies (diet, medications).
  - Potential for new **therapies**, e.g. ABCG8 inhibitors.

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Thank you for your attention.