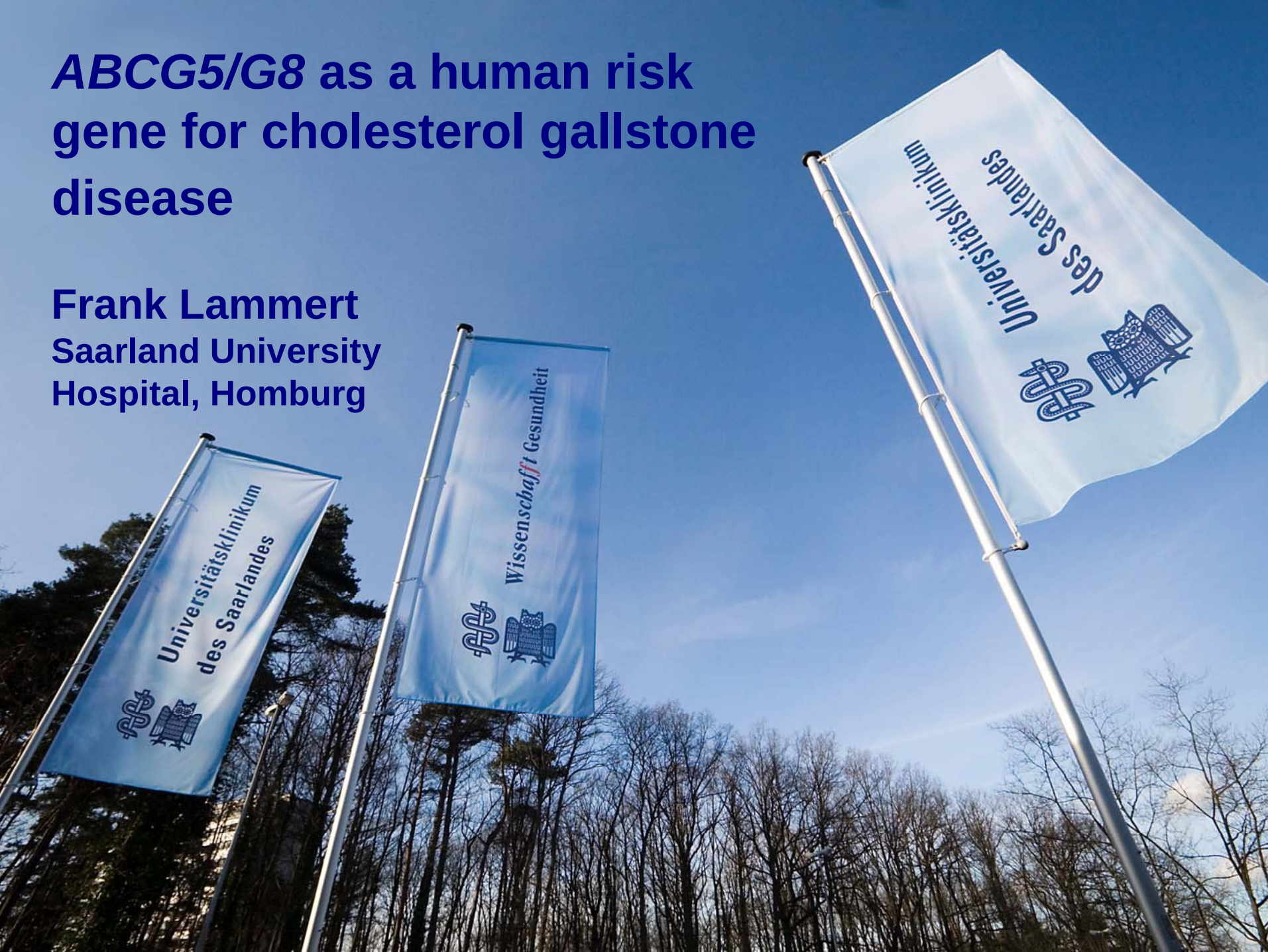
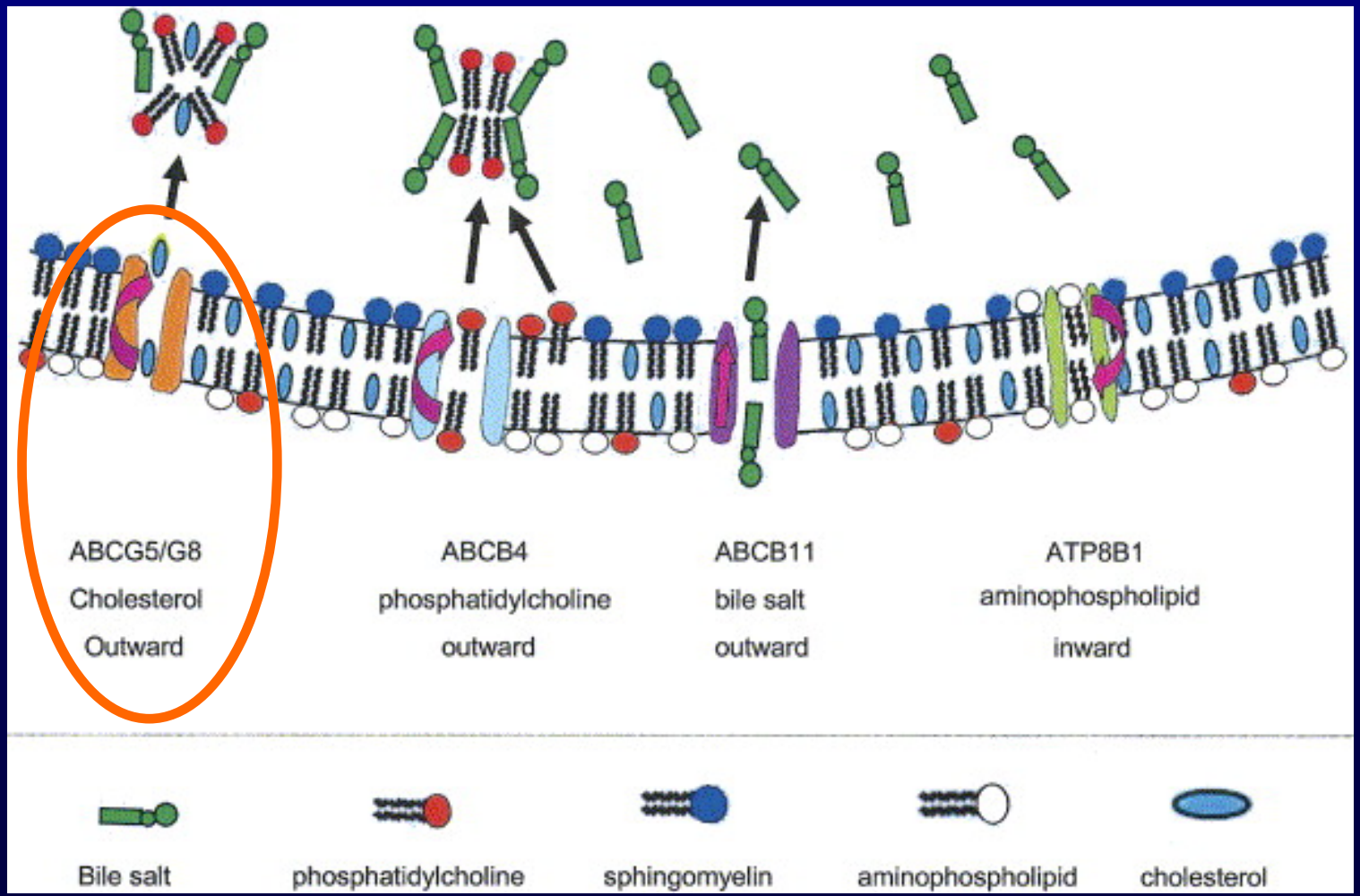
ABCG5/G8 as a human risk gene for cholesterol gallstone disease

Frank Lammert
Saarland University Hospital, Homburg



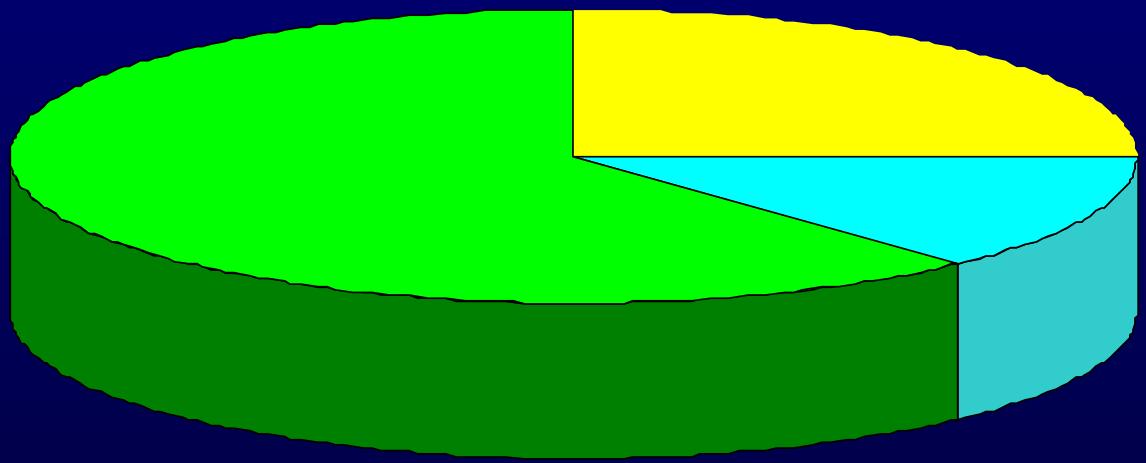
Hepatobiliary ABC Transporters



Oude Elferink et al. *Gastroenterology* (2006)

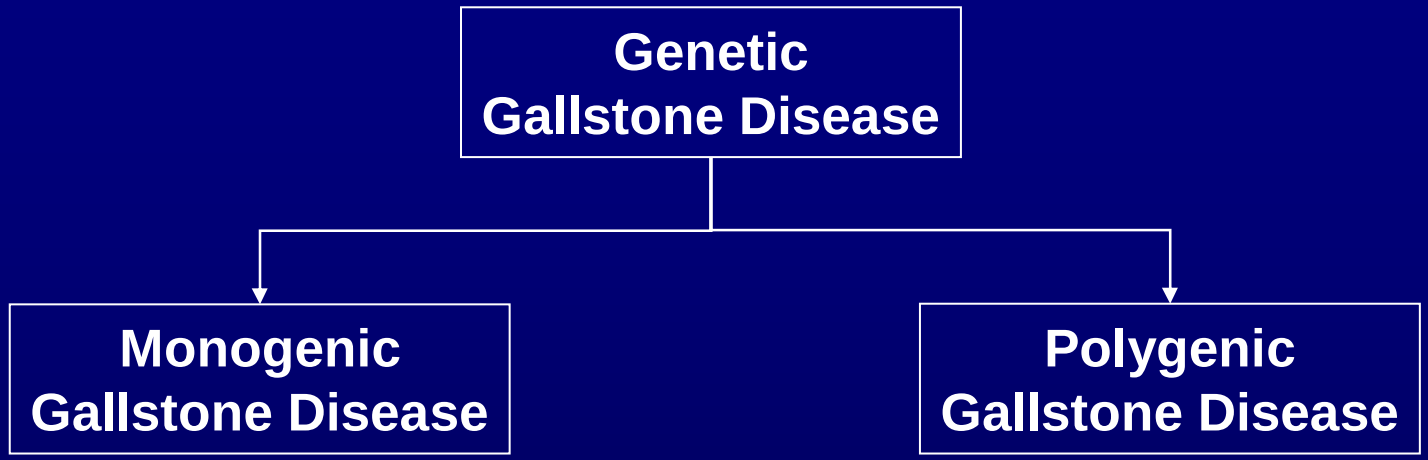
Gallstones - a Genetic Disease

Swedish Twin Study (N = 39,256)



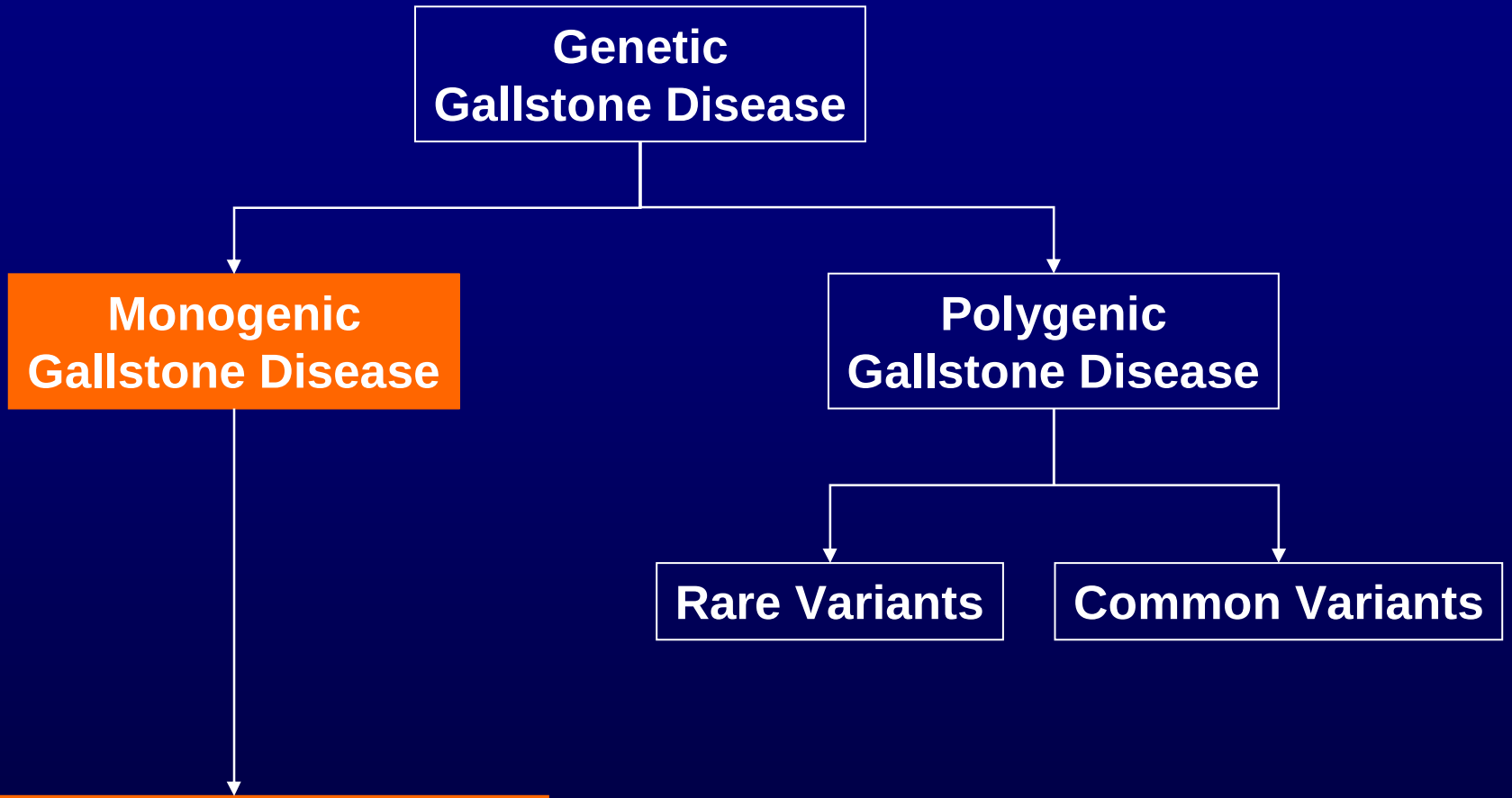
Katsika et al. *Hepatology* (2005)

Risk Genes for Cholesterol Gallstones



Wittenburg & Lammert *Semin Liver Dis* (2007)

Risk Genes for Cholesterol Gallstones



Van Mil et al.
Gastroenterology (2004)

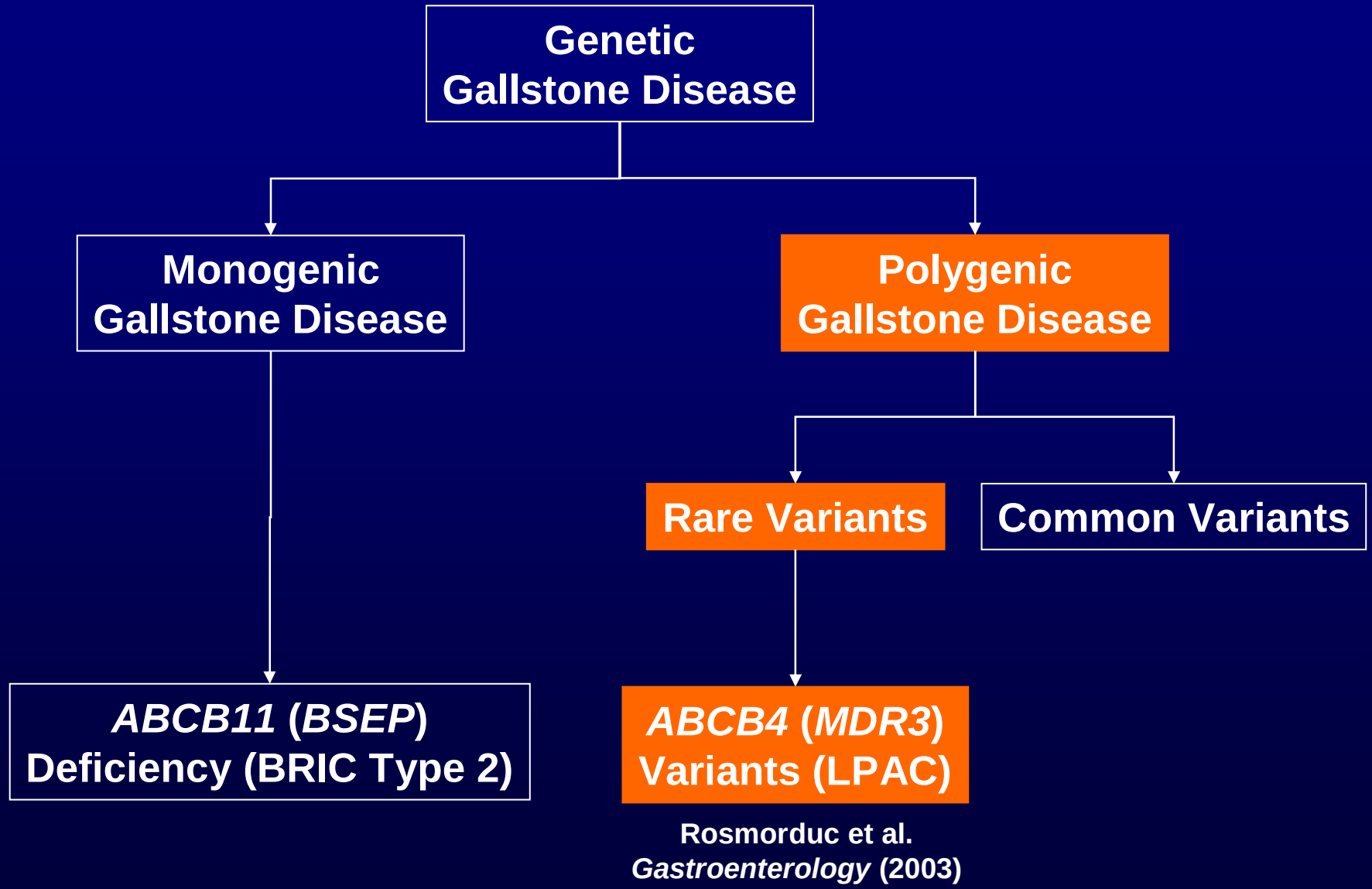
Wittenburg & Lammert *Semin Liver Dis* (2007)

Definition of Rare and Common Variants

Rare Variants	Common Variants
• Discovery by resequencing of candidate genes, preferably in early onset cases with affected relatives	• Discovery by genome-wide association studies (GWAS) in large case-control samples
• Risk allele frequency 0.1 - 1%	• Risk allele frequency > 5%
• Odds ratio mostly > 2	• Odds ratio mostly 1.2 - 1.5
• High penetrance	• Low penetrance
• Probably clinically relevant	• Contribute to understanding disease etiology

Bodmer & Bonilla *Nature Genet* (2008)

Risk Genes for Cholesterol Gallstones



Rosmorduc et al.
Gastroenterology (2003)

Gallstones: Inbred Mouse Models

Lithogenic *Paigen* Diet
(1% Cholesterol, 0.5% Cholic Acid, 15% Fat)

↓

Susceptible

C57L
PERA/Ei
SWR

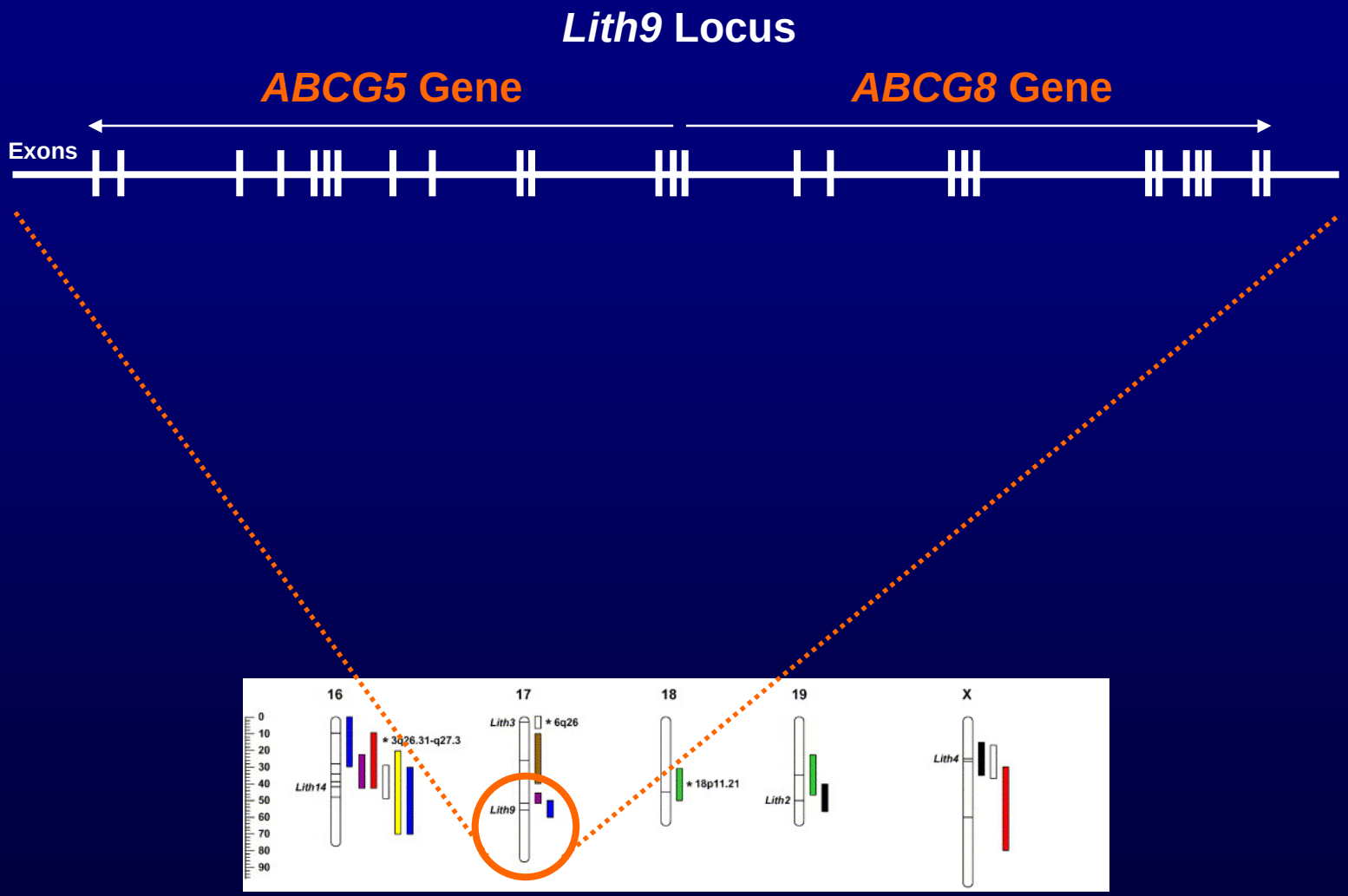
Resistant

A/J
AKR
I/LnJ

Inbred Mouse Strains
= Homozygous for all Alleles

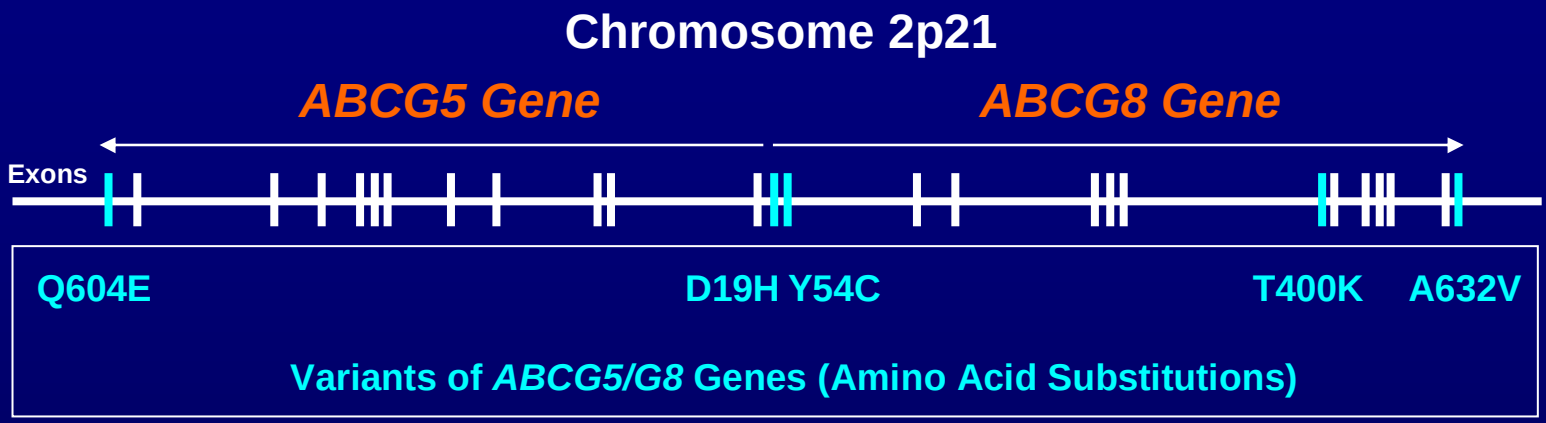
⇒ **Gallstone (*Lith*) loci determine the formation of cholesterol gallstones in mice**

ABCG5/G8 - a *Lith* Gene in Mice



Lyons & Wittenburg *Gastroenterology* (2006)
Wittenburg et al. *Gastroenterology* (2003)

ABCG5/G8: Affected Sib Pair (ASP) Study



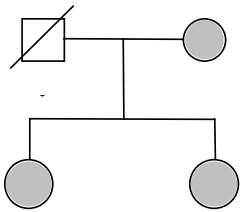
Berge et al. *J Lipid Res* (2002)

Gallstone-affected Sib Pairs (ASPs)

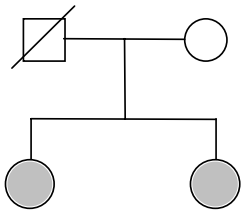
Pedigrees (N)	Affected Siblings per Pedigree	Independent ASPs per Pedigree	Total ASPs
75	2	1	75
8	3	2	16
1	4	3	3
84			94

Grünhage et al. *Hepatology* (2007)

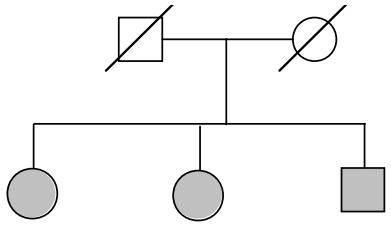
ABCG5/G8: Affected Sib Pair (ASP) Study



PED 1046



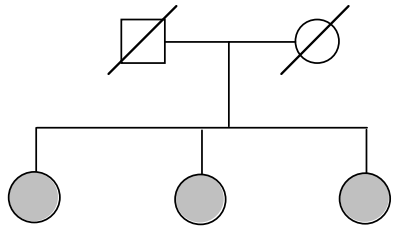
PED 1060
1063



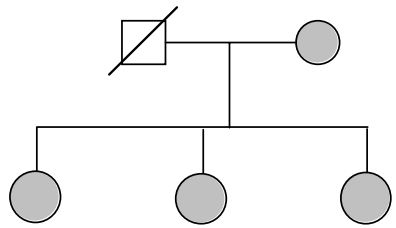
PED 1009
1014
1072

Total N	**178**
Age (median)	**55 yrs**
BMI (median)	**28 kg/m²**
Gender	
Female	**156 (88%)**
Male	**22 (12%)**
Phenotype	
Ultrasound	**41 (23%)**
Cholecystectomy	**137 (77%)**

1023 1047 1067
1025 1049 1068
1027 1051 1069
1030 1052 1070
1032 1053 1073
1033 1055 1077
1034 1056 1078
1035 1057 1079
1036 1058 1080
1037 1059 1081
1040 1061 1082
1043 1062 1084
1044 1064 1085
1045 1066



PED 1038
1071
1075
1076

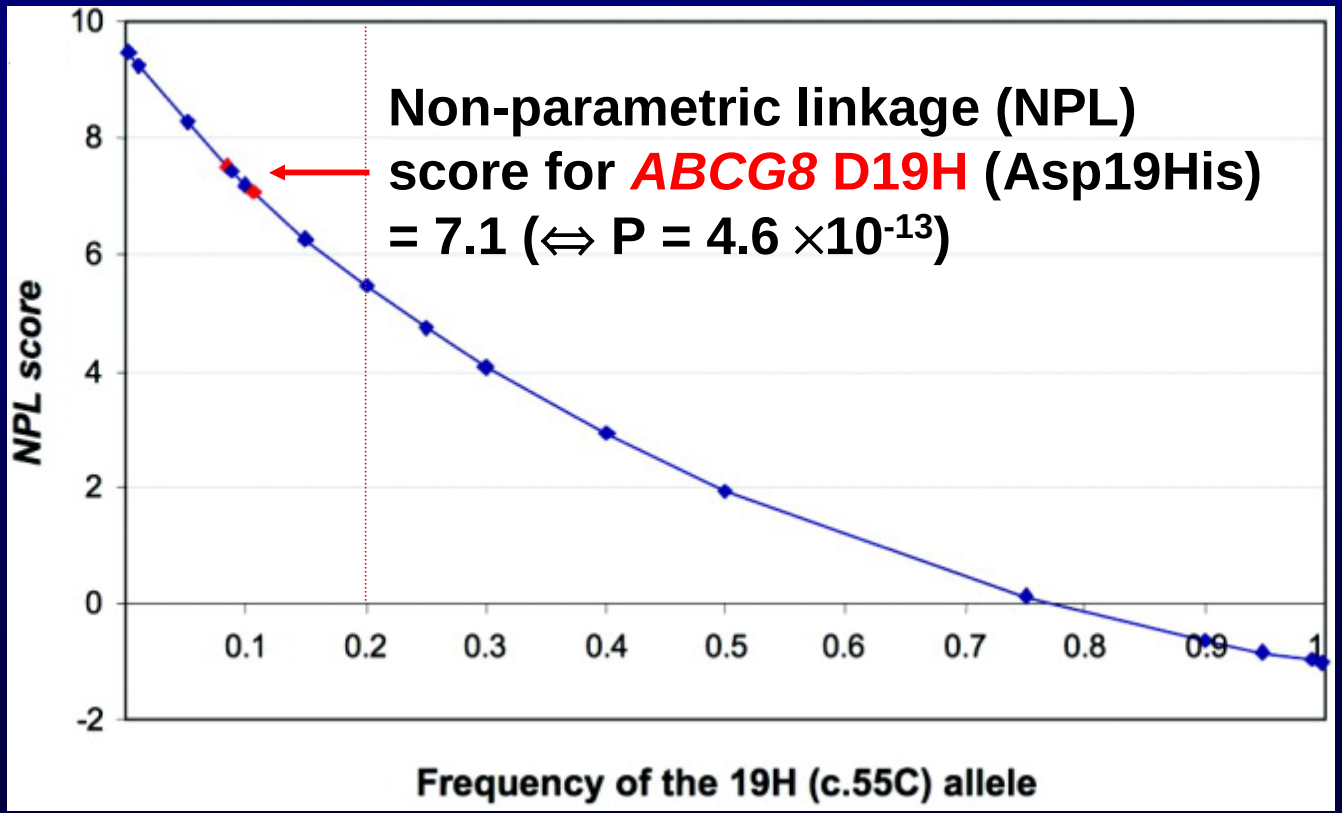


PED 1065

Grünhage et al. *Hepatology* (2007)

ABCG5/G8: Affected Sib Pair (ASP) Study

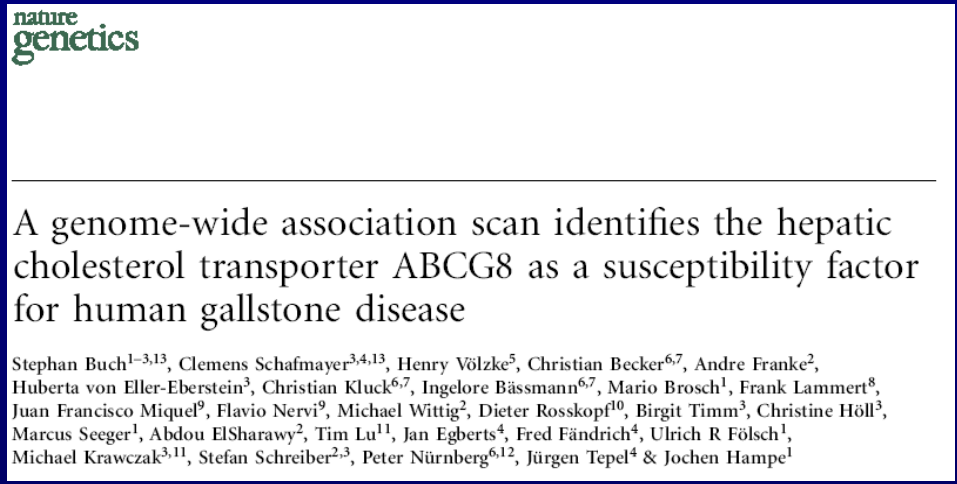
Rationale: If the disease is linked to a gene, affected sib pairs are more likely to carry the risk allele than is to be expected by chance.



Grünhage et al. *Hepatology* (2007)

ABCG8: Genome Wide Association Scan (GWAS)

Rationale: If the disease is associated with a gene, cases are more likely to carry the risk allele than controls.



nature genetics

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

Stephan Buch[1–3,13], Clemens Schafmayer[3,4,13], Henry Völzke[5], Christian Becker[6,7], Andre Franke[2], Huberta von Eller-Eberstein[3], Christian Kluck[6,7], Ingelore Bässmann[6,7], Mario Brosch[1], Frank Lammert[8], Juan Francisco Miquel[9], Flavio Nervi[9], Michael Wittig[2], Dieter Rosskopf[10], Birgit Timm[3], Christine Höll[3], Marcus Seeger[1], Abdou ElSharawy[2], Tim Lu[11], Jan Egberts[4], Fred Fändrich[4], Ulrich R Fölsch[1], Michael Krawczak[3,11], Stefan Schreiber[2,3], Peter Nürnberg[6,12], Jürgen Tepel[4] & Jochen Hampe[1]

- **Screening cohort: 280 cases and 360 controls**
- **> 380,000 Single Nucleotide Polymorphisms (SNPs)**
- **Association with *ABCG8* D19H ($P = 7.7 \times 10^{-9}$)**
- **Replication cohorts: 1.832 German and 167 Chilean patients**

Buch et al. *Nature Genet* (2007)

ABCG8 D19H and Gallstones: Summary of Studies

	Year	Population	N	Odds Ratio	Risk Allele Frequency
Buch et al.	2007	Germany Chile	1.832 167	2.2 1.9	5.0%
Grünhage et al.	2007	Romania	178	3.0	8.5%
Kuo et al.	2008	China	74	3.5	1.4%

ABCG8 - a Risk Gene for Cholesterol Gallstones in Mice and Humans

	Year	Population	N	Odds Ratio	Risk Allele Frequency
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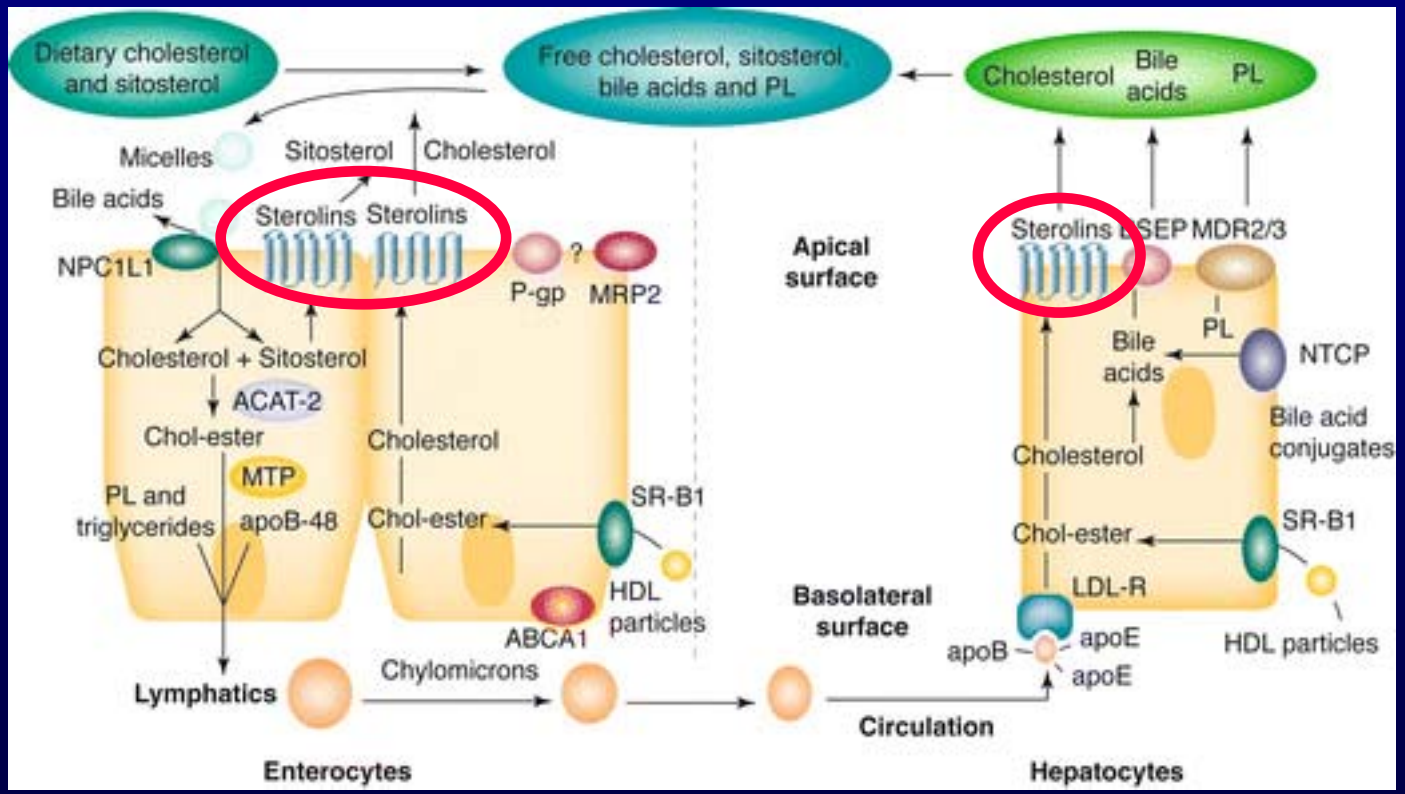
Grünhage et al.	2007	Romania	178	3.0	8.5%
Kuo et al.	2008	China	74	3.5	1.4%

- Linkage study in inbred mice
- Association and linkage studies in humans

  Population attributable fraction: 8 - 11%

Sterolins *ABCG5/G8* - Regulators of Whole Body Sterol Homeostasis

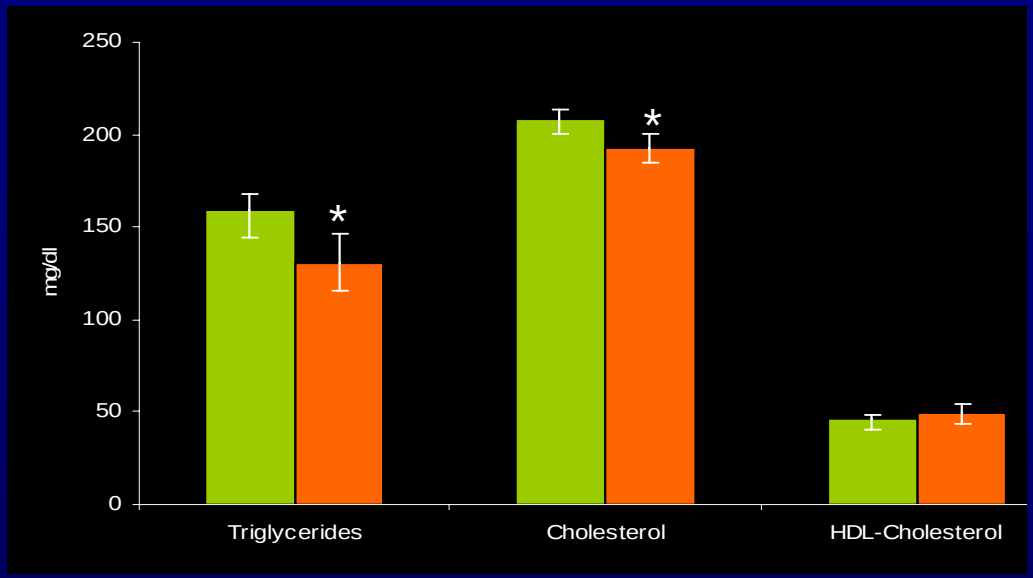


Hazard & Patel. *Pflügers Arch* (2006)

ABCG8 D19H and Serum Lipids

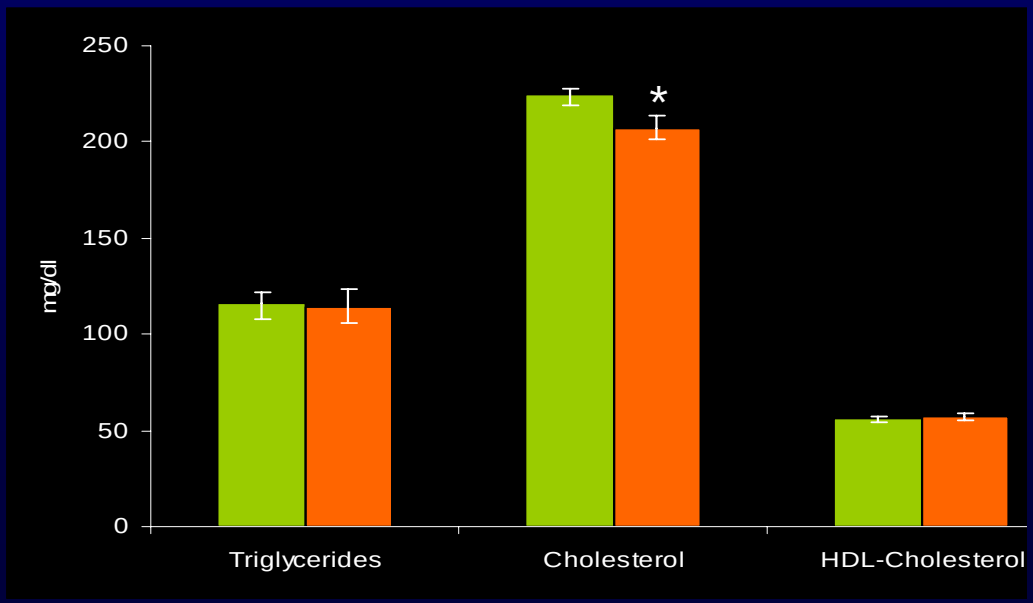
D19

D19H / 19H



Acalovschi et al.
***Eur J Intern Med* (2006)**

N = 72, *P < 0.05



Gylling et al.
***J Lipid Res* (2004)**

N = 262, *P < 0.05

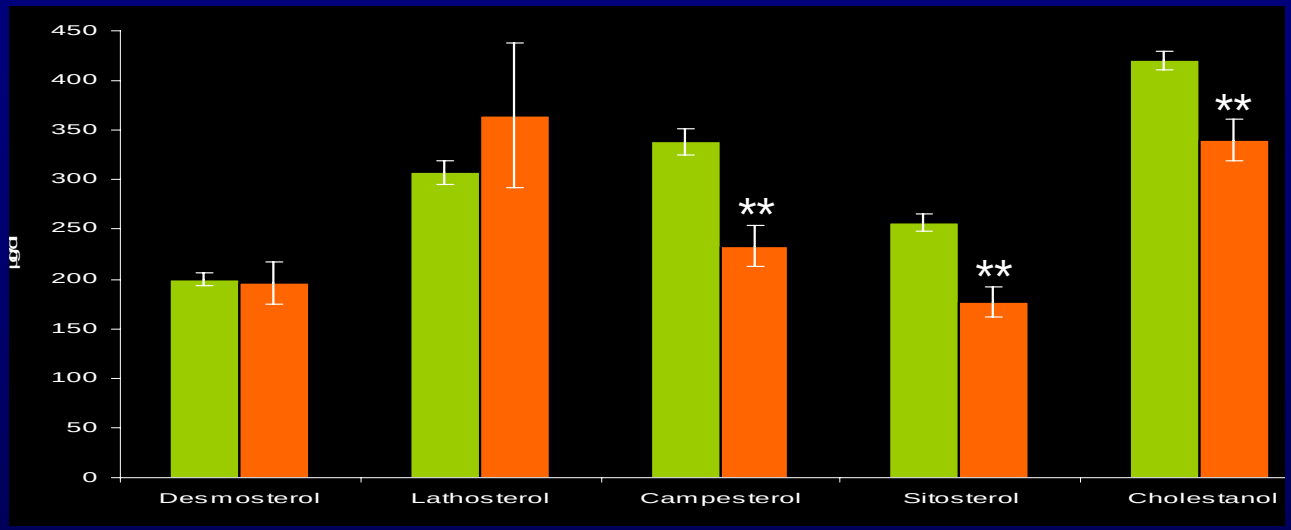
ABCG8 D19H and Noncholesterol Sterols

Cholesterol Precursors
= Cholesterol Synthesis Markers

Plant Sterols
= Cholesterol Absorption Markers

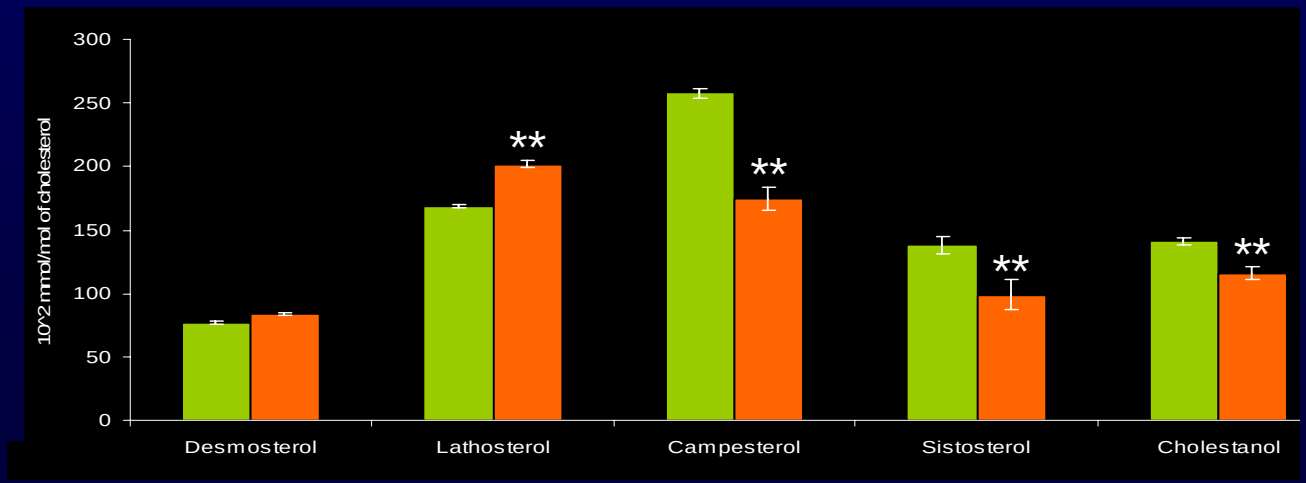
D19

19H / D19H



Berge et al.
***J Lipid Res* (2002)**

N = 142, **P < 0.01



Gylling et al.
***J Lipid Res* (2004)**

N = 262, **P < 0.01

Conclusion: The *ABCG8* D19H Variant Confers ...

- Cholesterol gallstone susceptibility
- Lower serum cholesterol levels
- Lower intestinal cholesterol absorption
- Higher hepatic cholesterol synthesis
- Better response to statins

⇒ ***ABCG8*** **D19H may represent a gain-of-function mutation that increases removal of sterols from the body**

Thank you

Monica Acalovschi
Juan F. Miquel
Dieter Lütjohann
Frank Grünhage

DFG / CONICYT