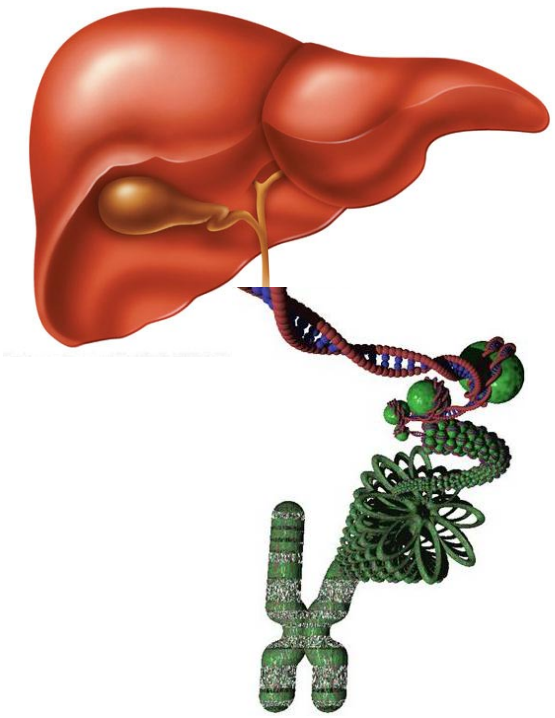


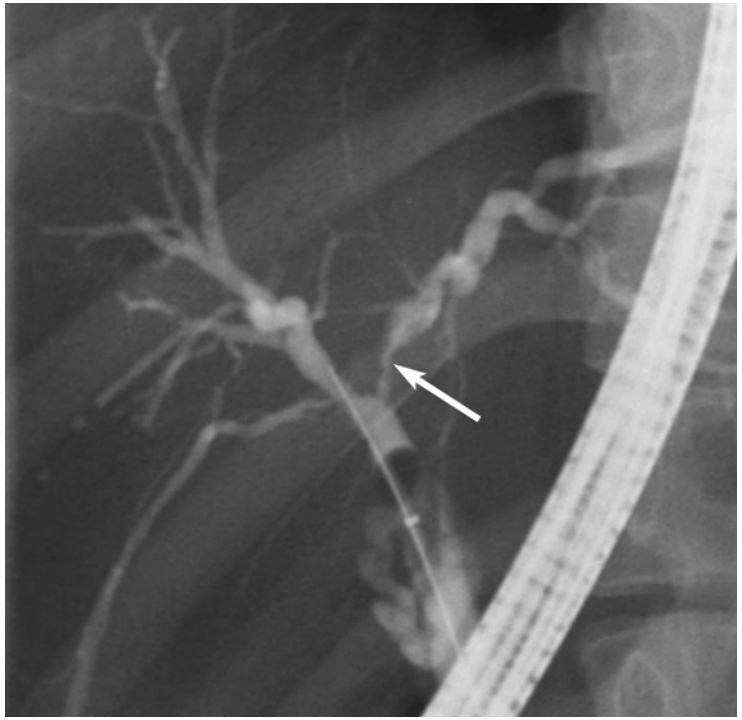
What can genetic studies do for PSC?

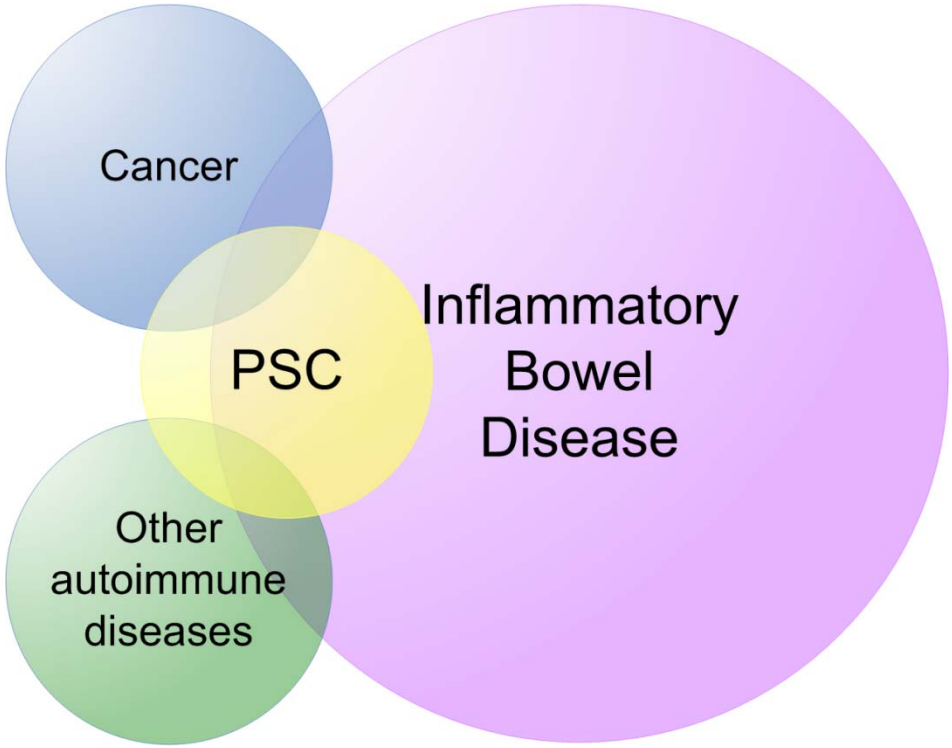
RIKSHOSPITALET

Tom Hemming Karlsen
Oslo, Norway

NOPSC

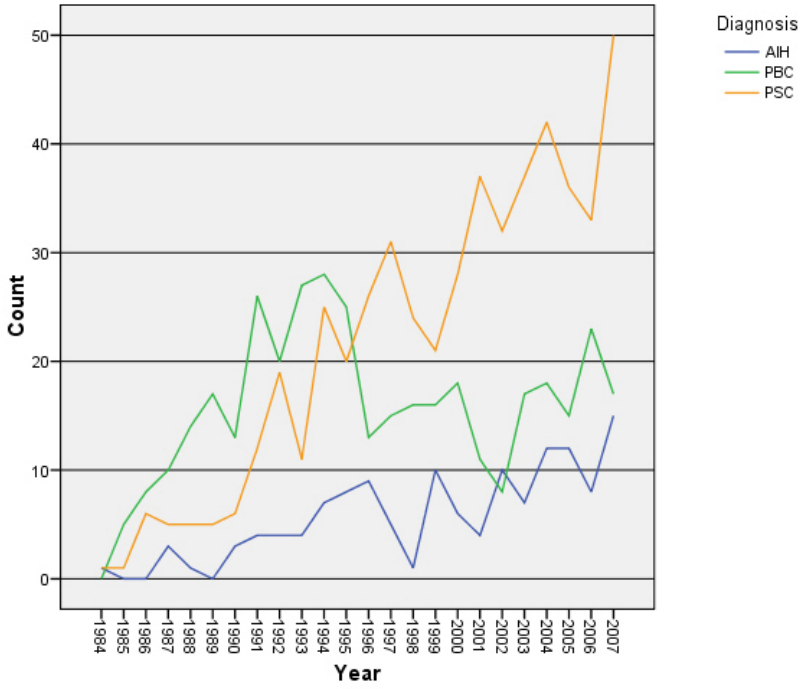
Primary sclerosing cholangitis





Why is PSC an important disease?

Diagnosis	2007 (%)	2006 (%)
Acute liver failure	8.8	11.3
Alcoholic liver cirrhosis	7.4	11.7
Biliary atresia	3.3	4.8
Budd-Chiari	0.4	2.0
Hepatocellular carcinoma	9.6	8.1
Other Malignancies	4.4	3.6
Post-hepatitis B cirrhosis	1.1	1.6
Post-hepatitis C cirrhosis	12.5	12.1
Metabolic liver disease	5.5	3.6
Missing diagnosis	1.1	2.4
Other liver disease	8.5	8.1
PBC	6.3	9.3
PSC	18.4	13.3
AIH	5.5	3.2
Cryptogenic cirrhosis	7.4	4.8



Data from the Nordic Liver Transplant Registry

Risk factors in PSC

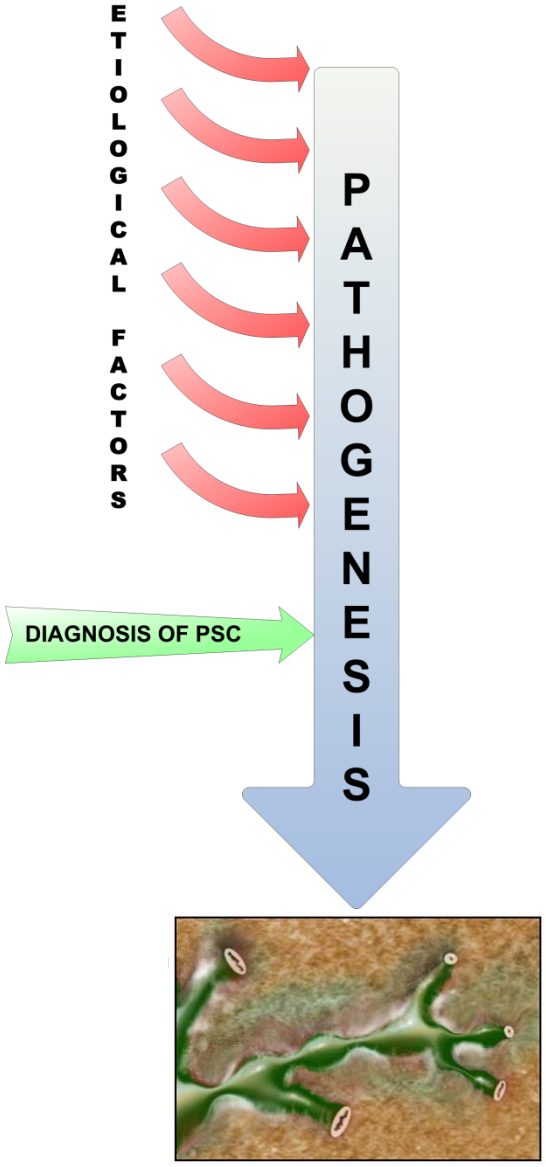


Figure: www.mayoclinic.org

Genetic:

→ ↑*80x first degree relatives*

→ *HLA genes*

→ *Other genes ?*

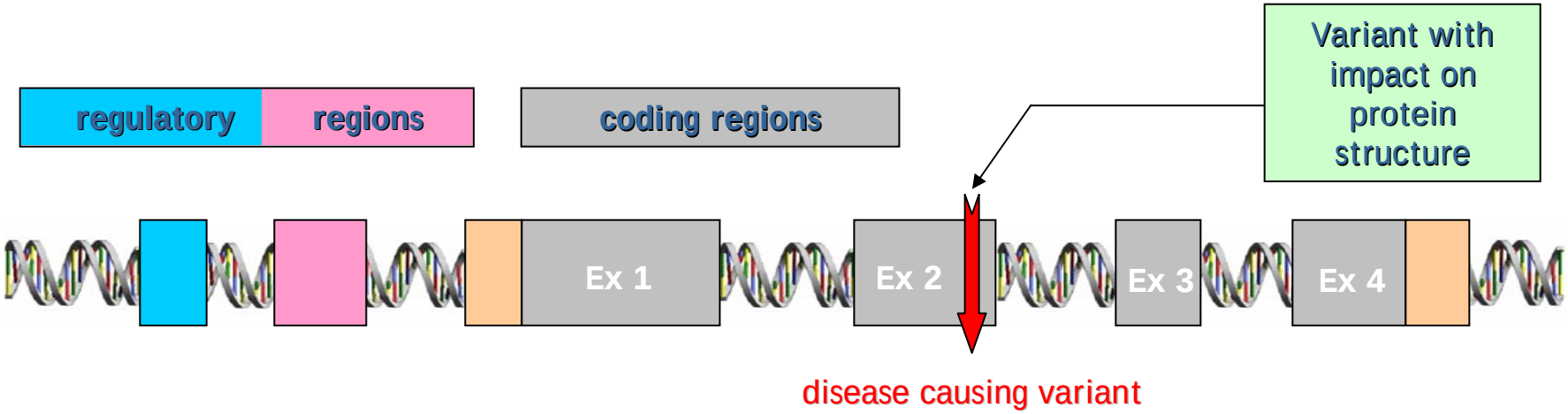
Environmental:

→ *Smoking protects*

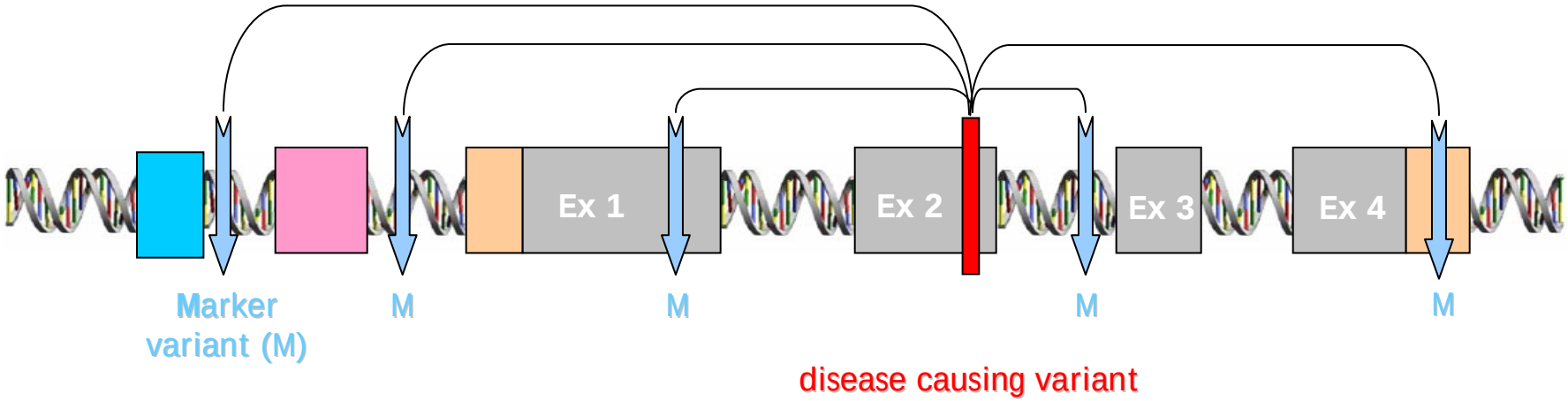
→ *Infectious trigger?*

→ *Unknown factors*

Causal variants versus genetic markers



Causal variants versus genetic markers



Topics of presentation

Genetic influence on PSC susceptibility

Genetic influence on particular characteristics of PSC (e.g. bile duct cancer, IBD, autoimmunity etc.)

Genetic influence on disease progression

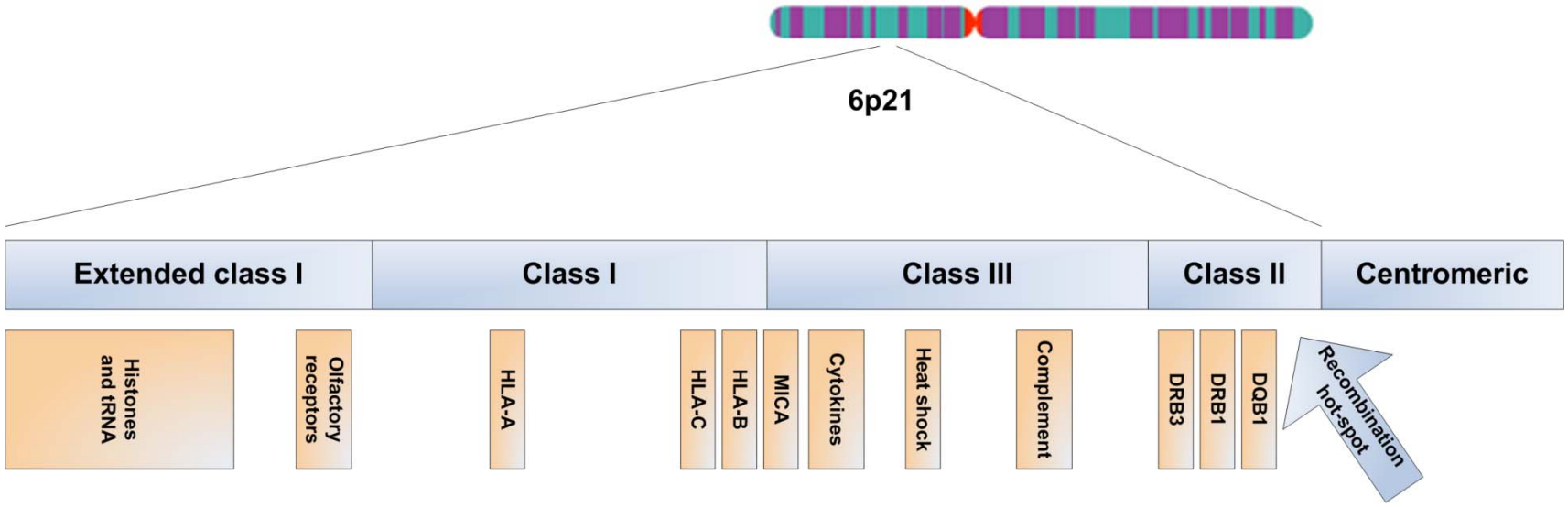
Topics of presentation

Genetic influence on PSC susceptibility

Genetic influence on particular characteristics of PSC (e.g. bile duct cancer, IBD, autoimmunity etc.)

Genetic influence on disease progression

HLA genes in PSC susceptibility



Key notions:

1982-83: HLA-B8 and DR3 (Schrumpf et al., Chapman et al.)

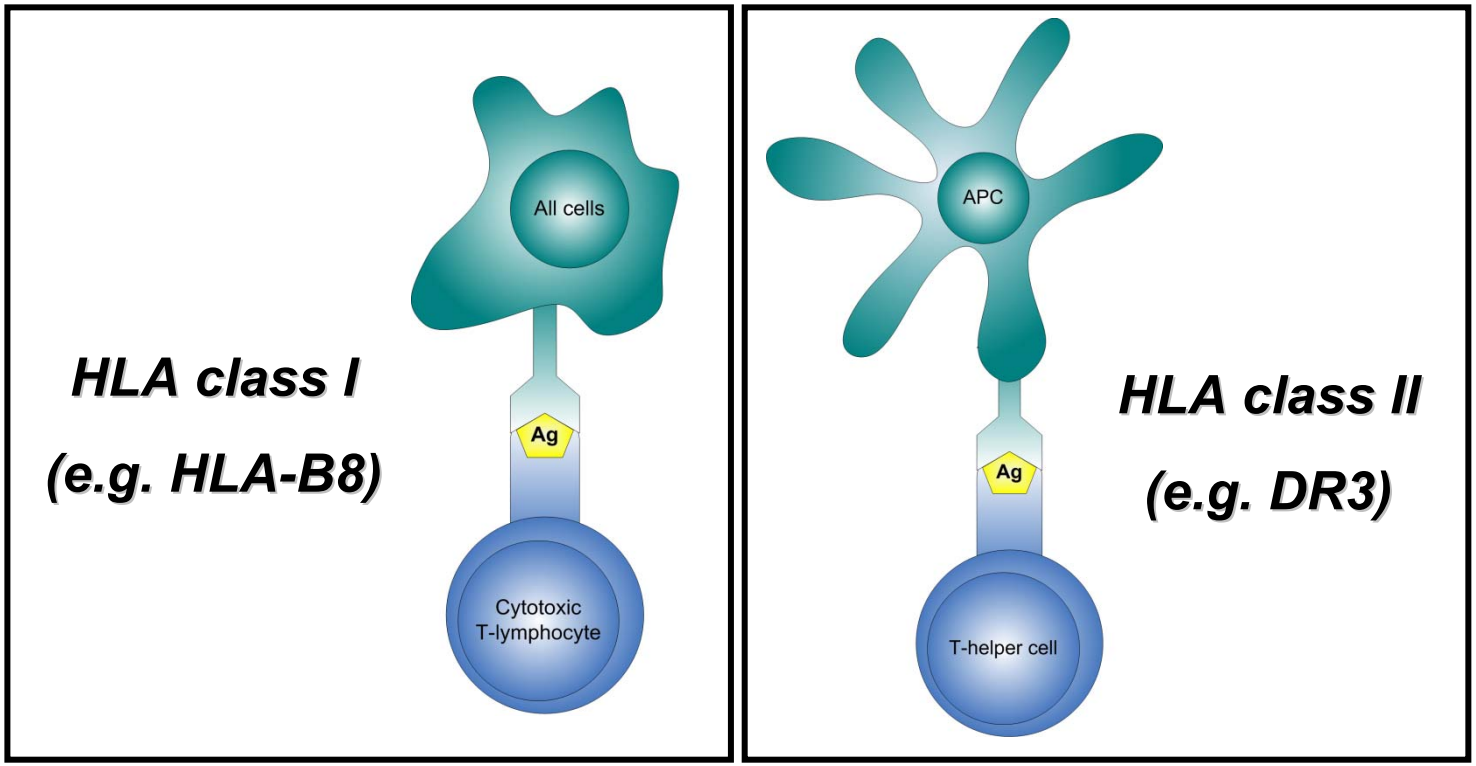
1991: Dual association of DR2 and DR3 (Donaldson et al.)

1999: Cross-European study substantiates DR3, DR2, DR6 and DR4 (Spurkland et al.)

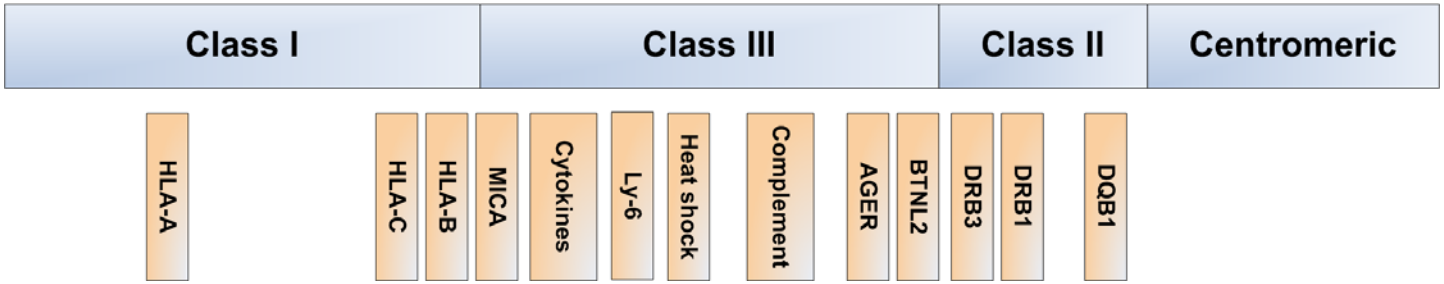
2001: MICA*008/5.1 (Norris et al., Wiencke et al.)

What does ”HLA associated” mean?

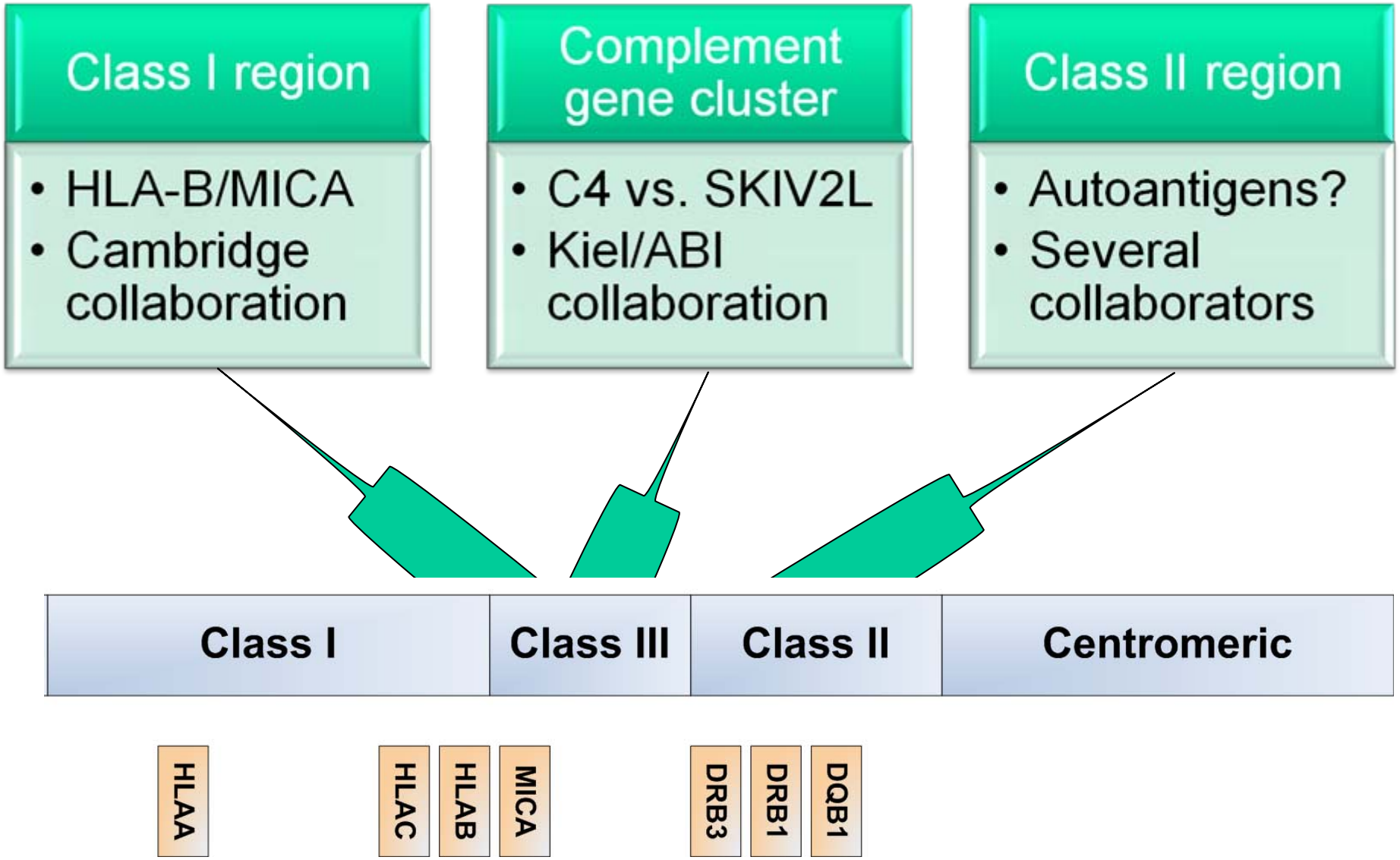
Possibility 1:



Possibility 2:



Likely scenario: multiple HLA risk factors

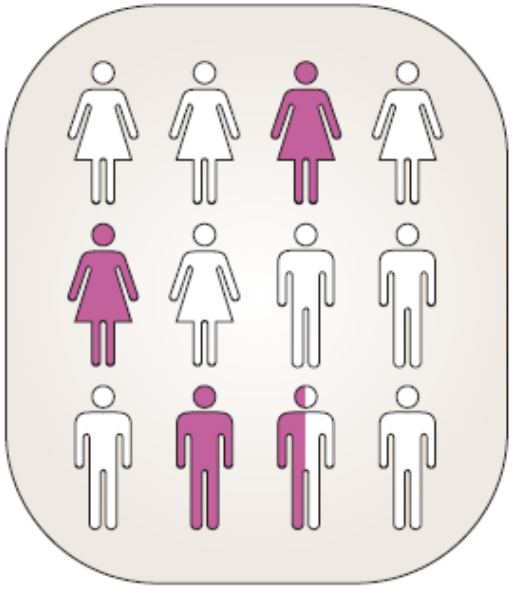


What about the rest of the genome?

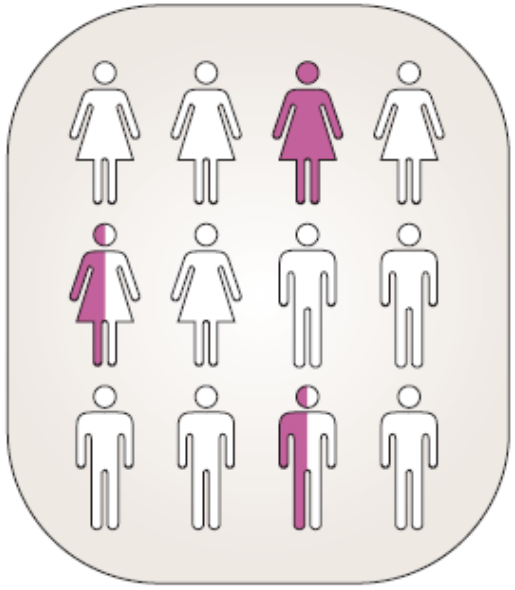
Genome-wide association studies

500.000-1.000.000 genetic markers

(e.g. A → G)

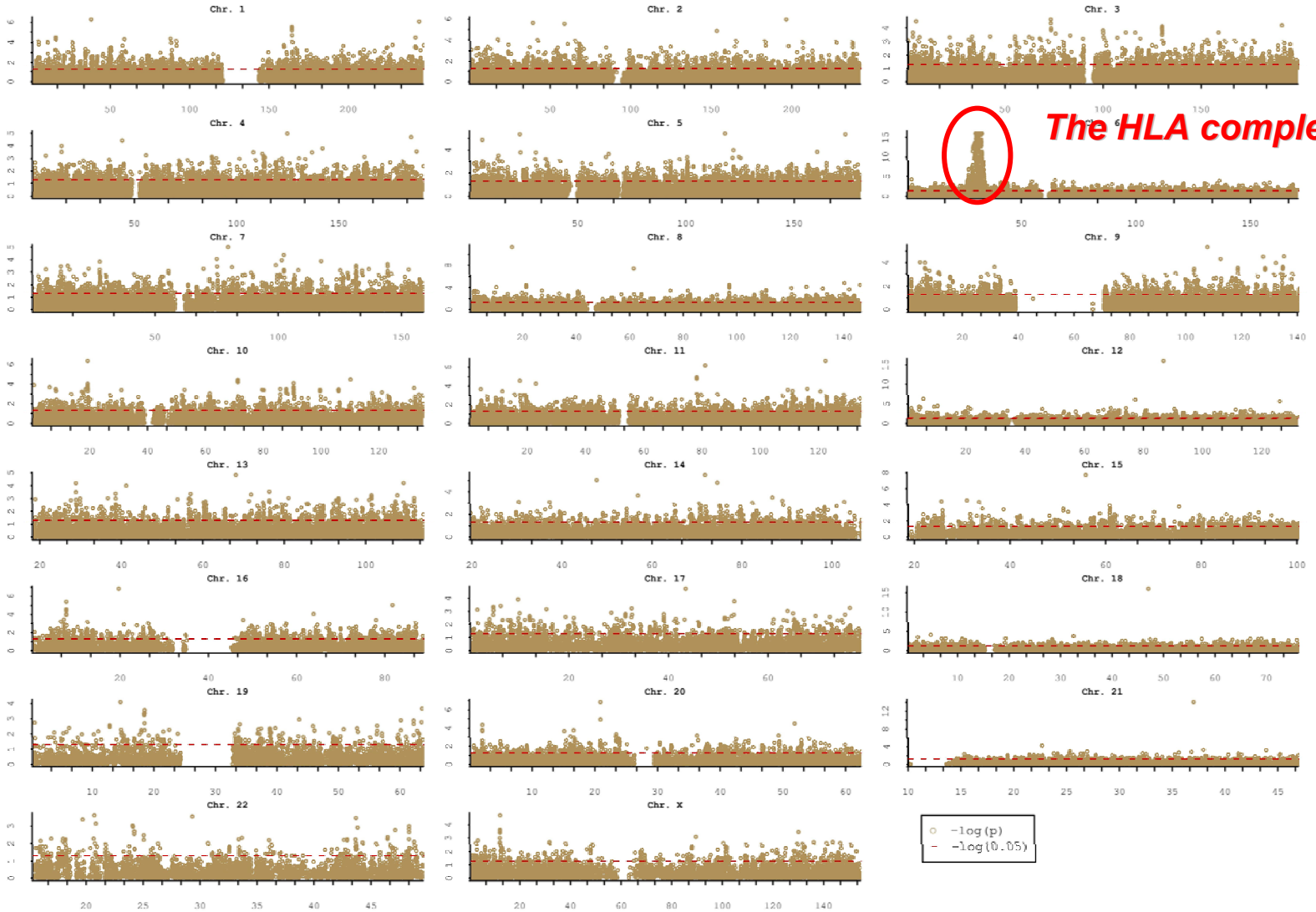


Patients



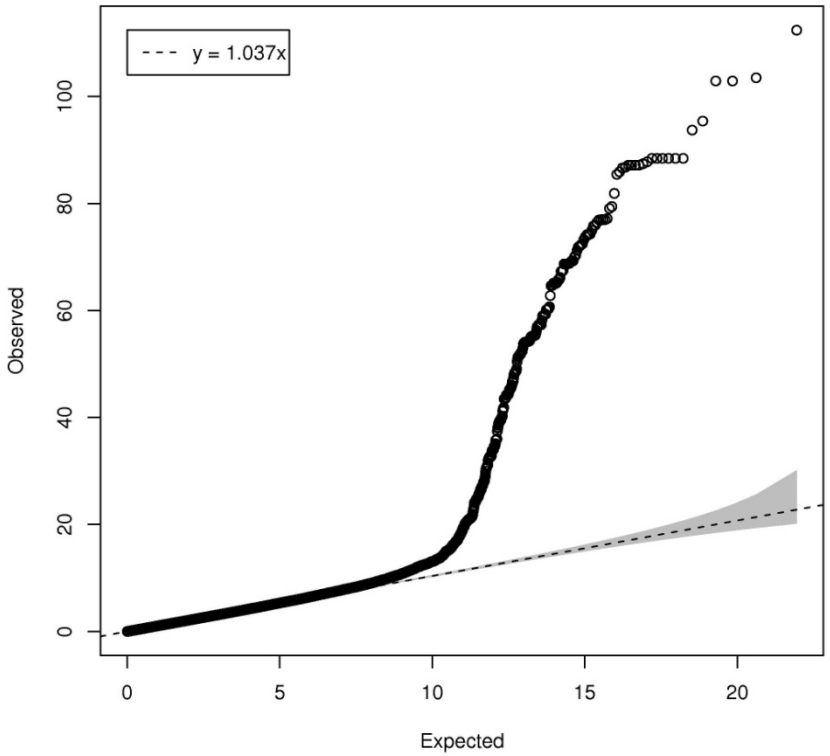
Healthy

500.000 markers in PSC GWAS

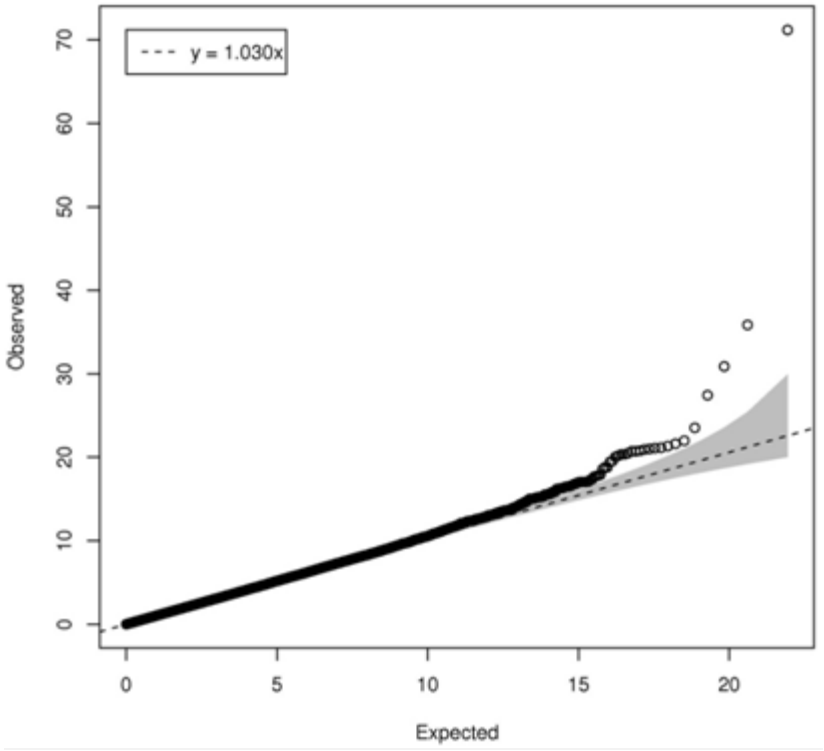


How important is actually the HLA in PSC?

Q-Q Plot of GWAS data with HLA



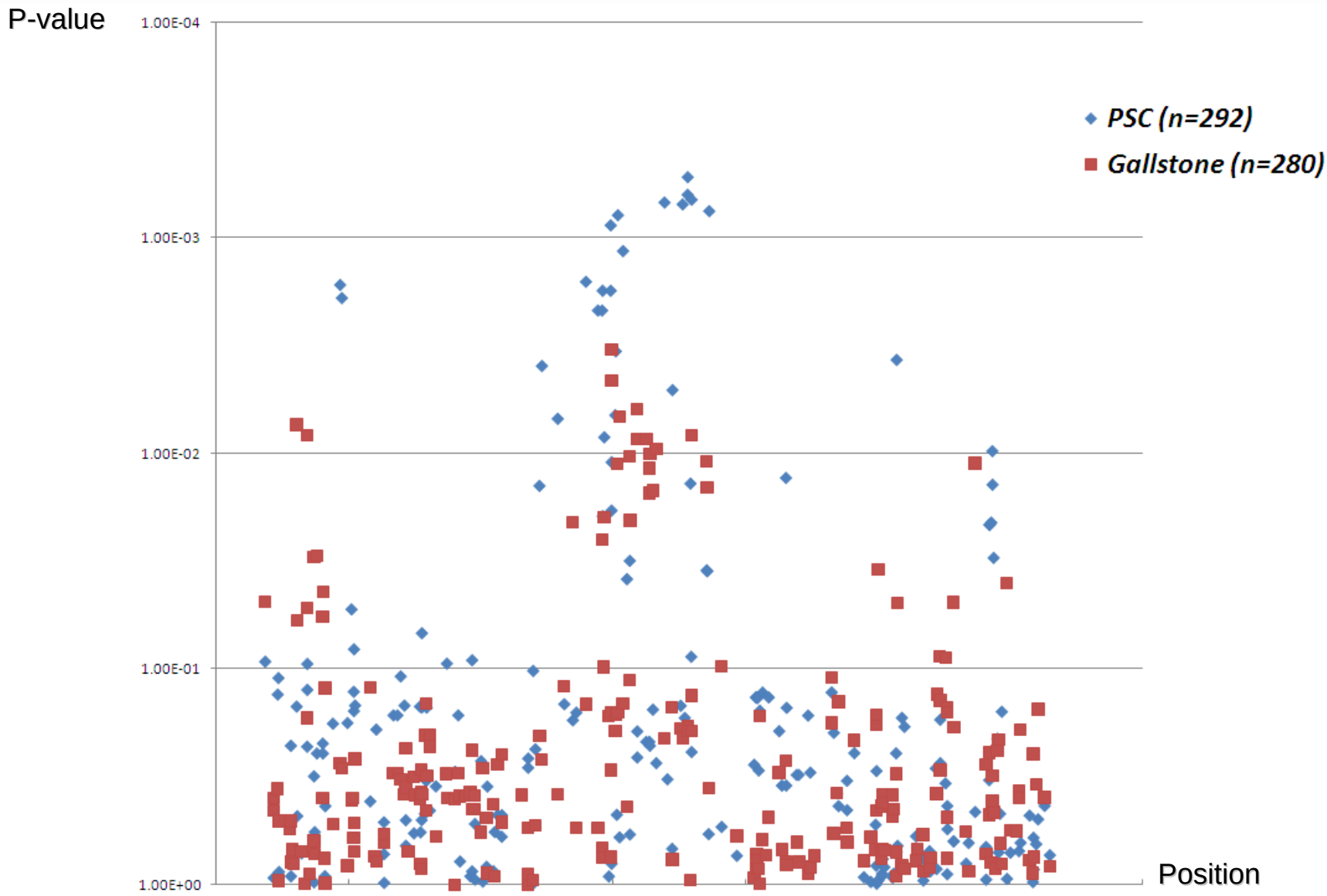
Q-Q Plot of GWAS data without HLA



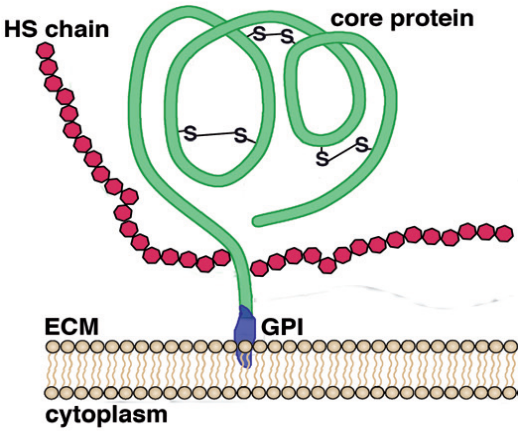
Independent verification of findings

Ethnicity	Controls	Cases
Norwegian	**298**	**289**
Dutch	365	85
Belgian	352	137
Swedish	359	132

New PSC gene on chromosome 13

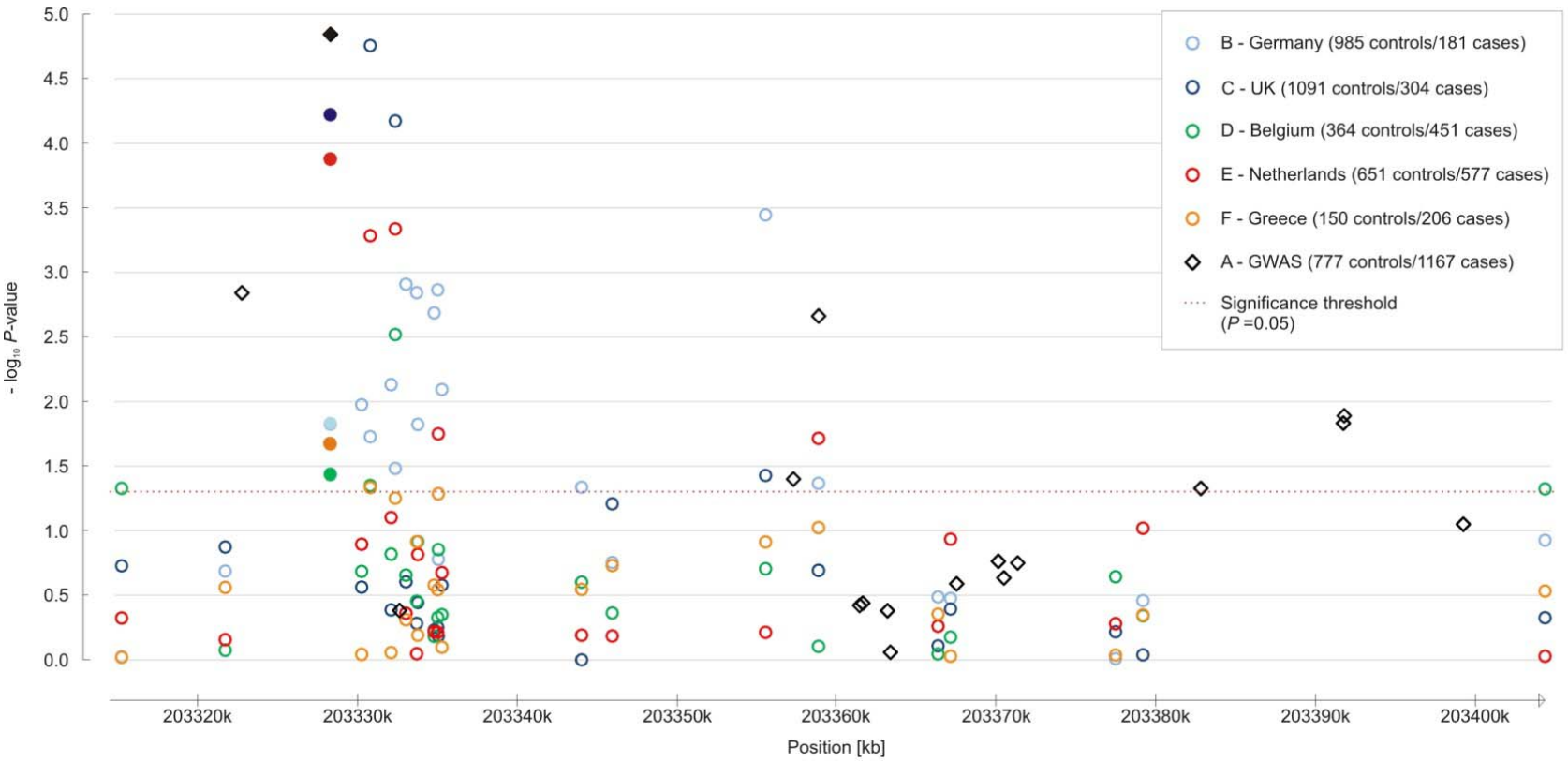


New PSC gene (GPC): unknown function



- heparane sulphate proteoglycan
- high expression in liver+colon
- fine-tuning of cell-to-cell signalling ?
- further studies needed

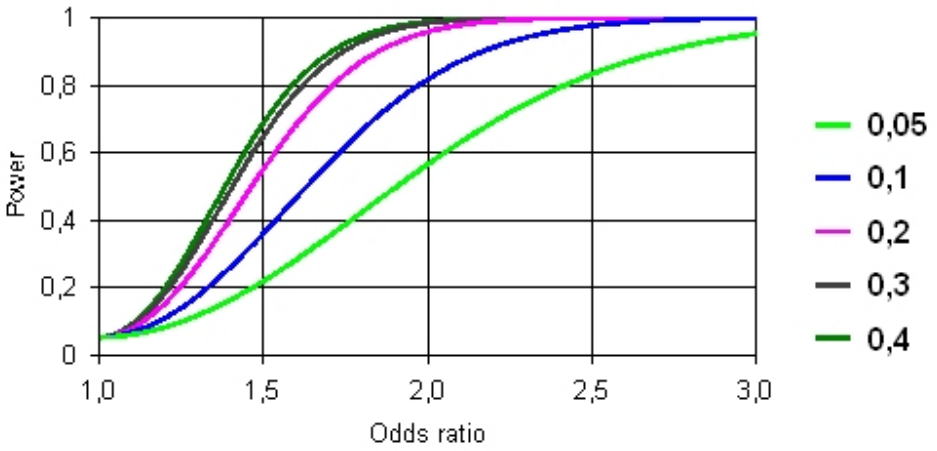
New UC gene (IL10): well-known function



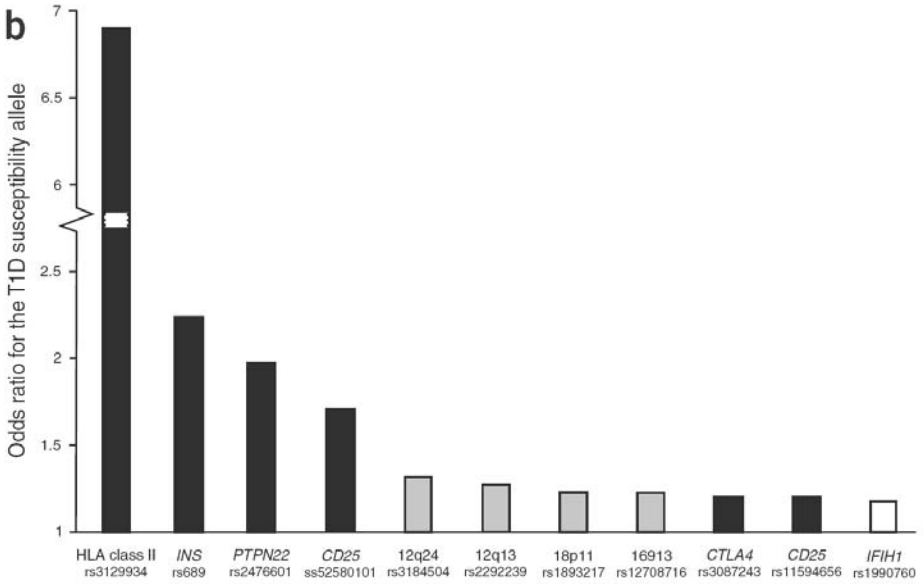
- **IL10 knockout mice: colitis**
- **IL10 delivery: ameliorates colitis**
- **Ten previous studies in UC: 8 negative, 2 ”borderline”**

Problem of genetics – statistical power

Power of PSC study



Type 1 diabetes genes



Does weak mean unimportant?

Table 1. Confirmed T2D susceptibility variants. Representative SNPs are shown for each signal with ORs and 95% CIs reported (for the Cochran-Armitage 1 df test) with respect to the risk allele (denoted in bold, with the ancestral allele underlined where known). SNPs selected for inclusion are those with the strongest evidence for association in the U.K. data sets (except in the case of *TCF7L2*, where, to maximize consistency across the data sets, rs7901695 is presented). In the case of *HHEX*, the U.K. meta-analysis combines data from rs5015480 and rs1111875 (r^2 = 1 in HapMap CEU). Because DGI and FUSION had not typed the identical SNPs in all samples, results shown for those studies feature the SNP generating the strongest association: In all cases, these were SNPs in strong LD (minimum r^2 0.95, except *TCF7L2*) and with consistent direction of effect with the SNP reported in the U.K. data (see table S3 for details). The use of different SNPs may result in slightly different estimates of *P* values and OR between the three studies. Combined estimates of the ORs were calculated by weighting the logORs of each study by the inverse of their variance.

rs	chr	position	A1	A2	Region	WTCCC 1924 cases 2938 controls OR (95% CI)	P_{add}	Replication meta-analysis 3757 cases 5346 controls OR (95% CI)	P_{add}	All UK sample meta-analysis 5681 cases 8284 controls OR (95% CI)	P_{add}	DGI 6529 cases 7252 controls OR (95% CI)	P_{add}	FUSION 2376 cases 2432 controls OR (95% CI)	P_{add}	All combined 14,586 cases 17,968 controls OR (95% CI)	P_{add}
rs8050136	16	52373776	**A**	C	*FTO*	1.27 (1.16–1.37)	2.0×10^{-8}	1.22 (1.12–1.32)	5.4×10^{-7}	1.23 (1.18–1.32)	7.3×10^{-14}	1.03 (0.91–1.17)	0.25	1.11 (1.02–1.20)	0.017	1.17 (1.12–1.22)	1.3×10^{-12}
rs10946398	6	20769013	A	**C**	*CDKAL1*	1.20 (1.10–1.31)	2.5×10^{-5}	1.14 (1.07–1.22)	8.3×10^{-5}	1.16 (1.10–1.22)	1.3×10^{-8}	1.08 (1.03–1.14)	2.4×10^{-3}	1.12 (1.03–1.22)	9.5×10^{-3}	1.12 (1.08–1.16)	4.1×10^{-11}
rs5015480	10	94455539	**C**	T	*HHEX*	1.22 (1.12–1.33)	5.4×10^{-6}	–	–	1.13 (1.07–1.19)	4.6×10^{-6}	1.14 (1.06–1.22)	1.7×10^{-4}	1.10 (1.01–1.19)	0.025	1.13 (1.08–1.17)	5.7×10^{-10}
rs1111875	10	94452862	C	**T**	*HHEX*	–	–	1.08 (1.01–1.15)	0.020								
rs10811661	9	22124094	**C**	T	*CDKN2B*	1.22 (1.09–1.37)	7.6×10^{-4}	1.18 (1.08–1.28)	1.7×10^{-4}	1.19 (1.11–1.28)	4.9×10^{-7}	1.20 (1.12–1.28)	5.4×10^{-8}	1.20 (1.07–1.36)	2.2×10^{-3}	1.20 (1.14–1.25)	7.8×10^{-15}
rs564398	9	22019547	C	**T**	*CDKN2B*	1.16 (1.07–1.27)	3.2×10^{-4}	1.12 (1.05–1.19)	8.6×10^{-4}	1.13 (1.08–1.19)	1.3×10^{-6}	1.05 (0.94–1.17)	0.5	1.13 (1.01–1.27)	0.039	1.12 (1.07–1.17)	1.2×10^{-7}
rs4402960	3	186994389	**G**	T	*IGF2BP2*	1.15 (1.05–1.25)	1.7×10^{-3}	1.09 (1.01–1.16)	0.018	1.11 (1.05–1.16)	1.6×10^{-4}	1.17 (1.11–1.23)	1.7×10^{-9}	1.18 (1.08–1.28)	2.4×10^{-4}	1.14 (1.11–1.18)	8.6×10^{-16}
rs13266634	8	118253964	**C**	T	*SLC30A8*	1.12 (1.02–1.23)	0.020	1.12 (1.04–1.19)	1.2×10^{-3}	1.12 (1.05–1.18)	7.0×10^{-5}	1.07 (1.00–1.16)	0.047	1.18 (1.09–1.29)	7.0×10^{-5}	1.12 (1.07–1.16)	5.3×10^{-8}
rs7901695	10	114744078	**C**	T	*TCF7L2*	1.37 (1.25–1.49)	6.7×10^{-13}	–	–	–	–	1.38 (1.31–1.46)	2.3×10^{-31}	1.34 (1.21–1.49)	1.4×10^{-8}	1.37 (1.31–1.43)	1.0×10^{-48}
rs5215	11	17365206	C	**T**	*KCNJ11*	1.15 (1.05–1.25)	1.3×10^{-3}	–	–	–	–	1.15 (1.09–1.21)	1.0×10^{-7}	1.11 (1.02–1.20)	0.014	1.14 (1.10–1.19)	5.0×10^{-11}
rs1801282	3	12368125	**C**	G	*PPARG*	1.23 (1.09–1.41)	1.3×10^{-3}	–	–	–	–	1.09 (1.01–1.16)	0.019	1.20 (1.07–1.33)	1.4×10^{-3}	1.14 (1.08–1.20)	1.7×10^{-6}

1 JUNE 2007 VOL 316 SCIENCE www.sciencemag.org

PPARG in type 2 diabetes: only ”gene” relevant to therapy (yet)

Topics of presentation

Genetic influence on PSC susceptibility

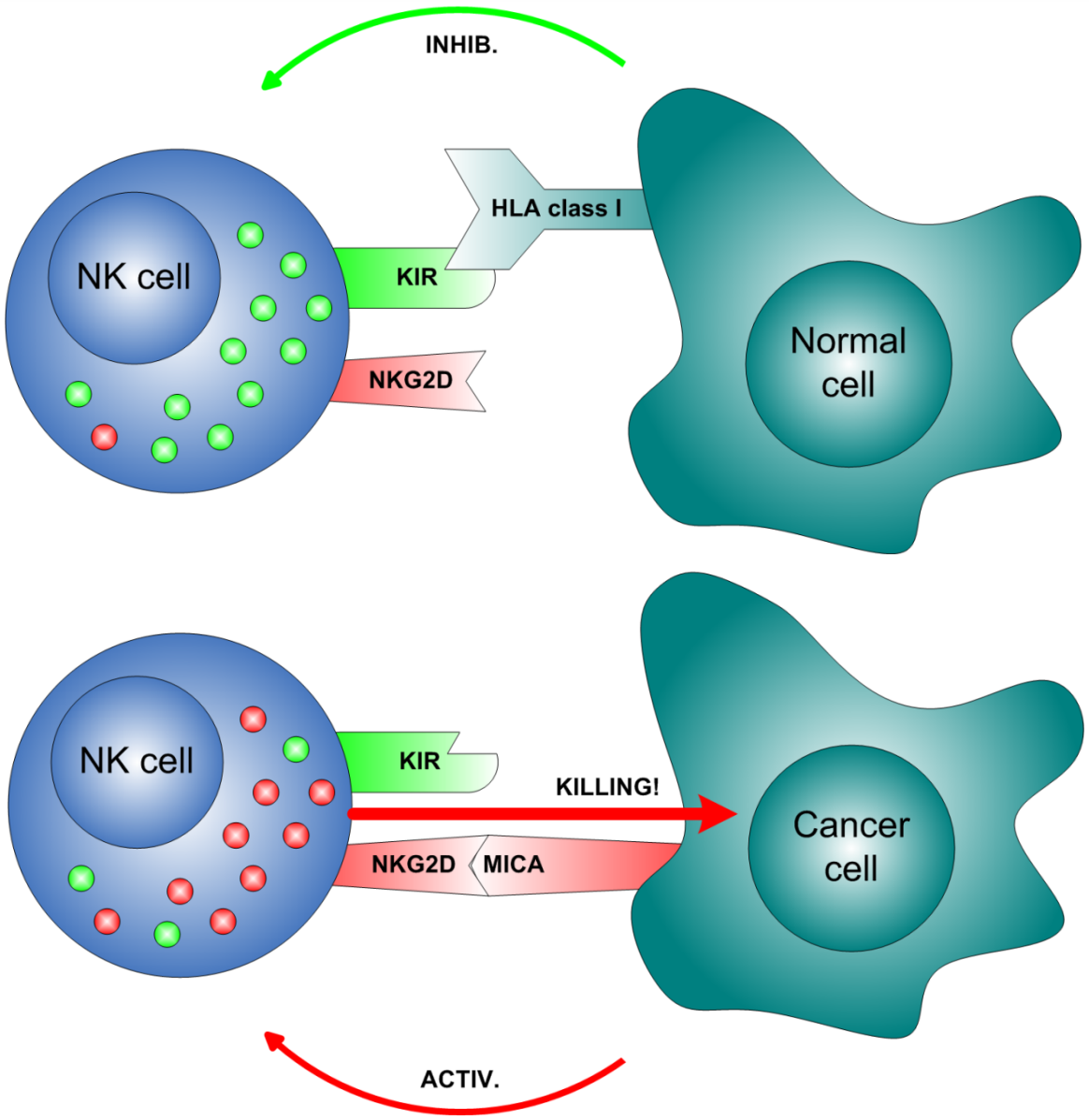
Genetic influence on particular characteristics of PSC (e.g. bile duct cancer, IBD, autoimmunity etc.)

Genetic influence on disease progression

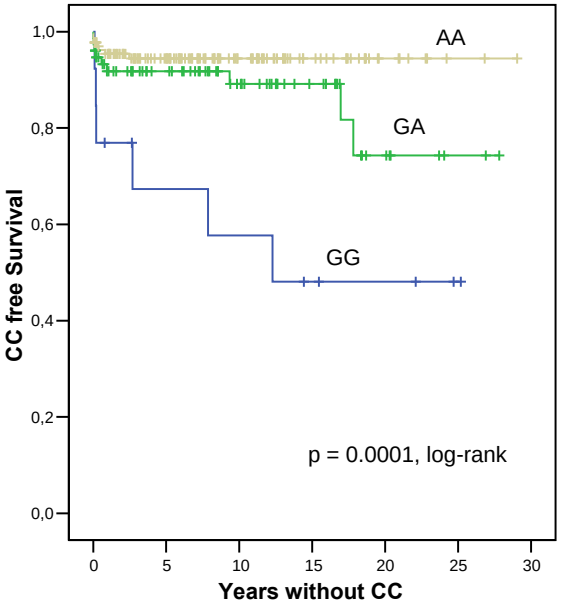
Cancer surveillance by natural killer cells

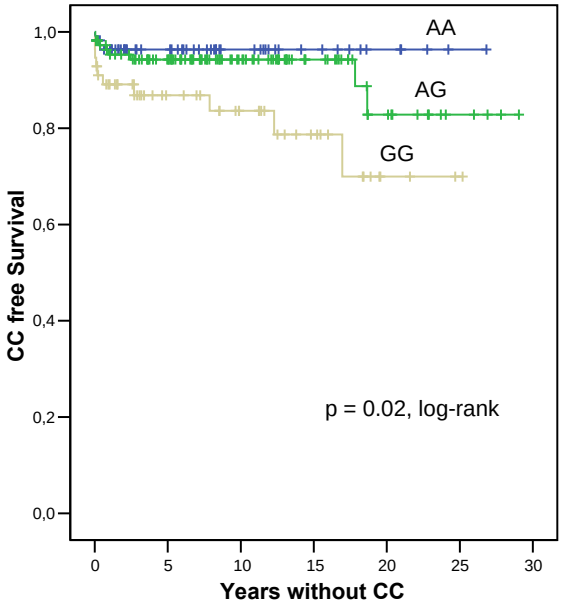
Normal situation

Cancer



Protection by high-cytotoxicity NKG2D variants





Carriership for one or more risk variants:

94% of the patients with bile duct cancer
75% of the remaining patients

Hypothethical test:

Sensitivity: **94%**
Specificity: **26%**
Positive predictive value: **17%**
Negative predictive value: **96%**

Topics of presentation

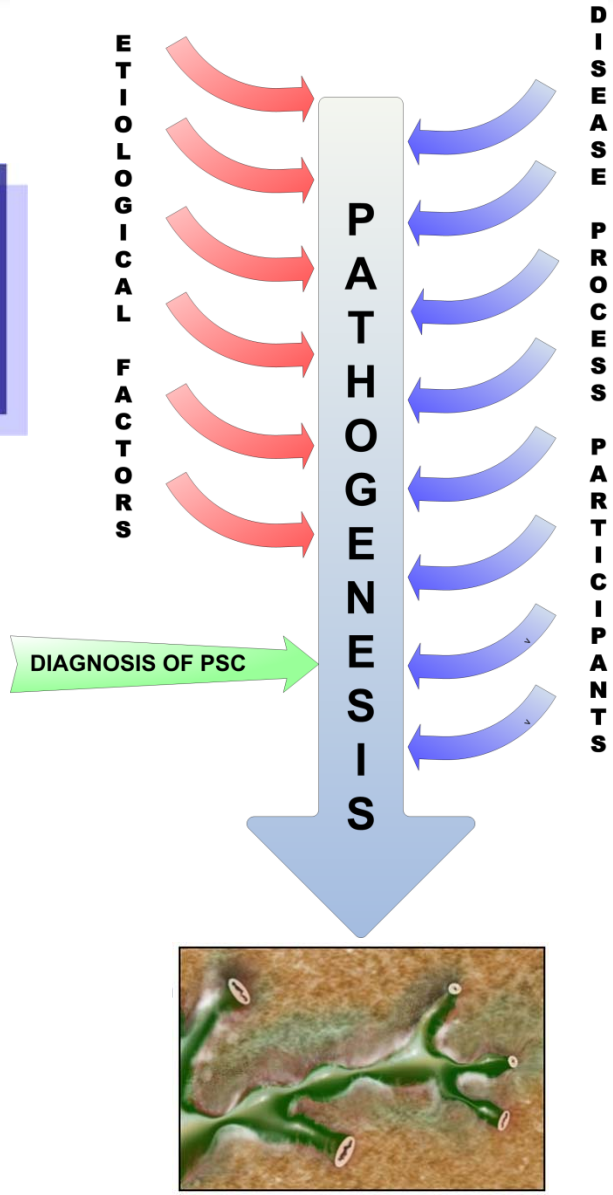
Genetic influence on PSC susceptibility

Genetic influence on particular characteristics of PSC (e.g. bile duct cancer, IBD, autoimmunity etc.)

Genetic influence on disease progression

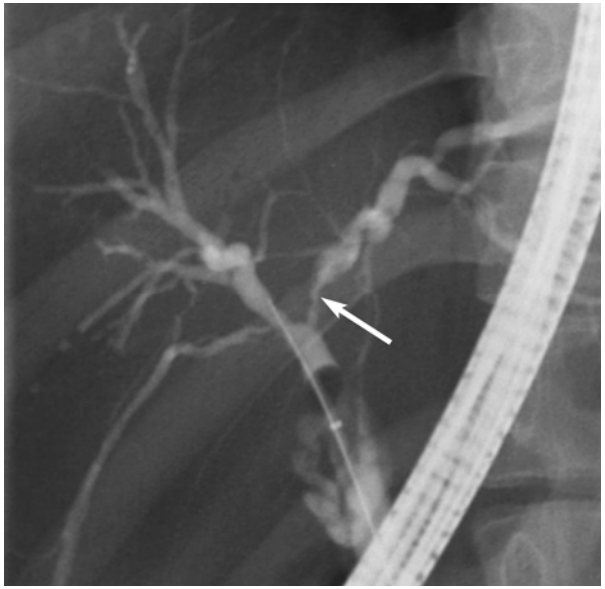
Genetic modifiers of PSC progression

Genetic factors
=
"Susceptibility genes"

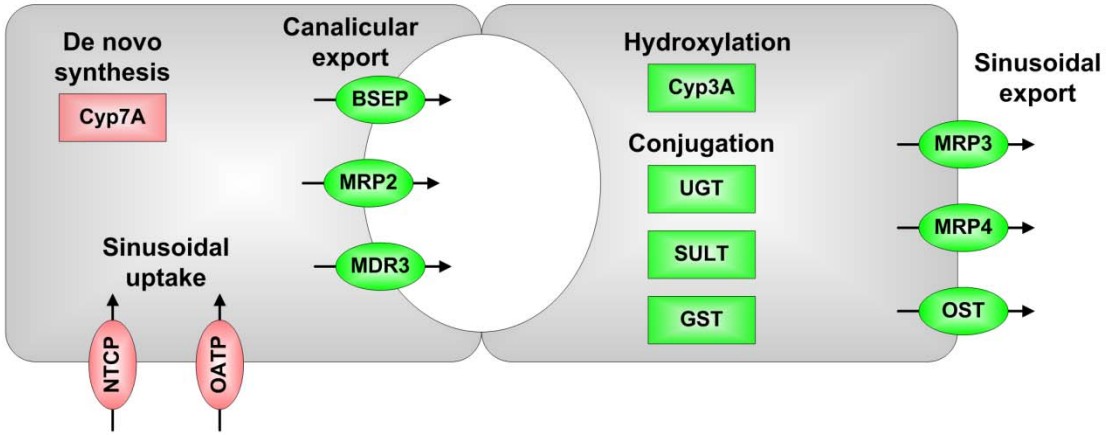


Genetic factors
=
"Modifier genes"

Adaption to accumulation of toxic bile acids



Liver cell in cholestasis:



PXR/SXR regulates adaptive mechanisms

The nuclear receptor PXR is a lithocholic acid sensor that protects against liver toxicity

Jeff L. Staudinger*†, Bryan Goodwin*, Stacey A. Jones*, Diane Hawkins-Brown‡, Kathleen I. MacKenzie§, Anne LaTour¶, Yaping Liu‖, Curtis D. Klaassen‖, Kathleen K. Brown**, John Reinhard§, Timothy M. Willson††, Beverly H. Koller¶, and Steven A. Kliewer*‡‡

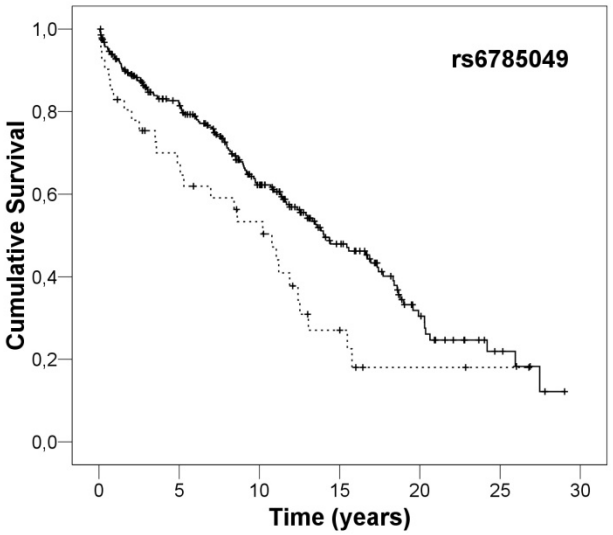
An essential role for nuclear receptors SXR/PXR in detoxification of cholestatic bile acids

Wen Xie*, Anna Radominska-Pandya†, Yanhong Shi*, Cynthia M. Simon*, Michael C. Nelson*, Erwin S. Ong*, David J. Waxman‡, and Ronald M. Evans*§¶

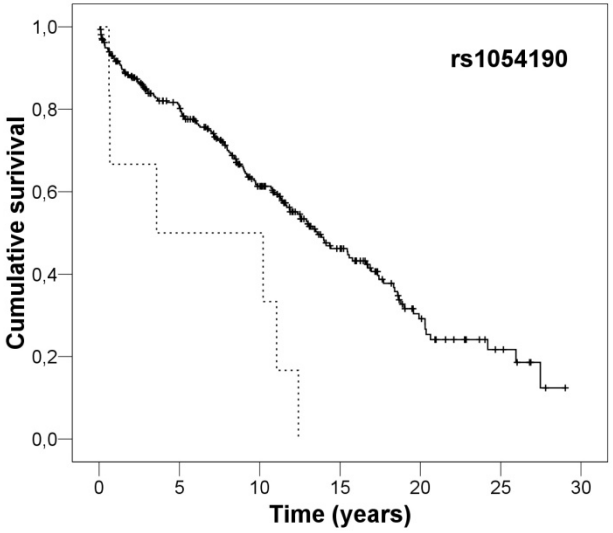
Nuclear receptors constitutive androstane receptor and pregnane X receptor ameliorate cholestatic liver injury

Catherine A. M. Stedman*†, Christopher Liddle*†, Sally A. Coulter*†, Junichiro Sonoda‡, Jacqueline G. A. Alvarez‡, David D. Moore§, Ronald M. Evans‡, and Michael Downes‡¶

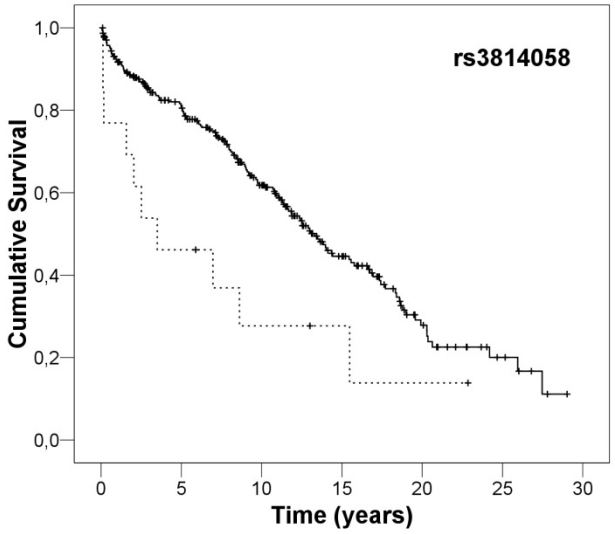
Genetic variants of SXR/PXR influence survival



Median 10.8 vs 14.0 yrs (p=0.01)

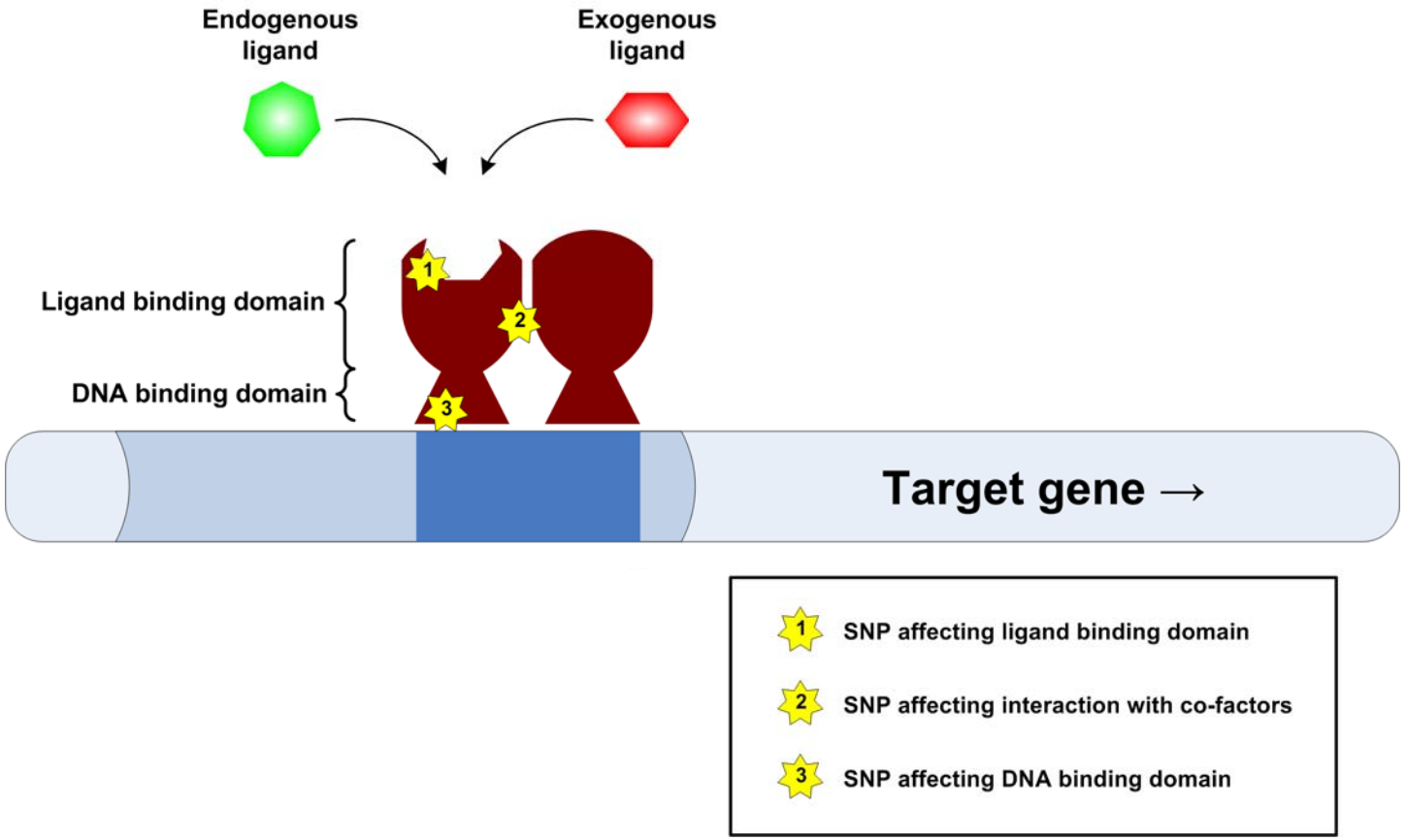


Median 3.6 vs 13.6 yrs (p=0.004)



Median 3.5 vs 13.3 yrs (p=0.01)

SXR is activated by drugs, not only bile acids



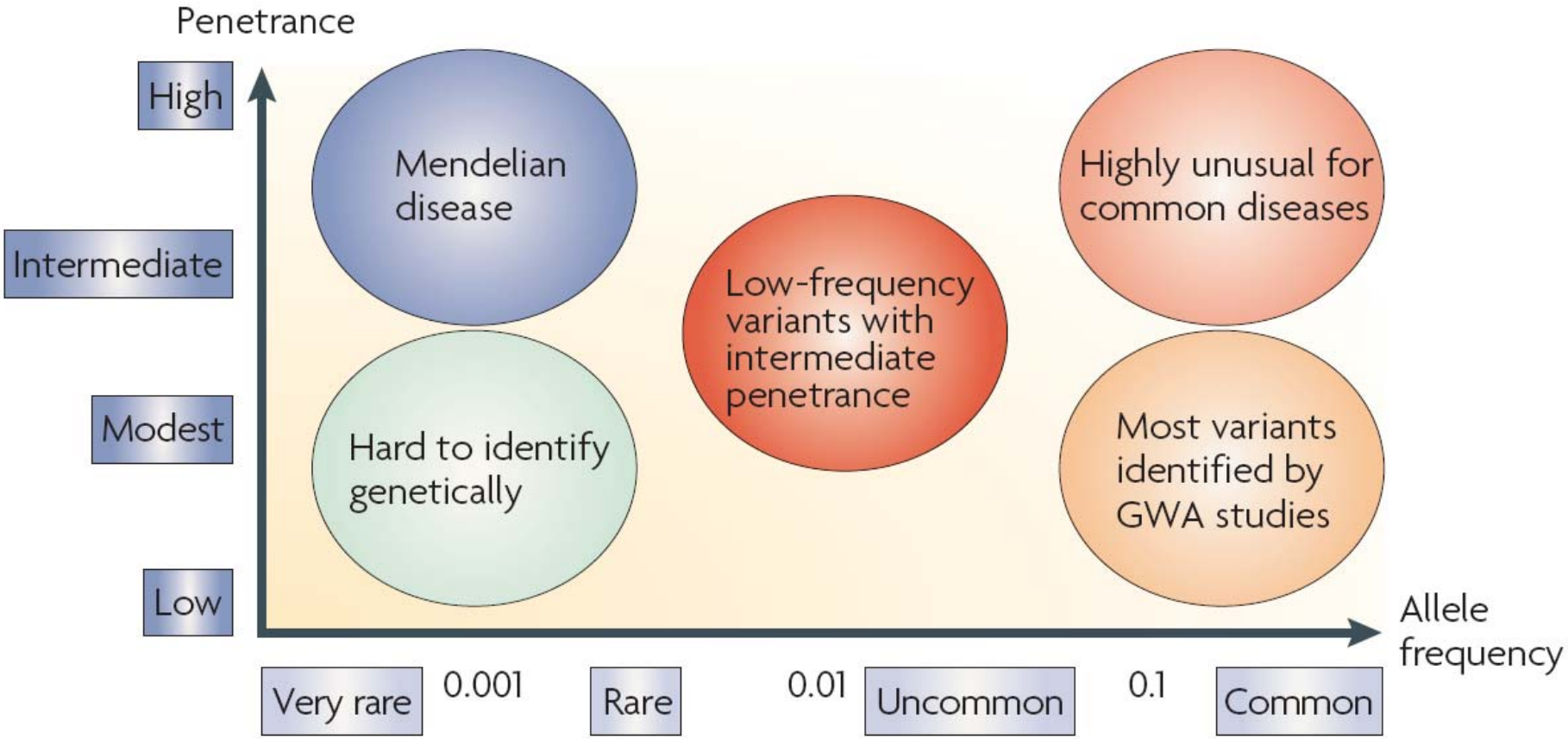
Summary: Prospects of genetics

- **Identification of biological systems as a basis for further studies of these systems (even weak effects may yield important insight → multi-center and multi-national collaborations are required).**
  - **Disease susceptibility: Understanding PSC.**
  - **Development of cancer: Prevent and treat?**
  - **Disease progression: Delay liver cirrhosis?**
- **Genetic testing? Problem: Specificity.**

Acknowledgements

- Erik Schrumpf
- Kirsten Muri Boberg
- Benedicte A. Lie
- Erik Thorsby
- Espen Melum
- Ulrika Broomé
- Annika Bergquist
- Andre Franke
- Peter Croucher
- Stefan Schreiber

Limitations of genetics



McCarthy et al, Nat Rev Genet 2008