New PSC Genes - What Should We Do with Them?

PSC partners meeting, Sacramento, April 30th, 2011

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Outline

- Genetic variants and disease
- New genetic findings in PSC
- Application of knowledge
- Norwegian PSC research center

GENETIC VARIANTS INFLUENCING DISEASE

Genetic variants

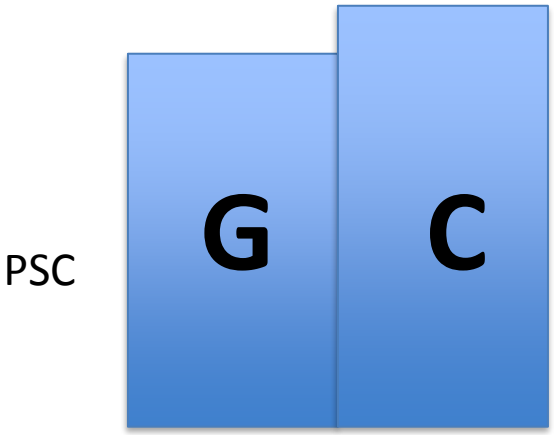
- Humans are at least 99.5% identical genetically

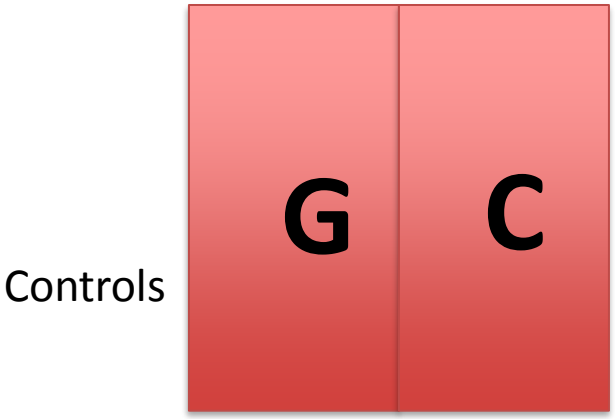
- The remaining variation is important in defining all human traits

Genetic variants and disease

- Genetic variants are also influencing diseases

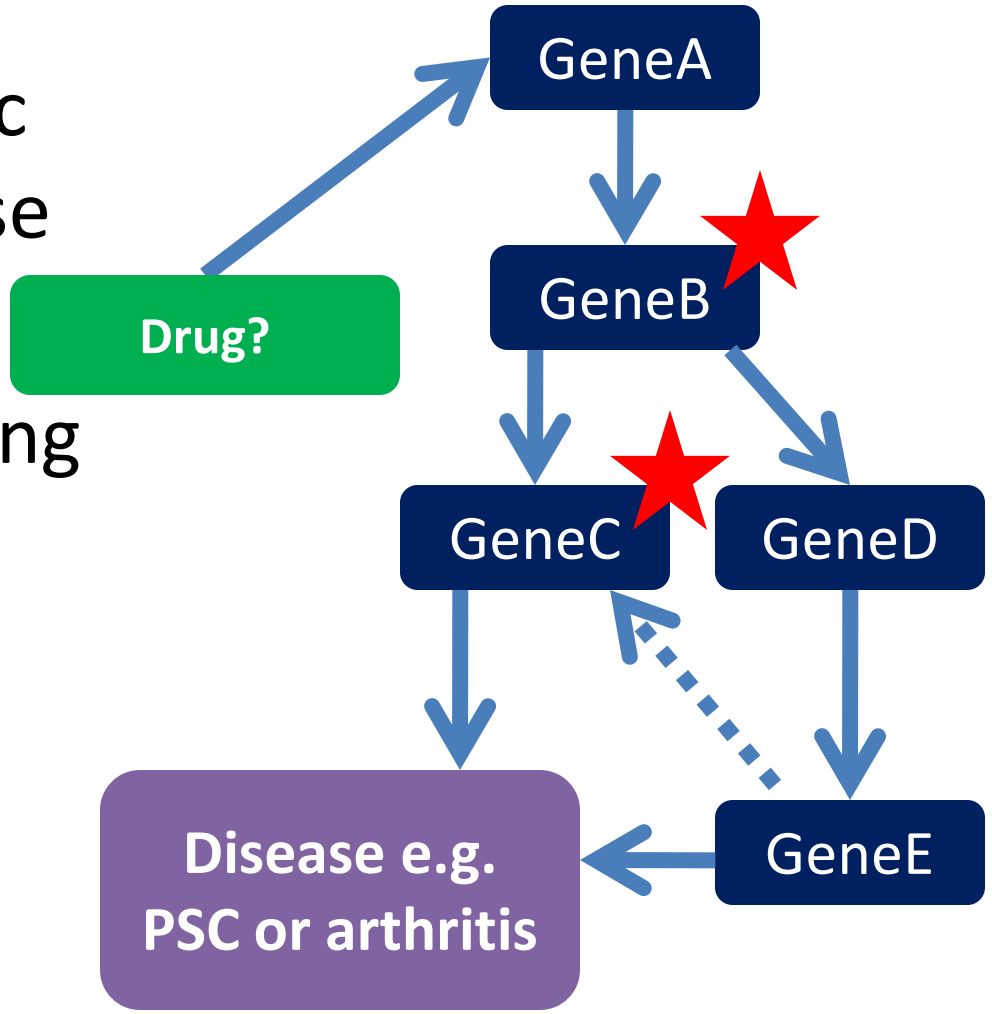
- Our tool: the simplest form of genetic variation
  - …ACT**G**TAA…. vs. …ACT**C**TAA….





Gene-hunting in complex diseases

- ***Aim:*** identify genetic variants that increase risk of disease
- Hypothesis generating research for identification of pathways



PSC GENETICS IN GENOME-WIDE STUDIES

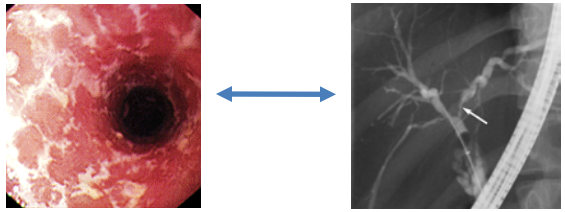
Two GWAS studies as part of a large international collaboration

- Karlsen, Franke, Melum *et al.* Gastroenterology 2010
  - 285 patients and 296 controls
  - The region encoding HLA is the most important genetic region

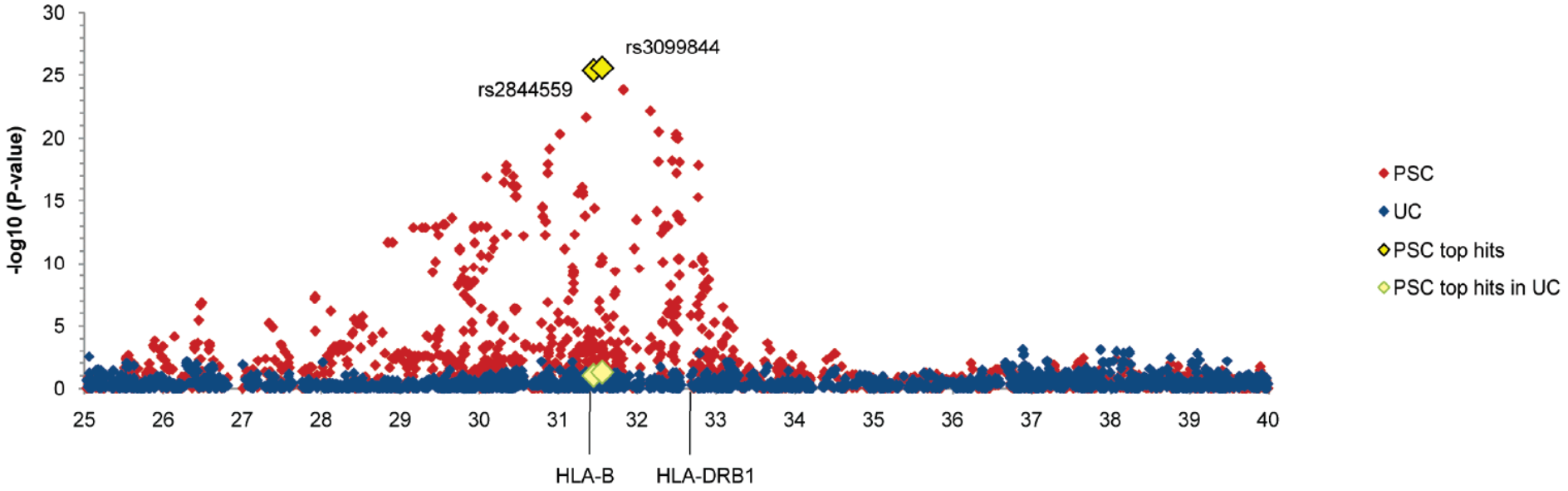
- Melum *et al.* Nature Genetics 2011
  - Two genes with “genomewide significance”
  - Strong suggestive evidence for one more gene involved in regulation of the immune system

The HLA association is the most important genetic risk factor

- Known since 1982 (Schrumpf *et al*.) – most important genetic region



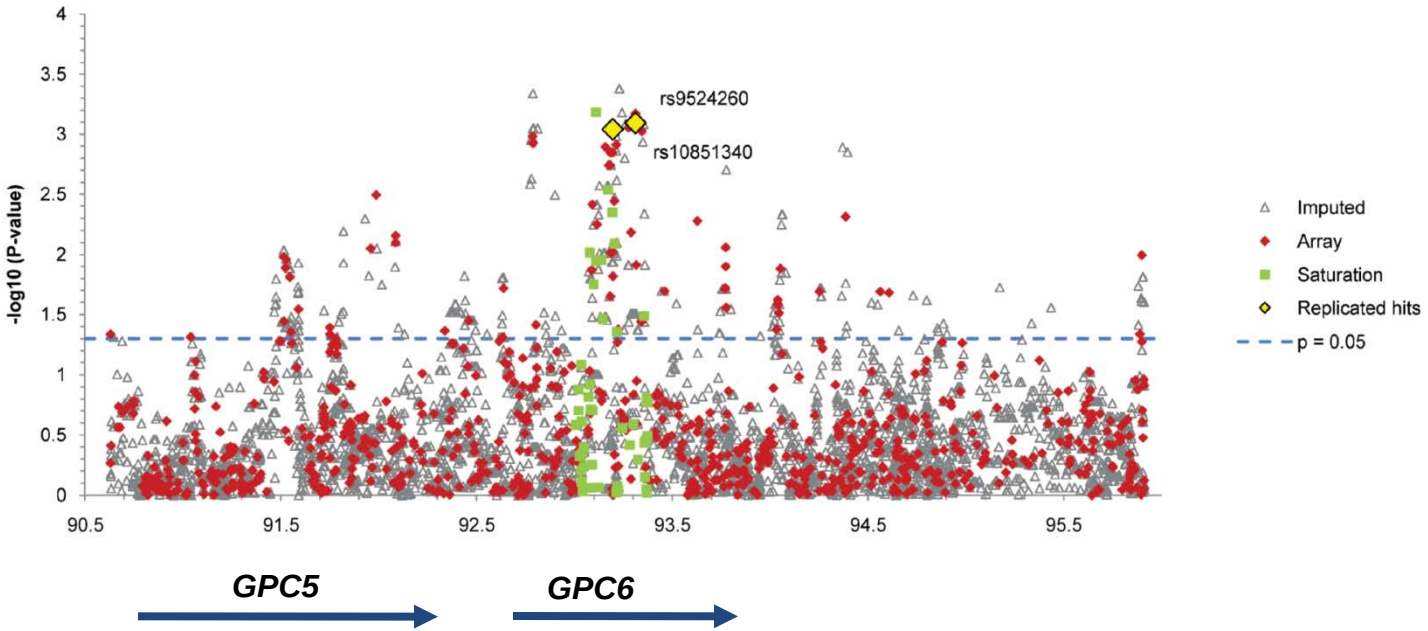
- No large overlap with ulcerative colitis



Glypican-6 (GPC6) variants

- Promising genetic variants in the initial study were tested in independent panels of patients and controls

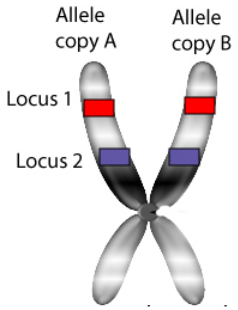
- Glypican-6 – Largely unknown function, but when turned off in cells from the bile ducts the cells produced markers of inflammation



INCREASE IN NUMBER OF MARKERS AND PATIENTS

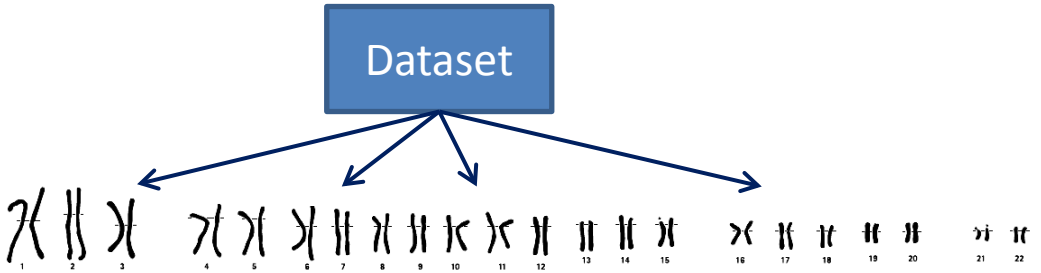
Genotyping → ”Imputation” → Association testing

- Total cohort (**715** patients and **2962** controls)
- Genotyping of 909.000 variants
- Increased number of variants by statistical techniques
- **2.5 million** variants tested for association with PSC



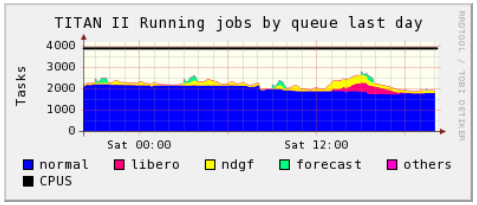
Demanding calculations

Up to 2 days run time pr. chromosome pr. cohort



High performance cluster
Start all calculations in parallel – 44 computers

`titan.uio.no`

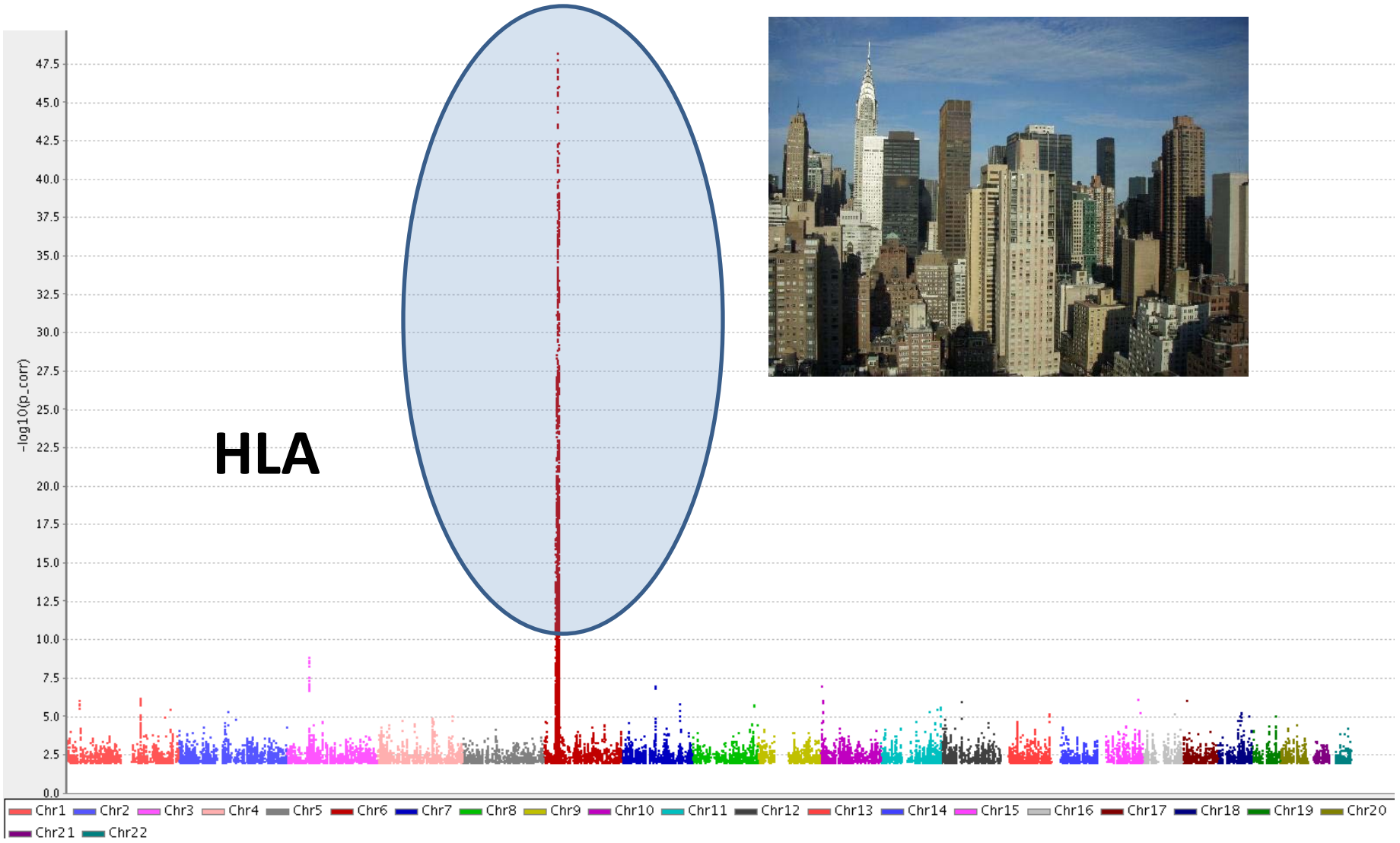


Collaboration between different disciplines

Collaboration between clinicians, biologists and informatics specialists along with access to high capacity computing is necessary!

Visit at the high performance computing cluster in Oslo

Overview ”Manhattan plot”

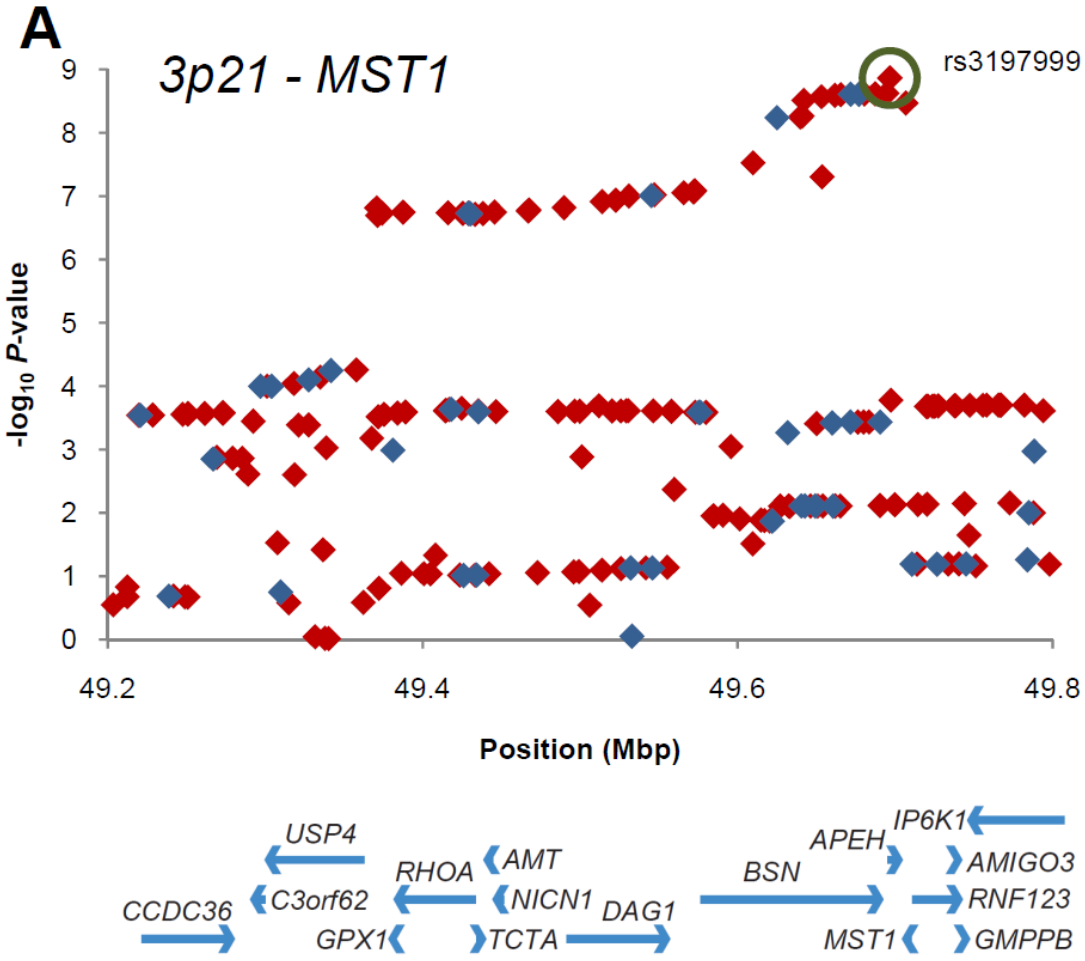


Replication cohorts

- 1. Germany
  - 171 cases
  - 524 controls
- 2. Belgium / Holland
  - 327 cases
  - 367 controls
- 3. Scandinavia
  - 259 cases
  - 729 controls
- 4. United States (Mayo Clinic, Rochester)
  - 268 cases
  - 554 controls

- **Total: 1025 cases and 2174 controls**

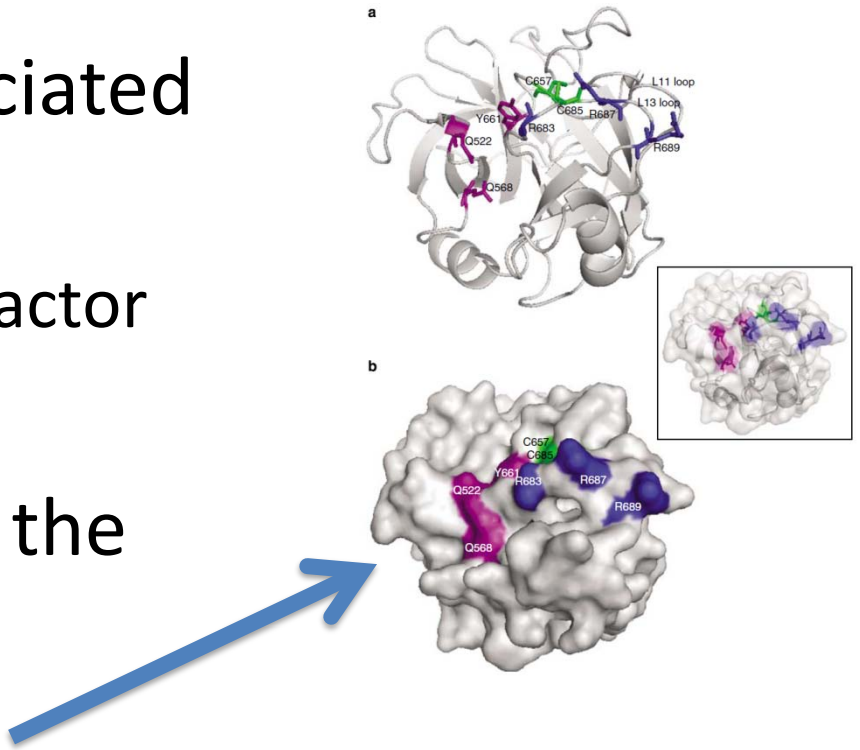
MST1



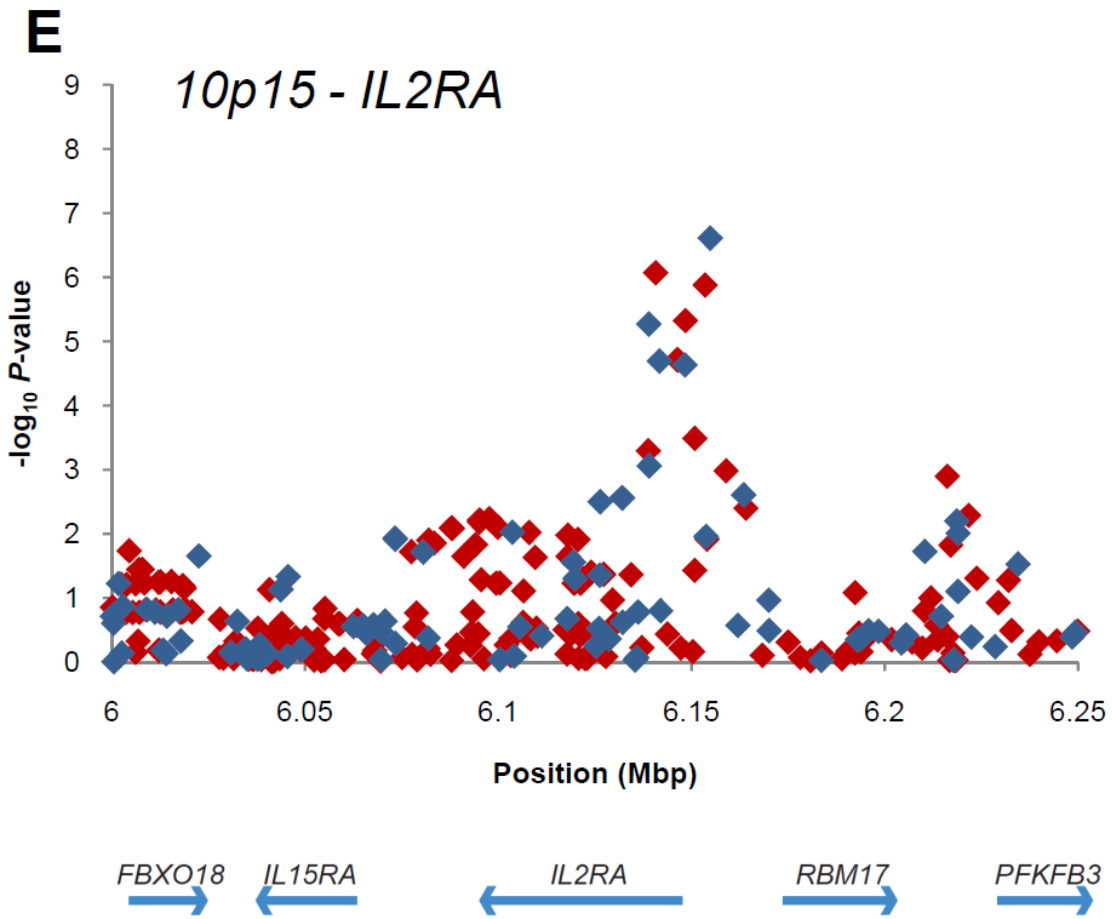
A gene involved in regulation of macrophages – a type of immune cells

MST1

- Also reported to be associated with IBD
  - Overlapping genetic risk factor
- Changes the structure of the protein



IL2RA



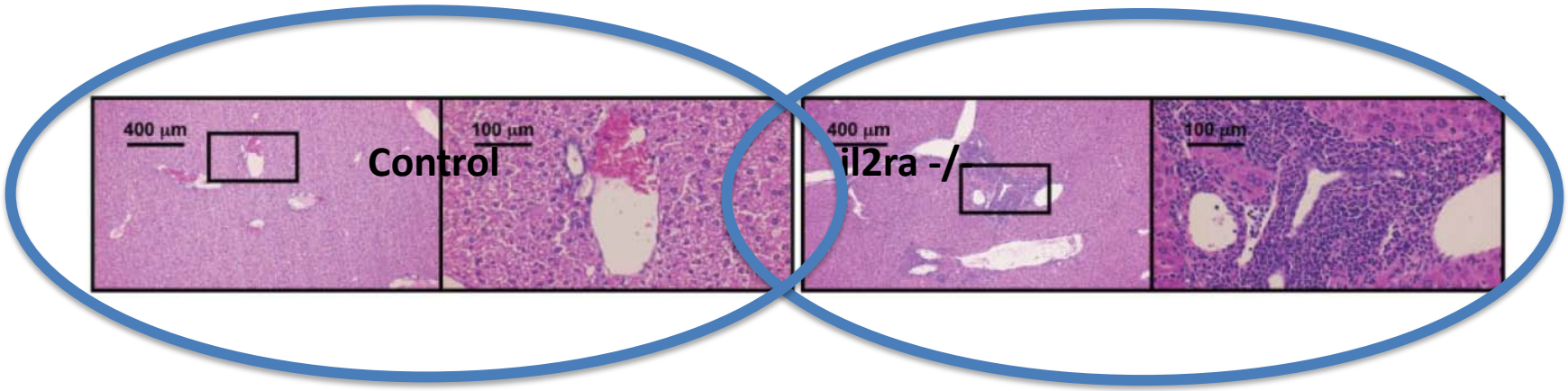
A gene involved in regulation of the immune response

Likely to be differences in different populations

IL2RA

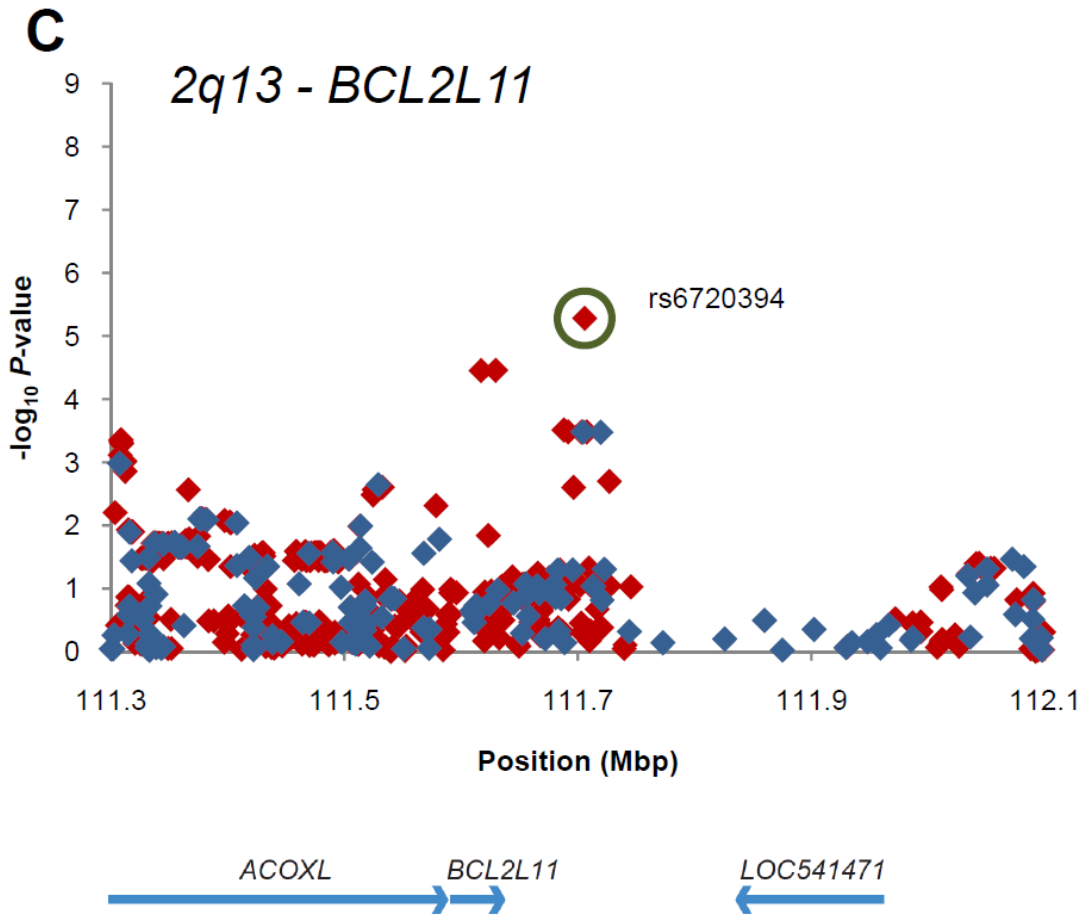
- Mice generated in laboratories missing this gene develop inflammation in the colon (resembling UC) and in the bile ducts (resembling PBC)

- Rare mutations give rise to severe autoimmune diseases.



(Hsu et al, Hepatology 2009)

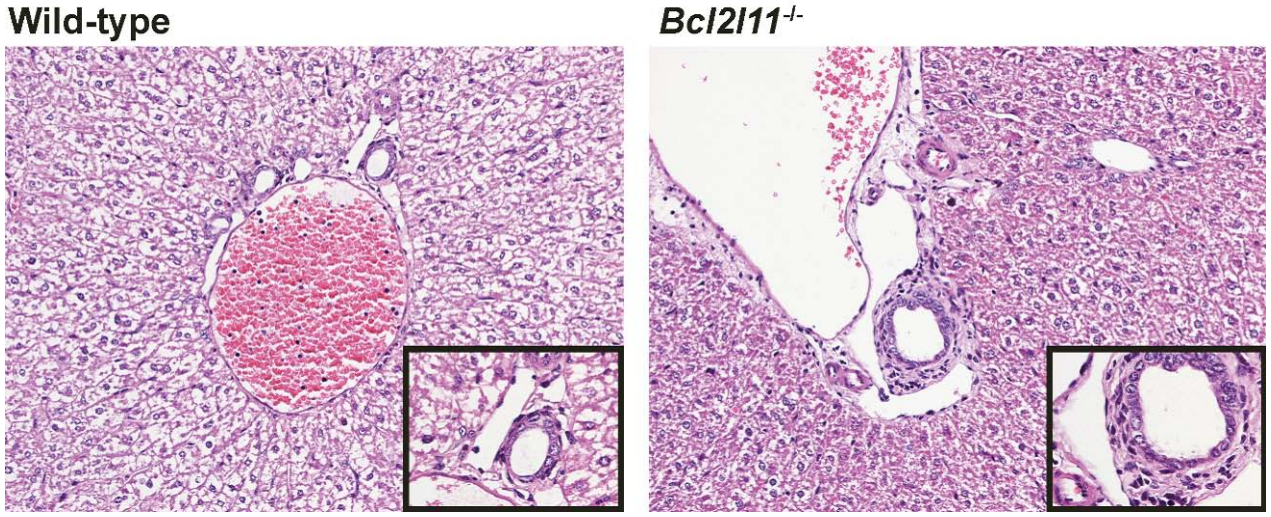
BCL2L11



Not reported in any autoimmune disease

Plays a role in eliminating immune cells that are overreactive

BCL2L11



Dr. Andreas Villunger and Dr. Felix Offner

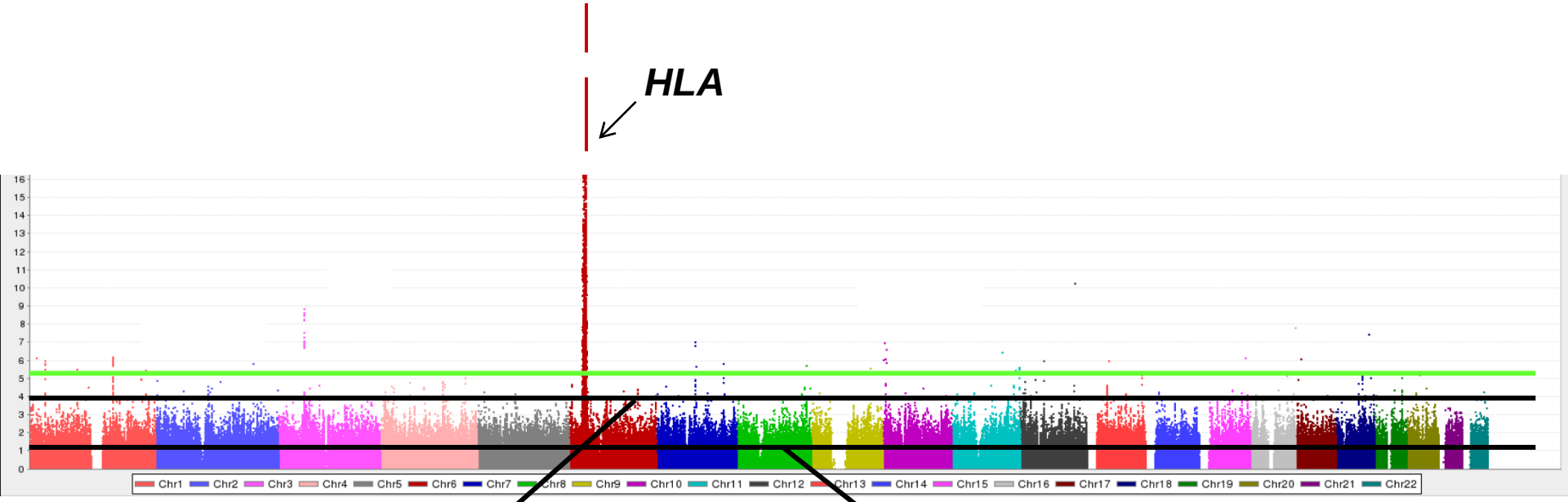
Little known about role of *BCL2L11* in the liver from before

Livers from mice missing this gene had more immune cells present

Only the tip of the iceberg…

- In IBD over 70 genes has so far been found
- The scenario is likely to be similar in PSC!

More PSC genes?

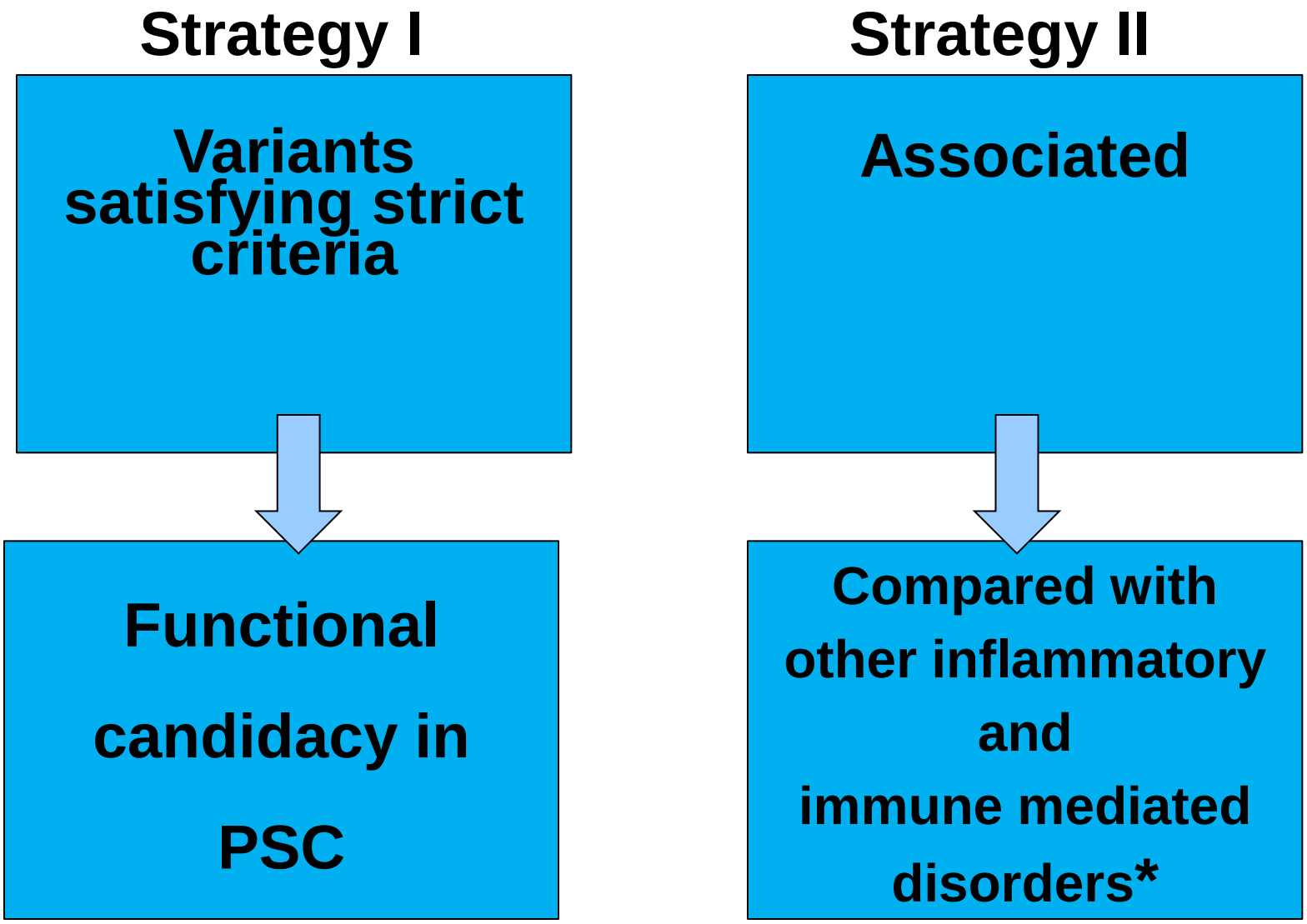


Strict criteria

379 non-HLA variants

Associated

134,329 non-HLA variants

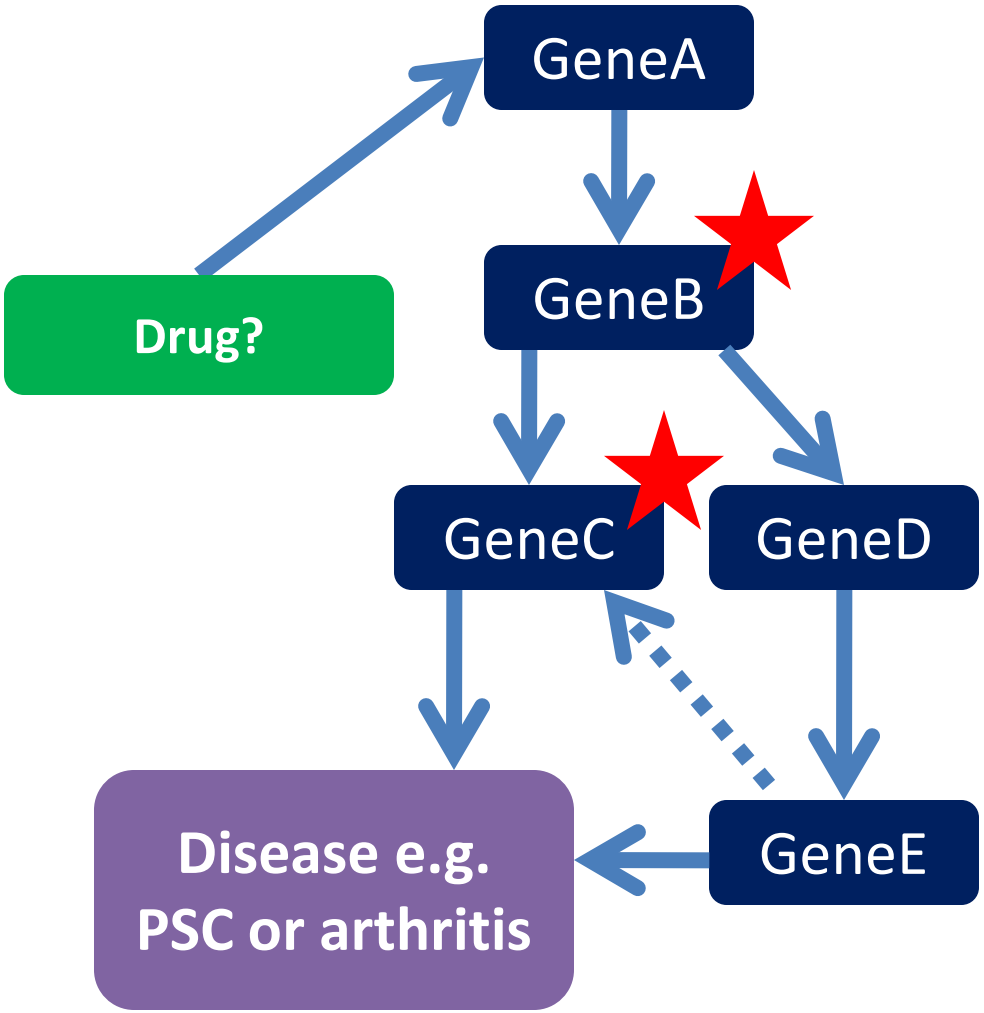


* Listed in the Catalog of Genome-Wide Association Studies (www.genome.gov. 26525384)

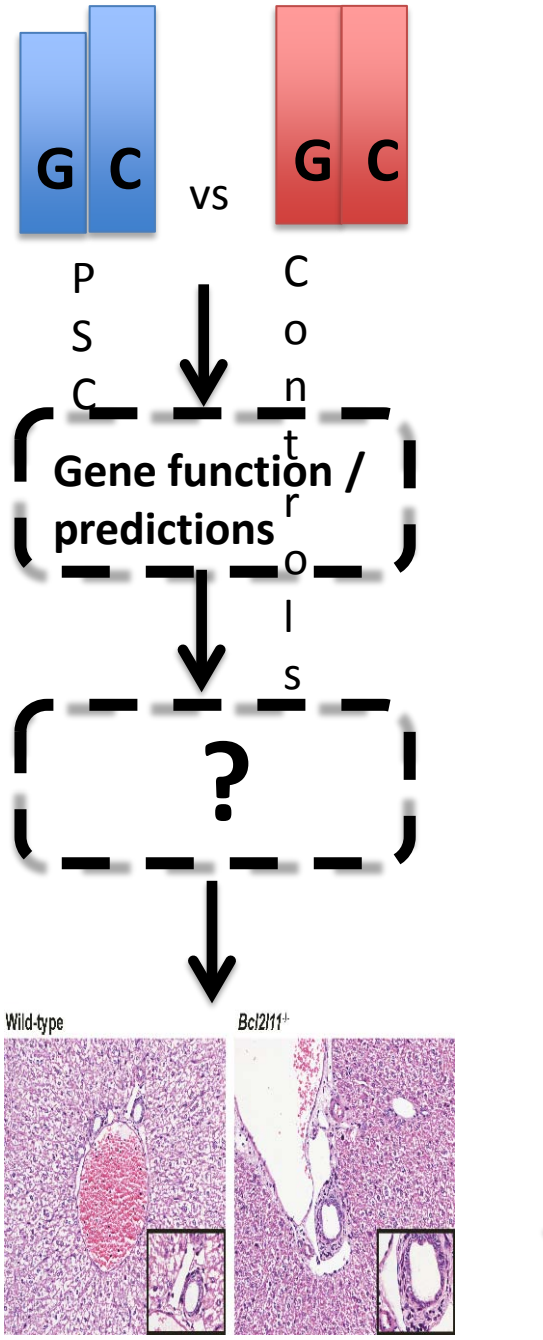
Overlap with other diseases

PSC loci	PBC	UC	Crohn's disease	Celiac disease	Diabetes	RA	MS	SLE	Other AIDs
MMEL1									
IL2/IL21									
CARD9									
CLEC16A									
REL									
FUT2									
BCL2L11									
MST1									

APPLICATION OF GENETIC FINDINGS



=Simplified model



Genetic association

Mechanism

Effect in animals models

Intervention?

“The effective management of PSC and its variants is hindered by uncertainties regarding pathogenesis of disease and factors responsible for its progression.”

Culver and Chapman, Aliment Pharmacol Ther 2011

Testing of individual patients?

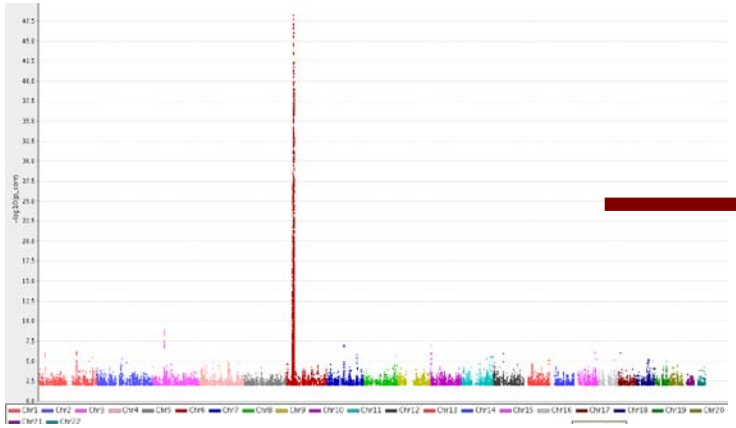
- The effect sizes are low (Odds ratio's 1.2-1.5)
  - GWAS detect common variants with low effects

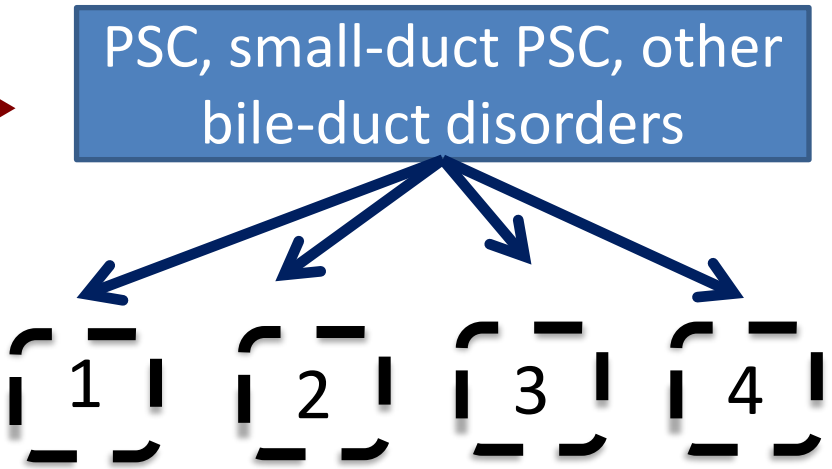
- Can not be used for prediction and the vast majority of people carrying the predisposing variants do not have PSC

- ***Important:*** for a test to be employed it needs to pick up as many people with the disease as possible AND a negative test must be very good at saying that the individual do not have the disease

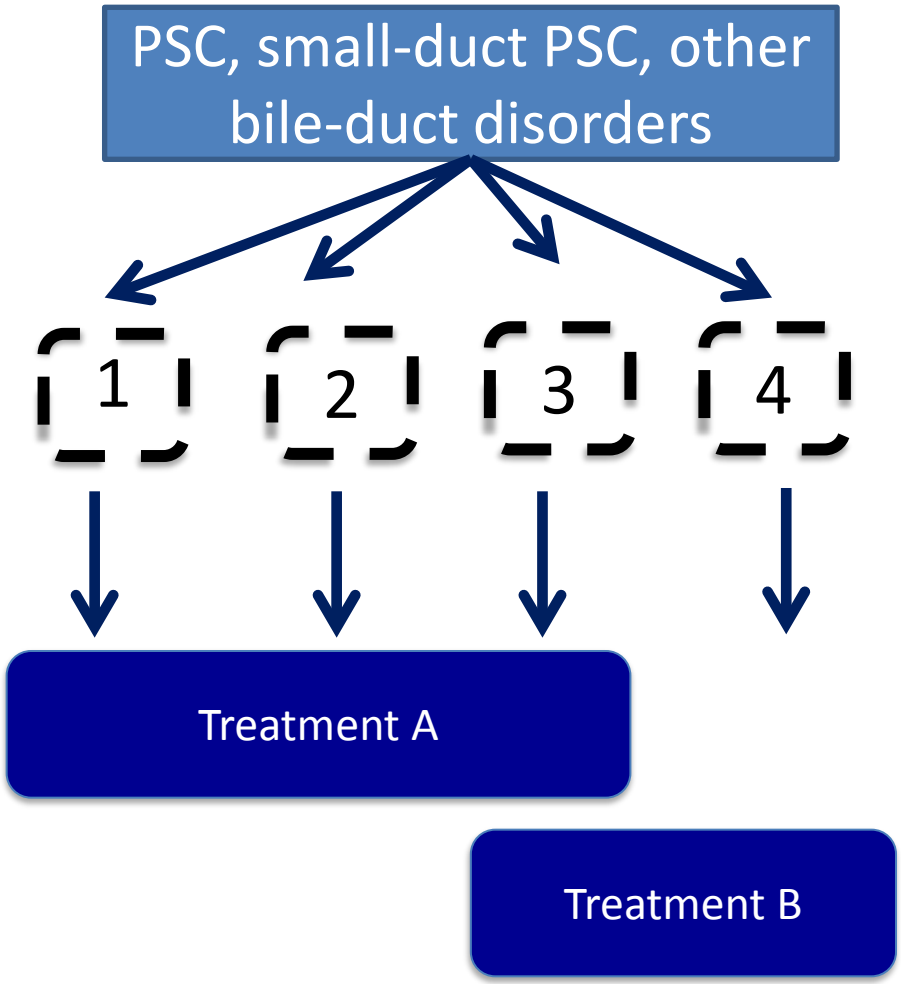
Redefining disease classifications

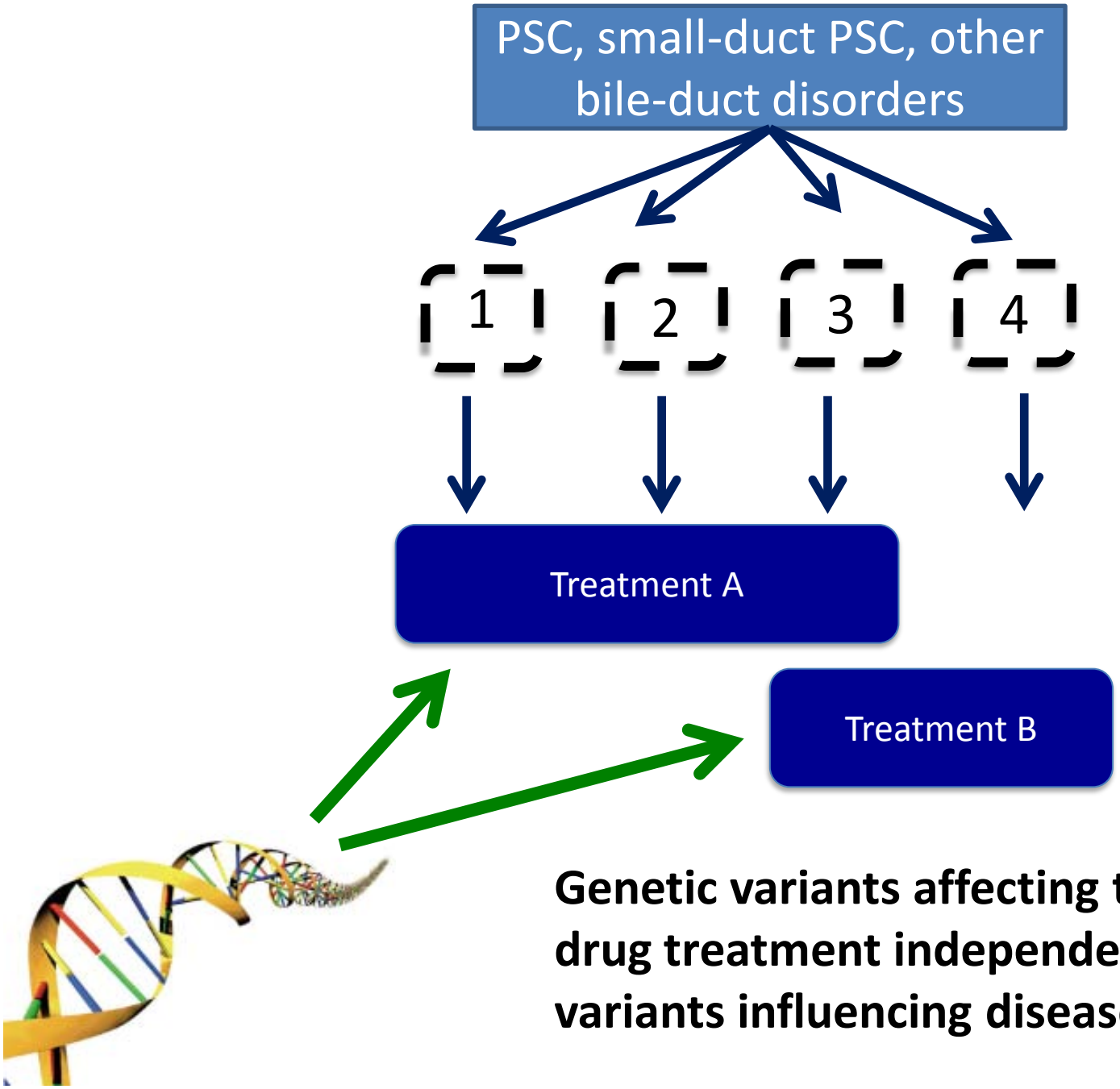
- "Molecular phenotyping" = diseases defined based on genetic variants





Possible scenario:





Genetic variants affecting the effect of drug treatment independent of the variants influencing disease

Summary

- Genome-wide associations studies are effective for uncovering genetic variation
- Several new PSC genes have been discovered, but the vast amount remains to be found
- Findings will help us understand the biology and pathogenesis of PSC
- The small impact of each of the associated variants means that the genetic variants do not have any current use in clinical medicine

Norwegian PSC Research Center

- PSC has been an important research focus at Oslo University Hospital, Rikshospitalet for 30 years

- Extended in 2007 following a private donation with establishment of the Norwegian PSC Research Center
  - 125 mill NOK, approximately 23 million USD over a 10 year period

NO PSC
Norwegian PSC Research Center

Organization

- Advisory board (six members)
- Management group:
  - Prof. Erik Scrumpf, Leader of the Management Group
  - Dr. Kirsten Muri Boberg
  - Dr. Tom Hemming Karlsen, Executive Manager of the Research Center
- Core facility
  - runs support functions of general importance for the project units, e.g. general administration, biobank, data registry, laboratory assistance and computer support. A total of 5 persons are presently employed in this unit.
- Project units
  - The research are organized within four different work packages

Current staff NoPSC

Acknowledgements

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