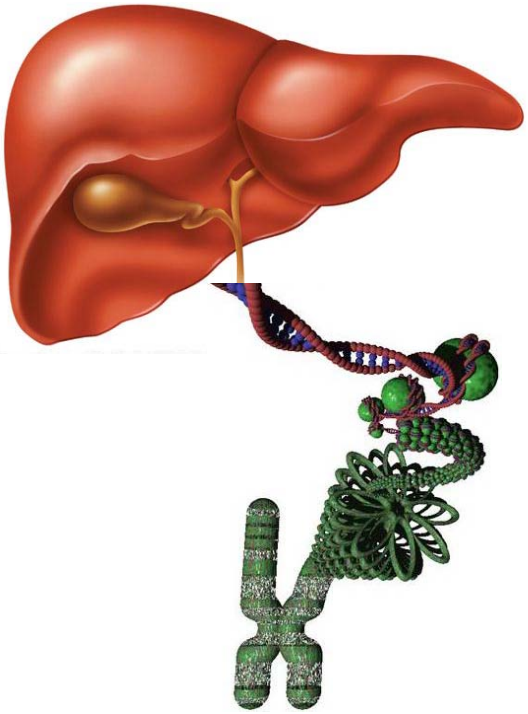


Results of PSC Genome Studies in Norway

Trine Folseraas, MD
Clinic for Specialized Medicine and Surgery
Oslo University Hospital, Rikshospitalet
Oslo, Norway

PSC –a complex genetic disease

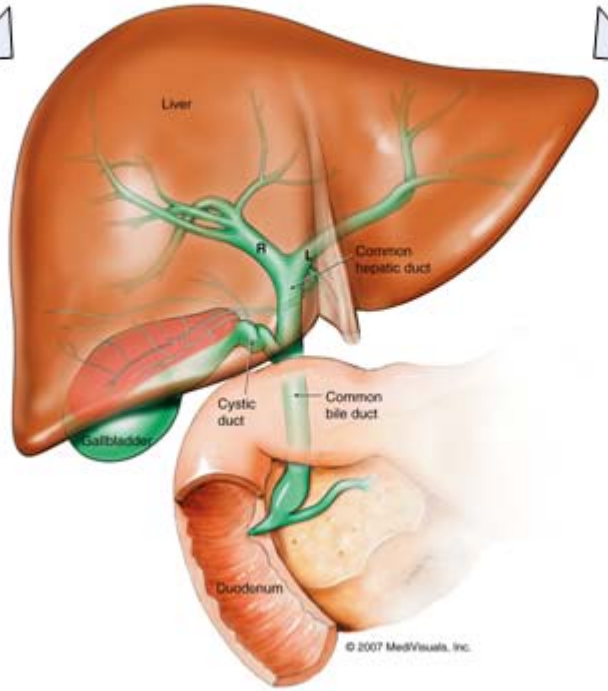
ENVIRONMENTAL FACTORS

Smoking (protects)

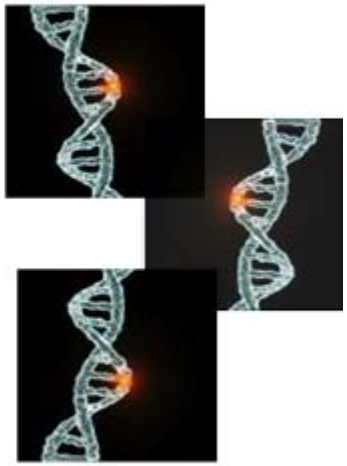
Infectious triggers?

Unknown factors

?



GENETIC FACTORS



Heritability in PSC

Heritability: λ_s~9-39

Heritability in PSC

Disease	Heritability (relative sibling risk)
Monogenic (dominant, autosomal)	>1000x
Monogenic (recessive, autosomal)	>200-500x
PSC	~9-39x (Bergquist et al., 2008)
Crohn's disease	~5-35x
Primary biliary cirrhosis	~10x
Ulcerative colitis	~6-9x
Ulcerative colitis in PSC siblings	~8x (Bergquist et al., 2008)

PSC

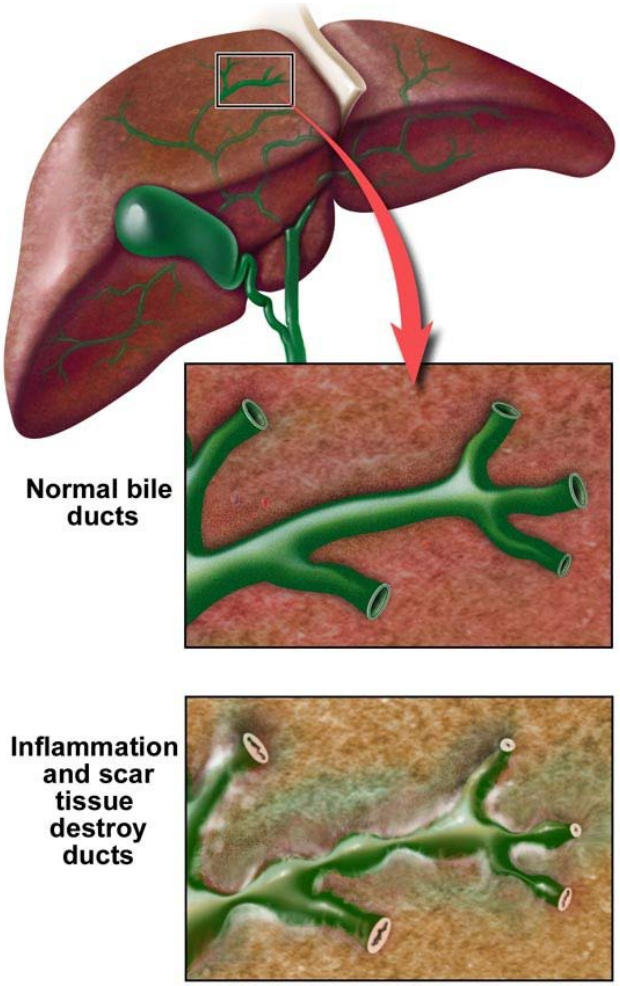
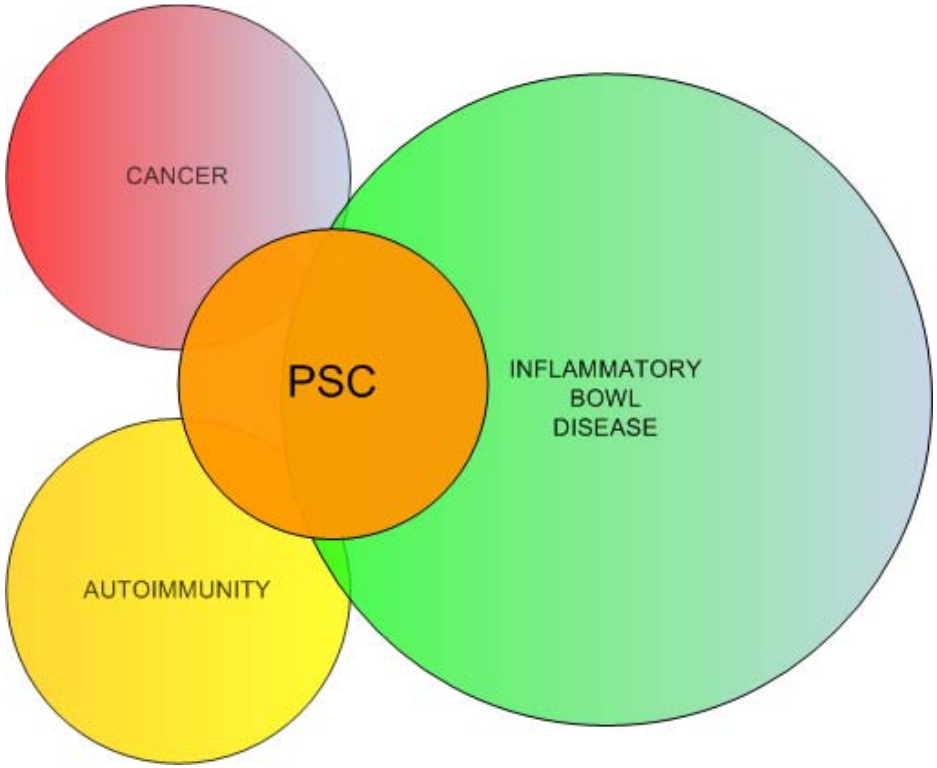


Figure:.mayoclinic.org

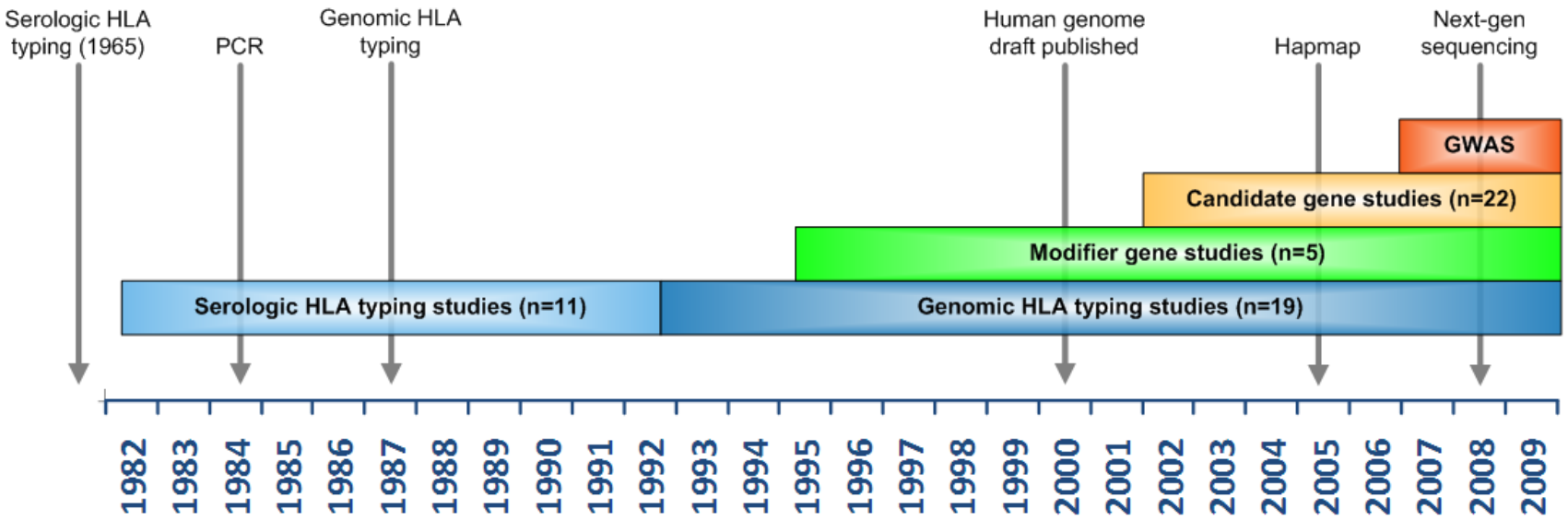
PSC



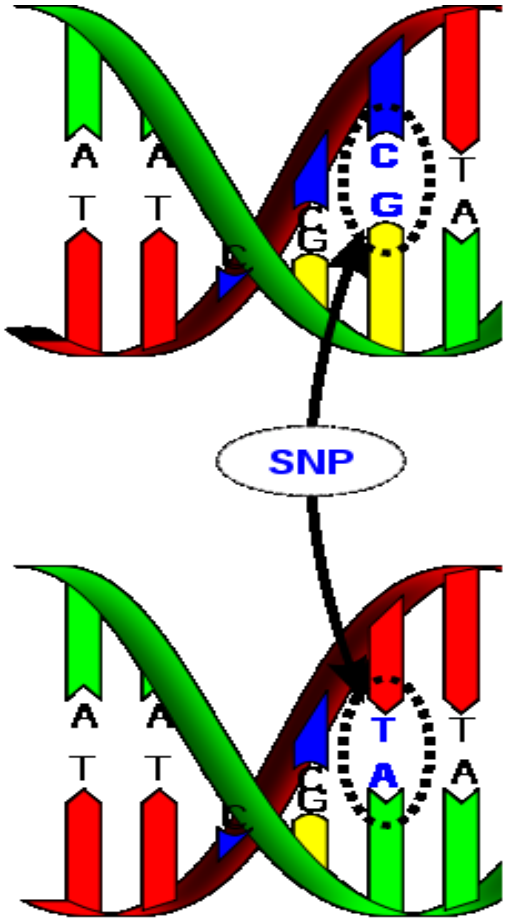
→ **Prevalence ~1/10.000**

→ **Geographical differences in prevalence**

History of the genetics of PSC

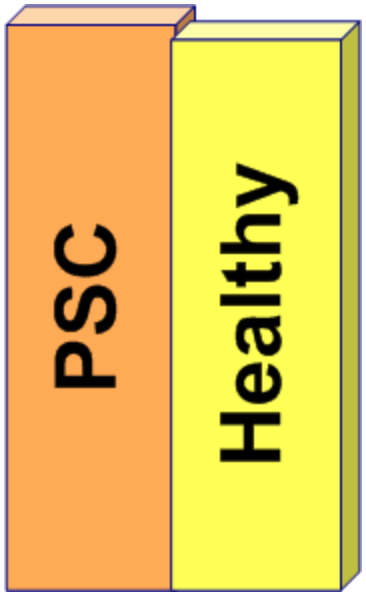


Single-nucleotide polymorphisms

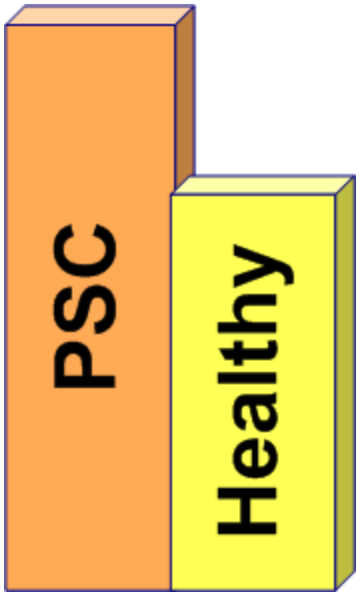


Association

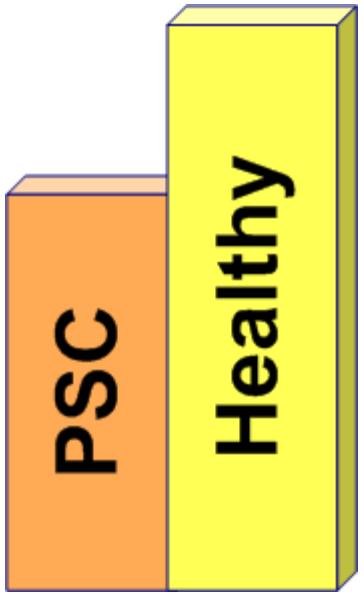
No association



Coincidence?



PSC associated

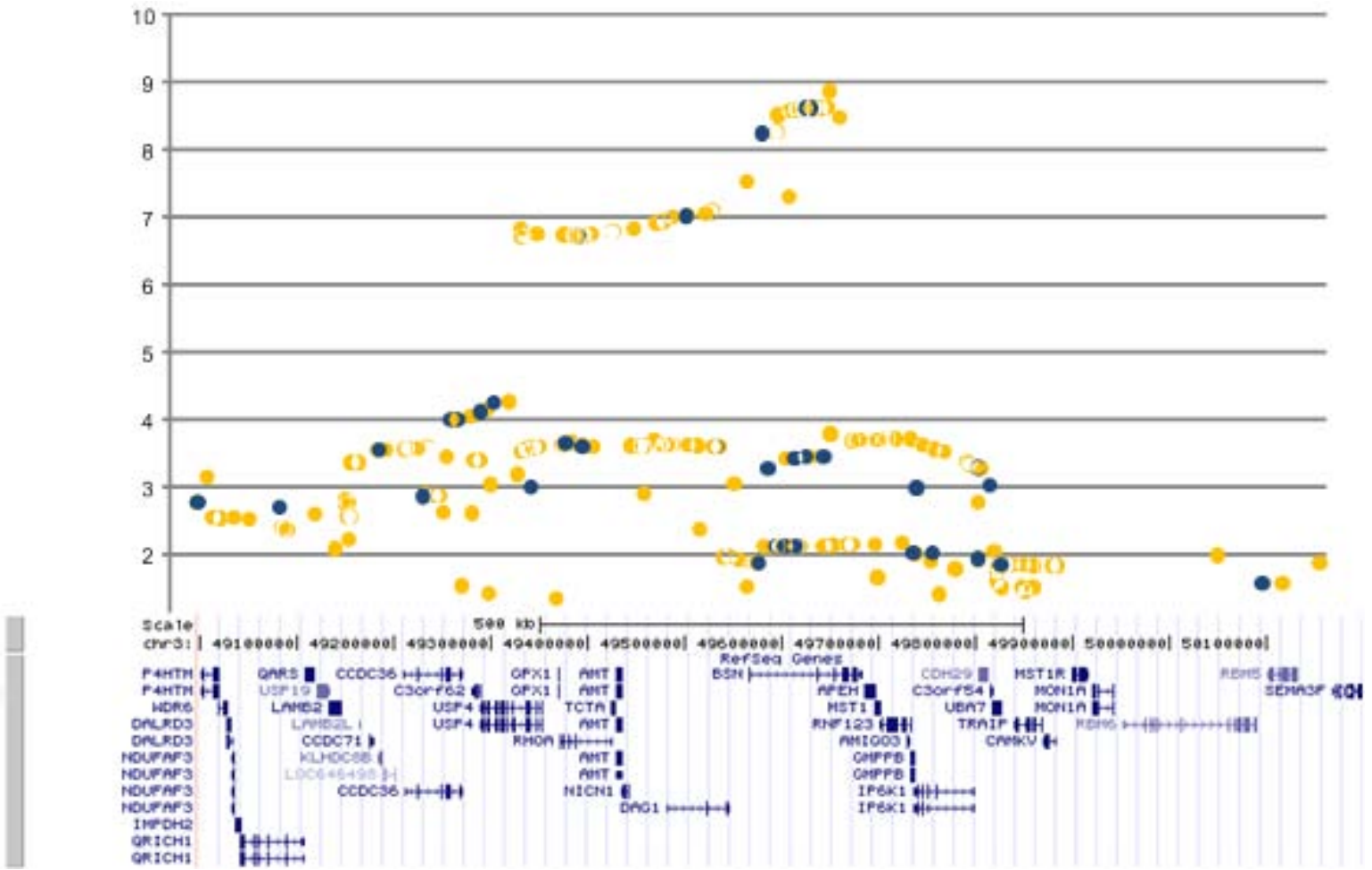


PSC associated

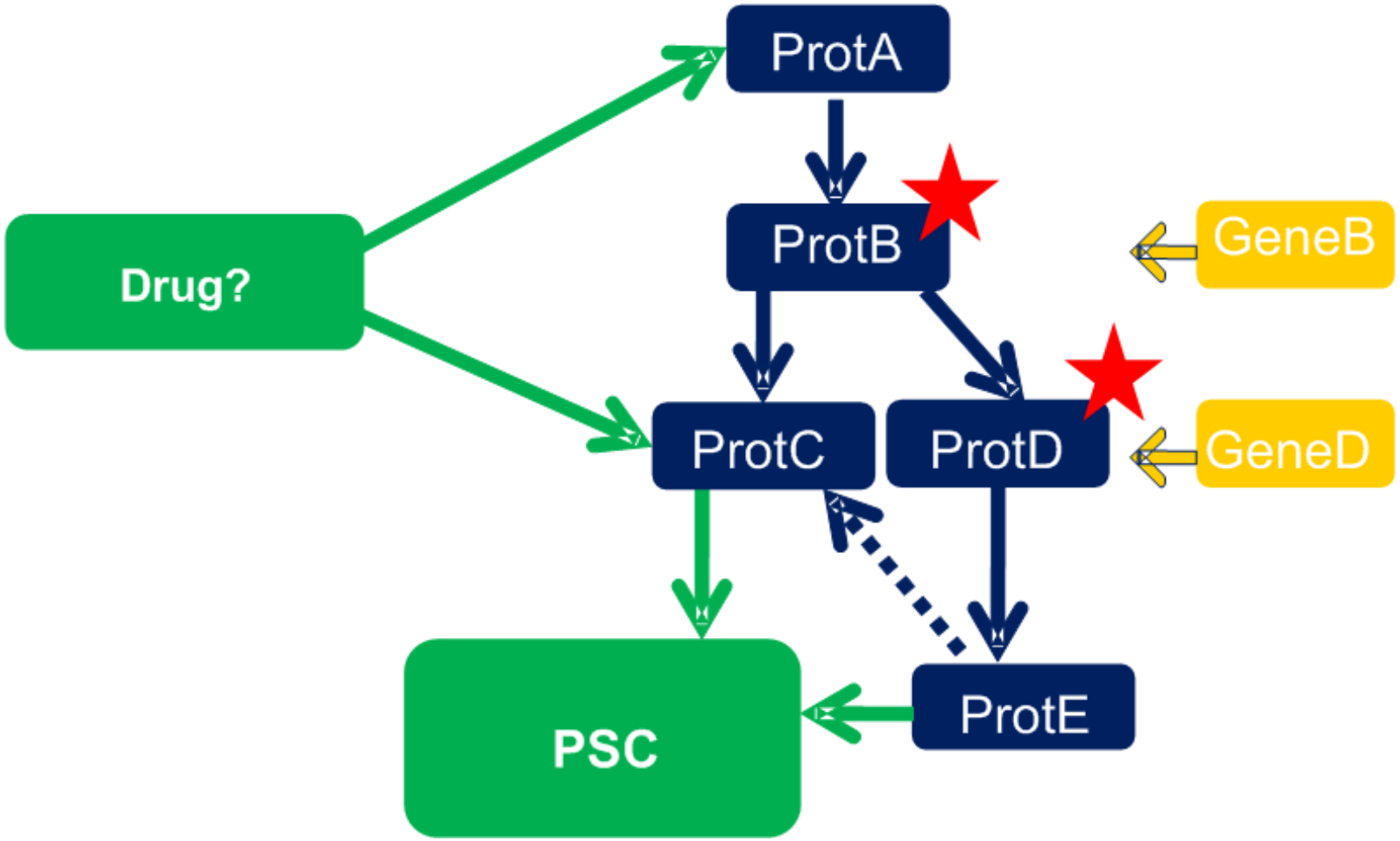
Genome -wide association studies ”GWAS”

- Examines 0.5-2 mill genetic markers/SNPs across the genome in two groups; people with the disease (cases) and people without the disease (controls)
- Replicates/affirms the findings in a new group with cases and controls

Association

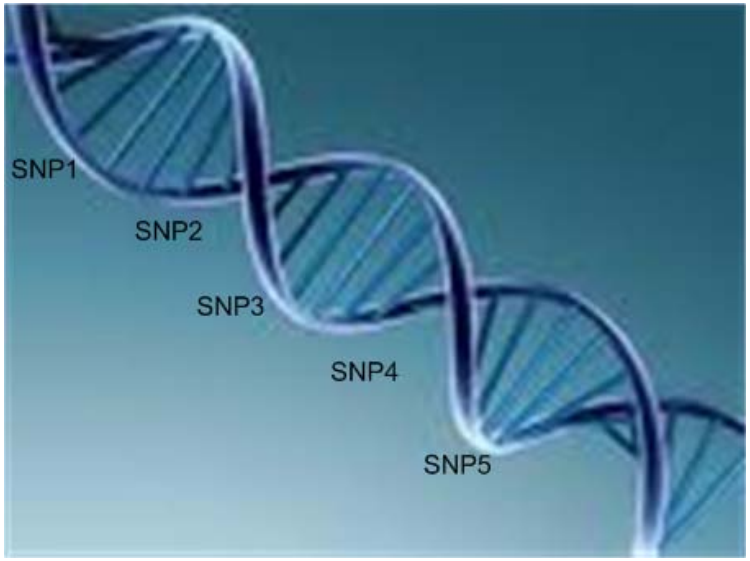


Interpretation and translation



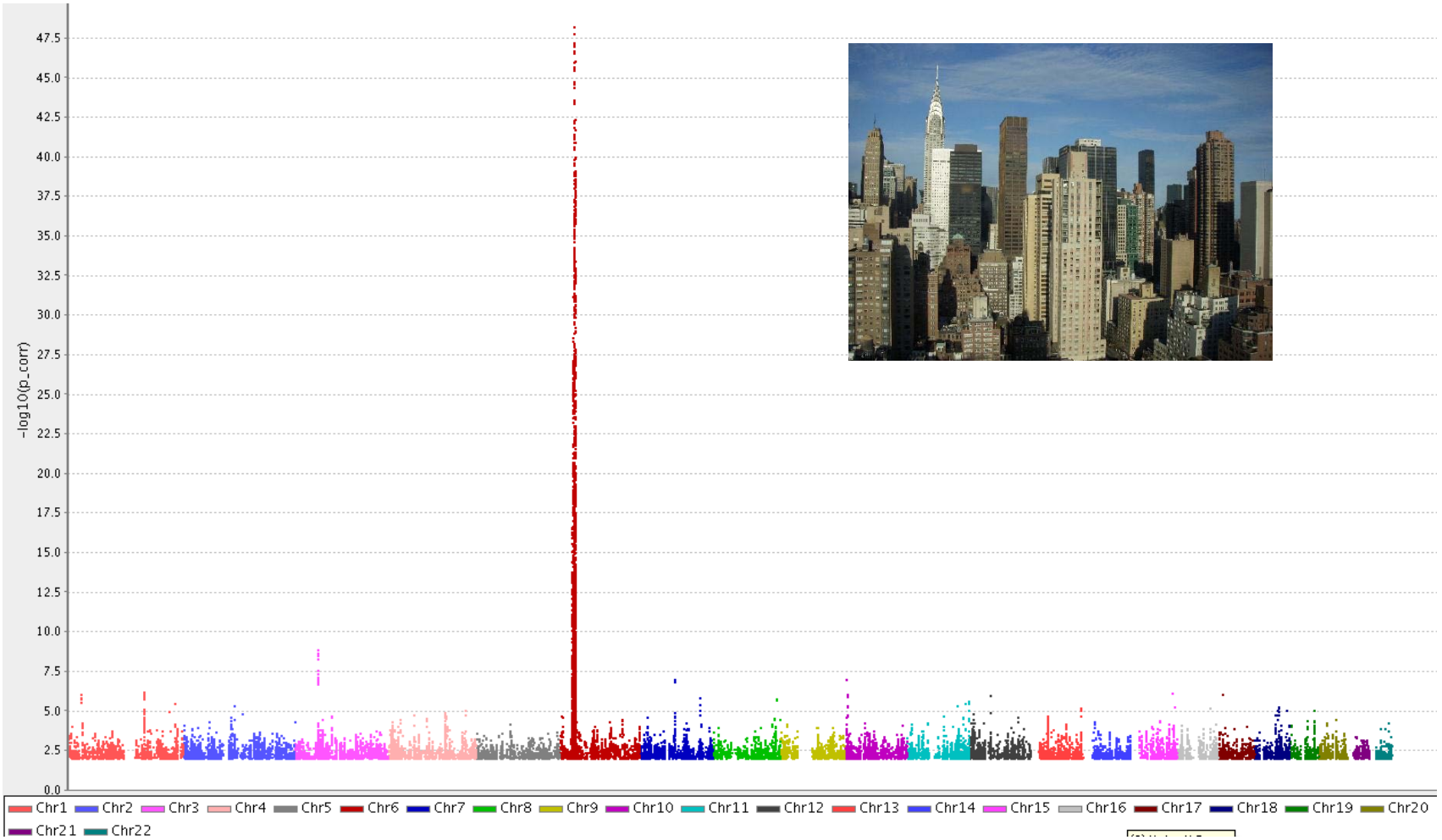
The first GWAS in PSC

PSC-patients: 285
Healthy controls: 298

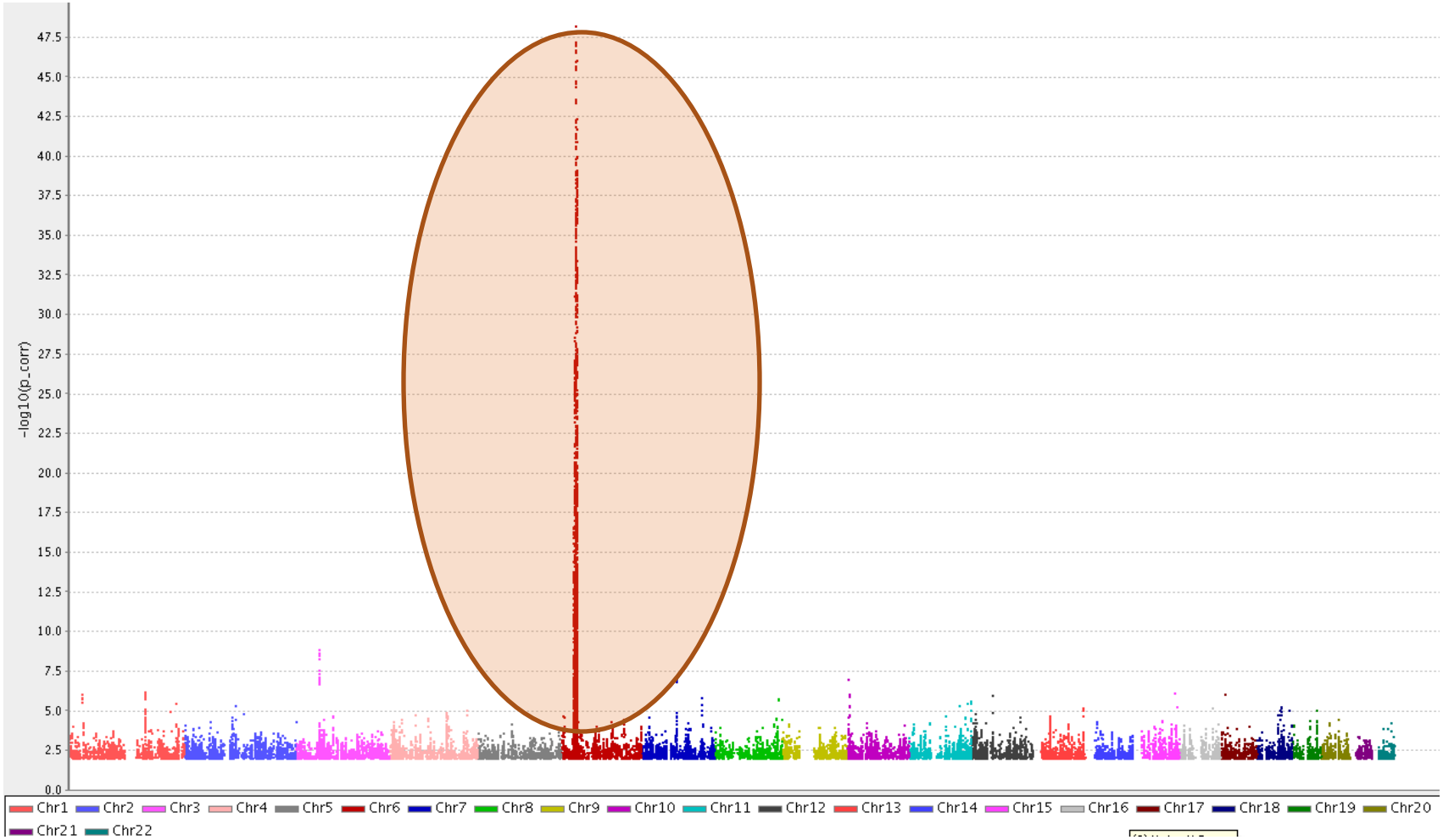


PSC-patients: 766
Healthy controls: 2935

Genetic architecture in PSC



Genetic architecture in PSC



Published suscetibility loci in PSC by May 2010

Locus	Effect size (odds ratio)	Putative gene(-s)	Other associated conditions
6p21	4-5	Unknown	Most autoimmune and infectious diseases
3p21	1.3	*MST1* ?	Ulcerative colitis Crohn's disease
2q35	1.2	*GPBAR1* ?	Ulcerative colitis
13q31	0.8	*GPC5/GPC6* ?	Multiple sclerosis Lung cancer (non-smokers) Sudden cardiac arrest

6p21: HLA

Locus	Effect size (odds ratio)	Putative gene(-s)	Other associated conditions
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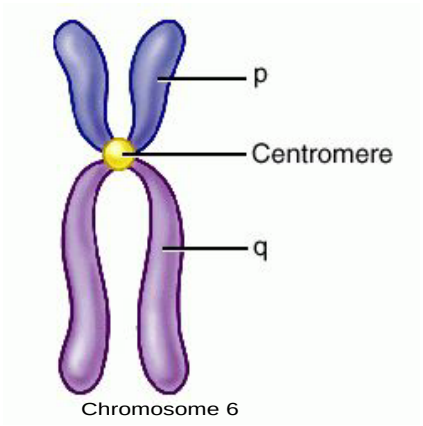

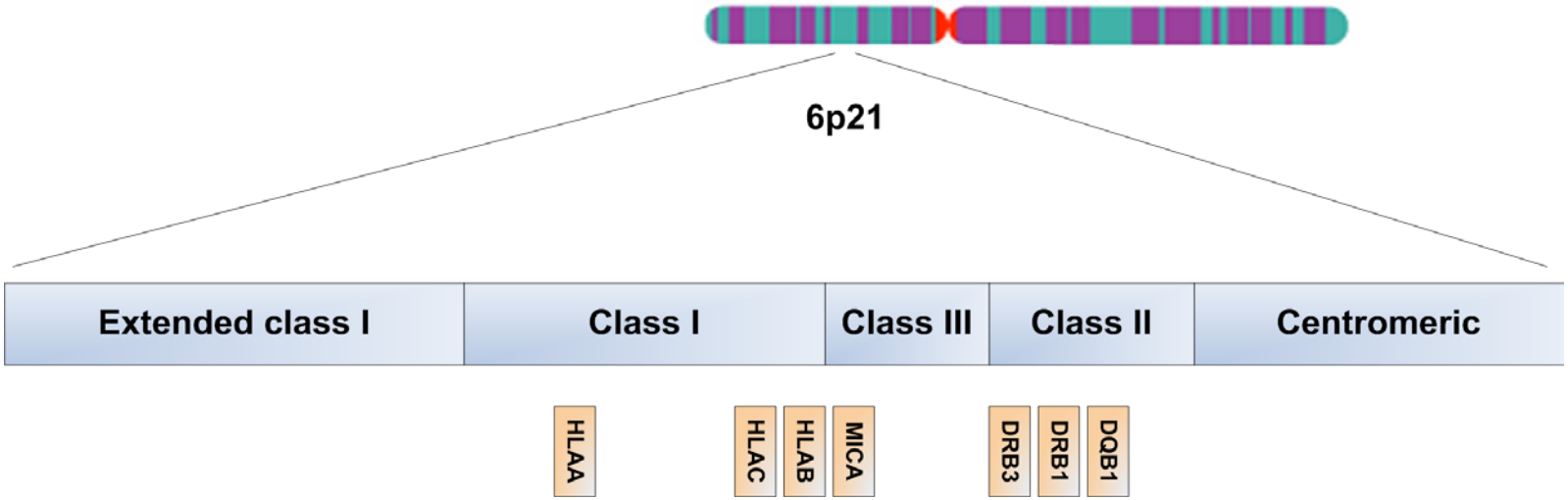

3p21: MST1?

Locus	Effect size (odds ratio)	Putative gene(-s)	Other associated conditions
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2q35	1.2	*GPBAR1* ?	Ulcerative colitis
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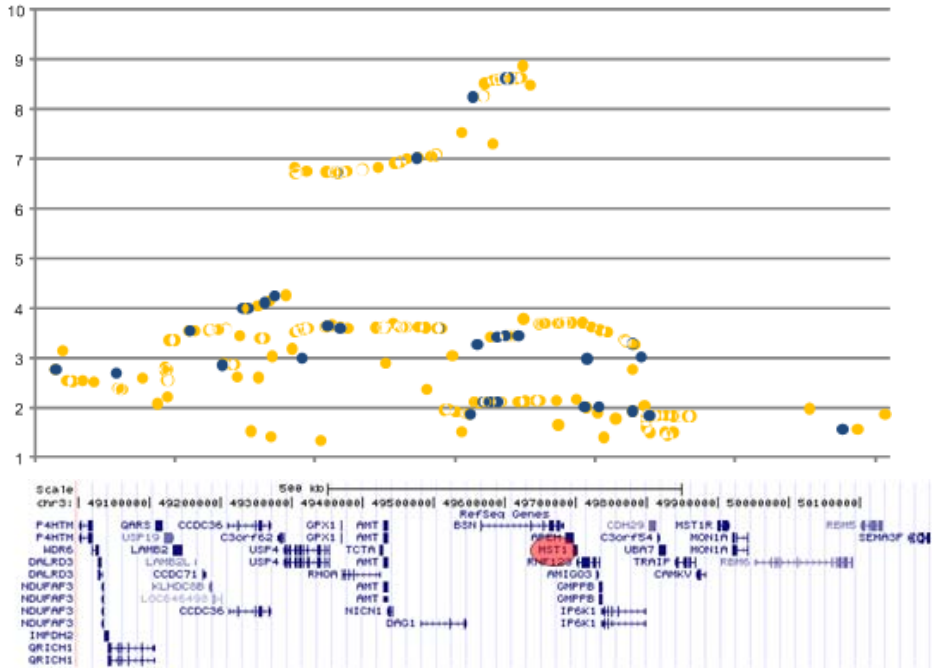
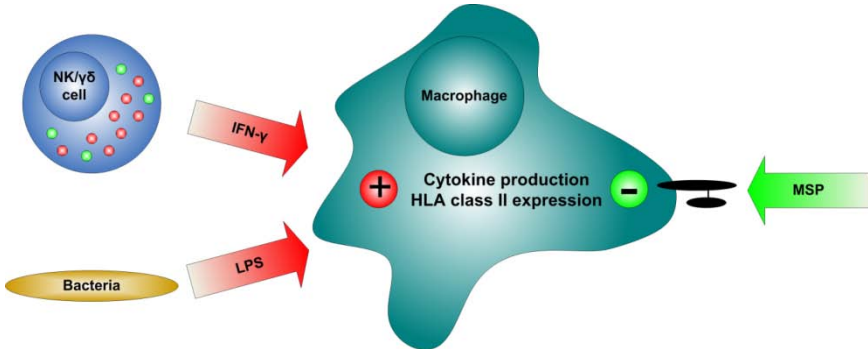
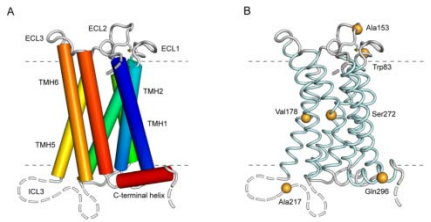




2q35: TGR5



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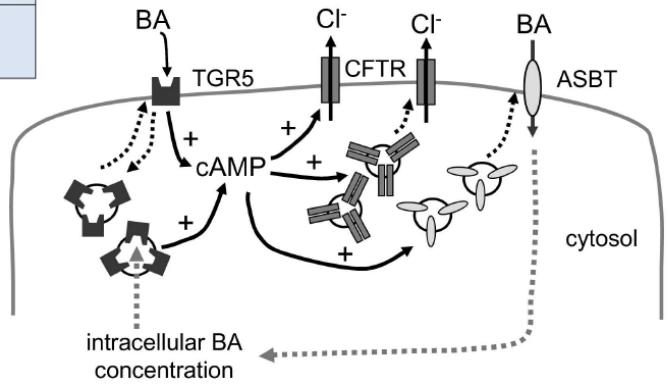
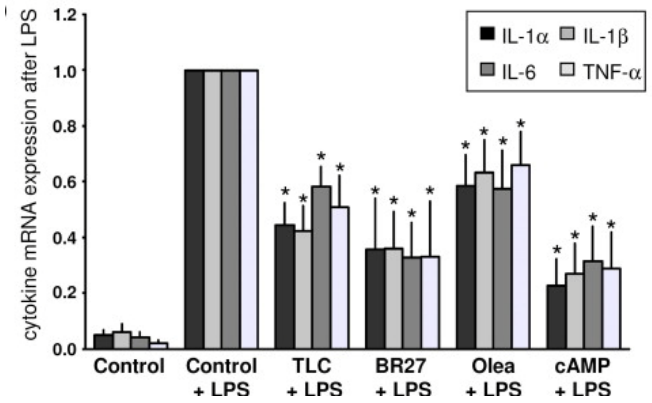
Bile ducts



(Keitel et al., Hepatology 2009)

Macrophages



(Keitel et al., BBRC 2008)

13q31: GPC5/GPC6?

Locus	Effect size (odds ratio)	Putative gene(-s)	Other associated conditions
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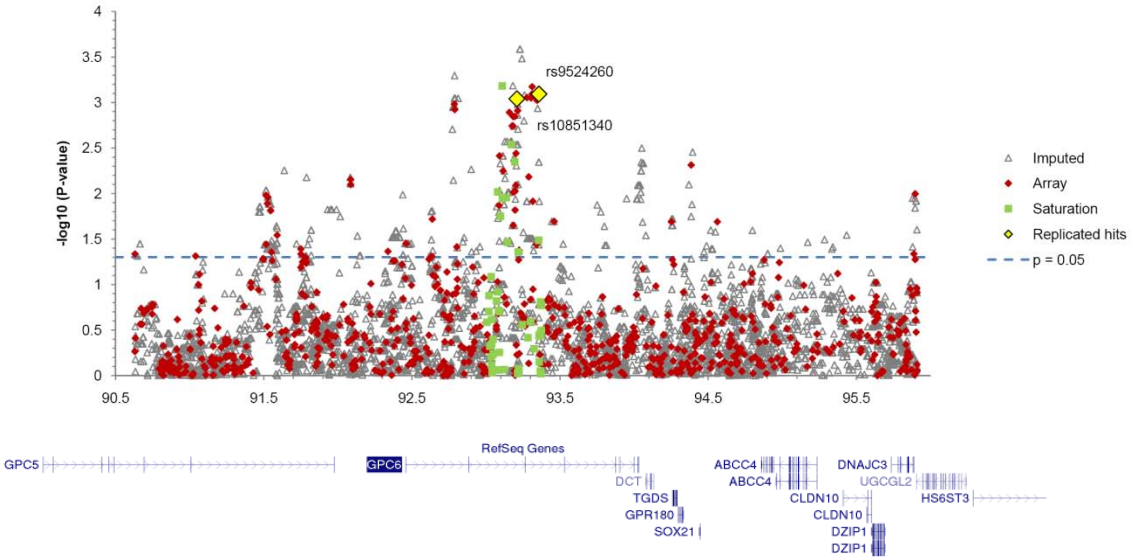

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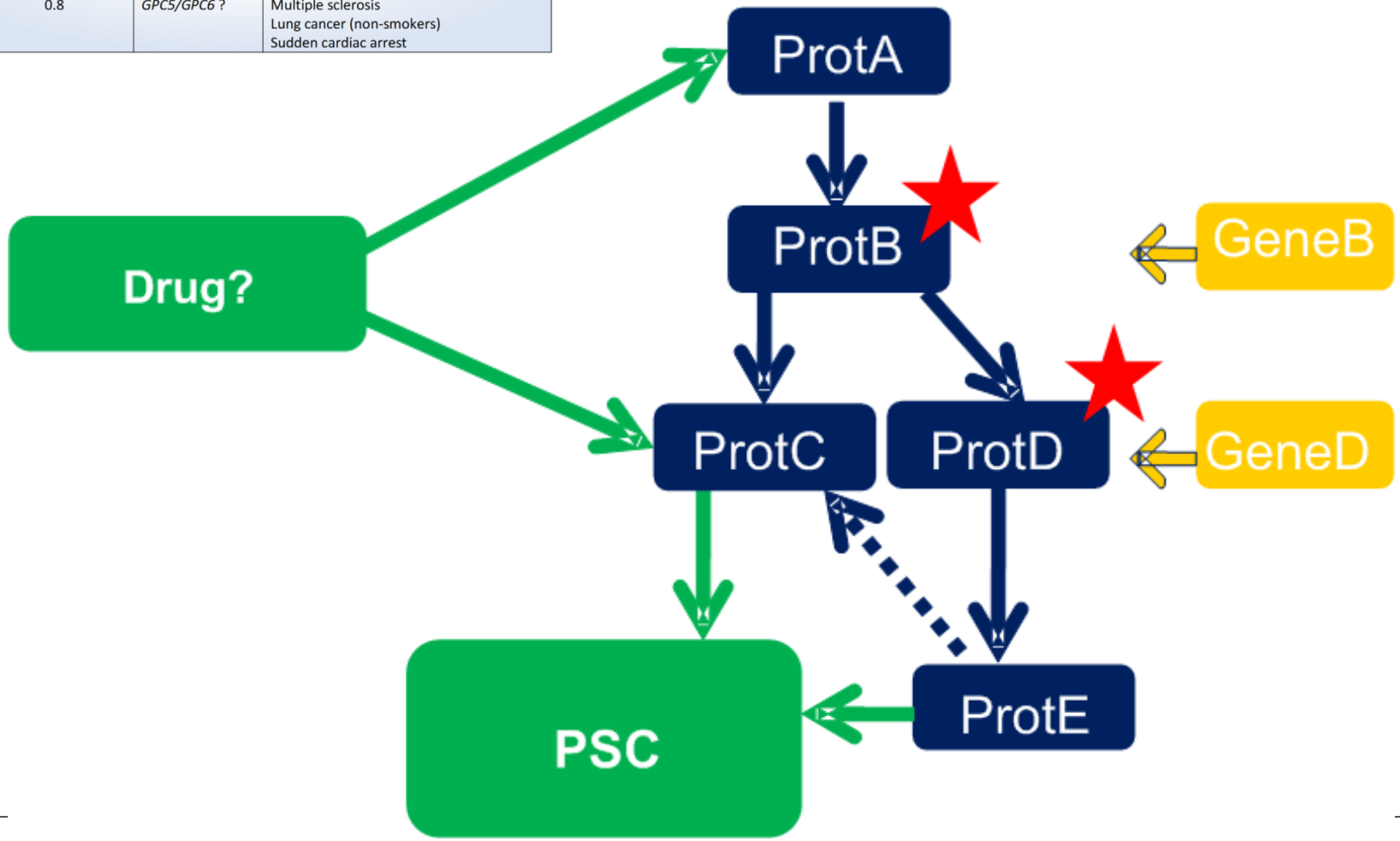
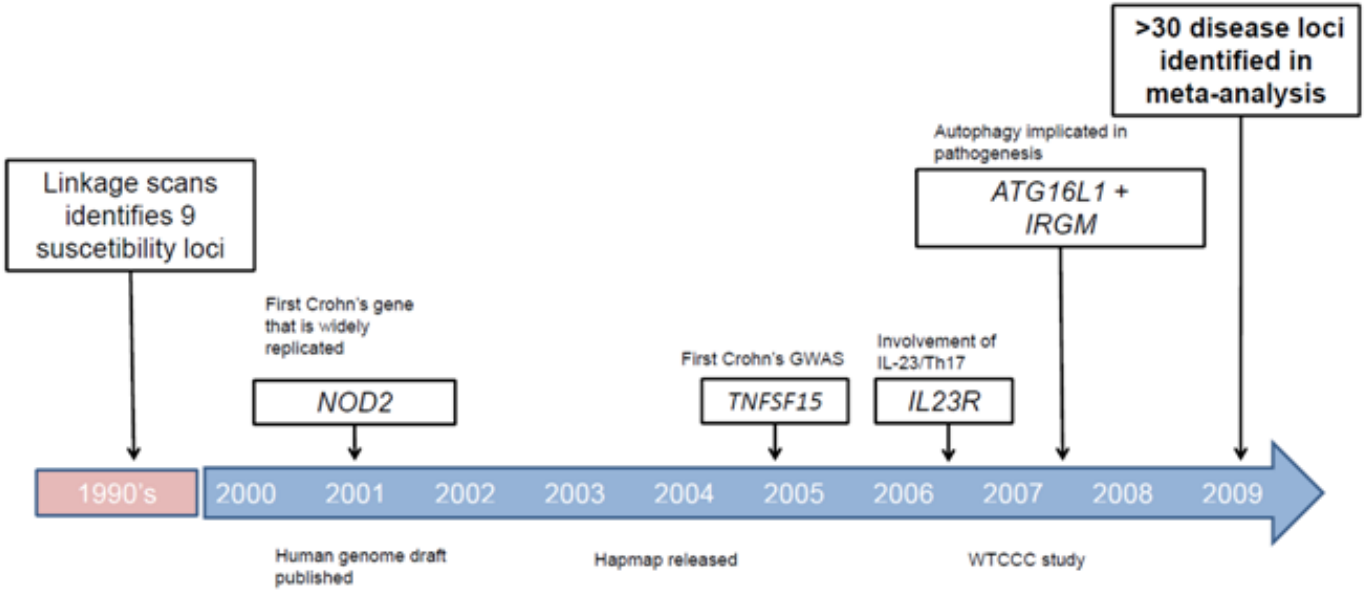


Will we find more genes in PSC?

Example;
Crohn´s disease



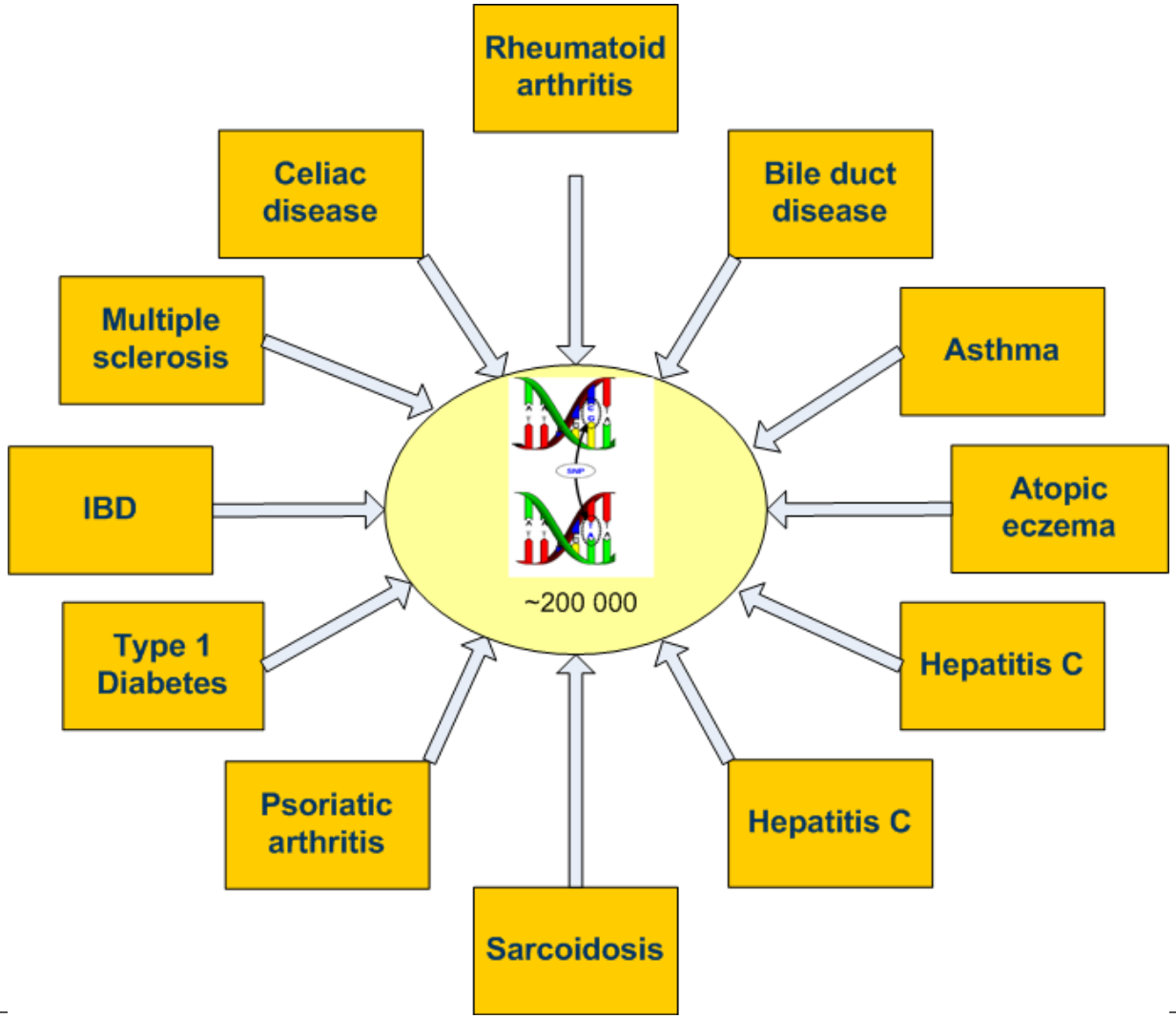
New GWAS in PSC

- Total cohort 715 PSC patients and 2962 healthy controls
- Genotyping 909 000 SNPs
- Two additional GWAS in preparation in UK and US

Future prospects in PSC

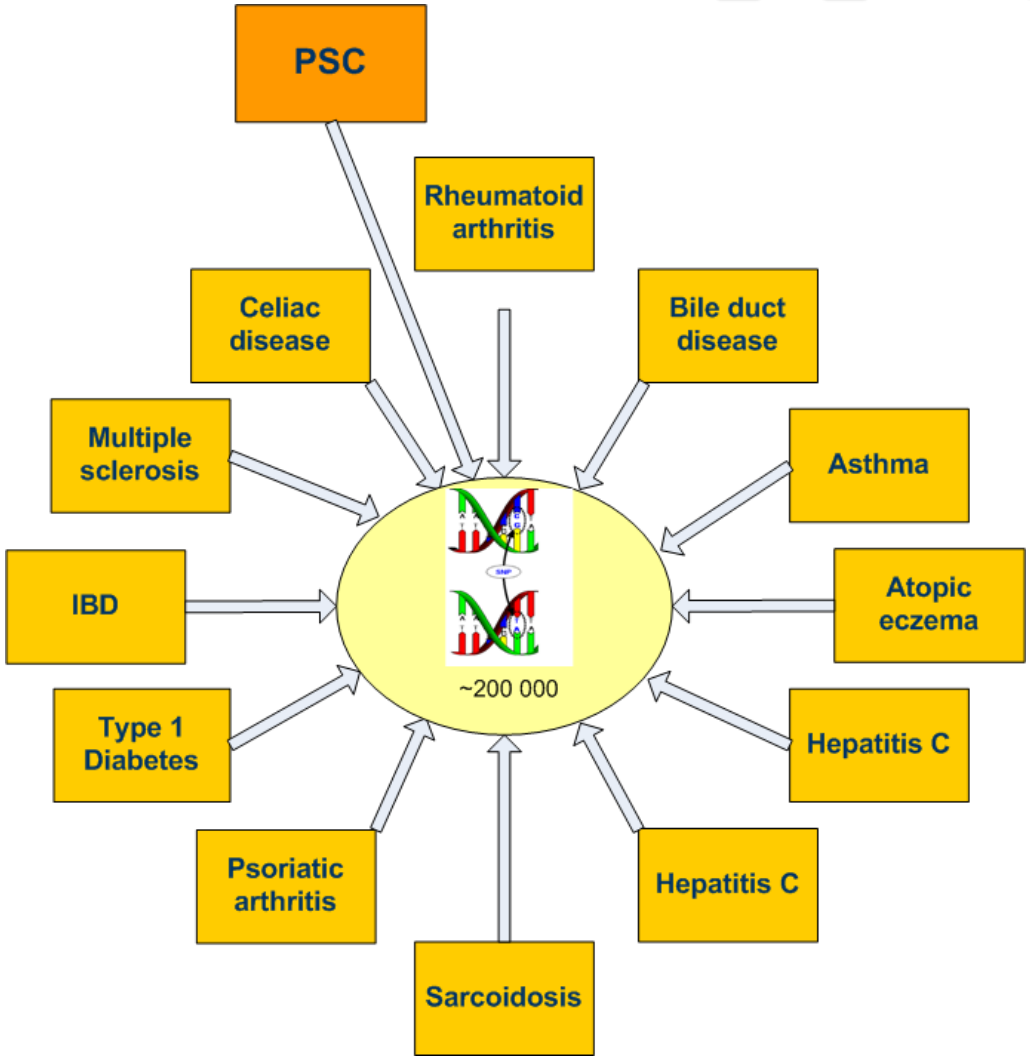
- International collaboration
- Existing data
- Further dissection of HLA
- Gene expression studies
- Exome family project
- PSC-IBD overlap
- Immunochip

The immunochip project

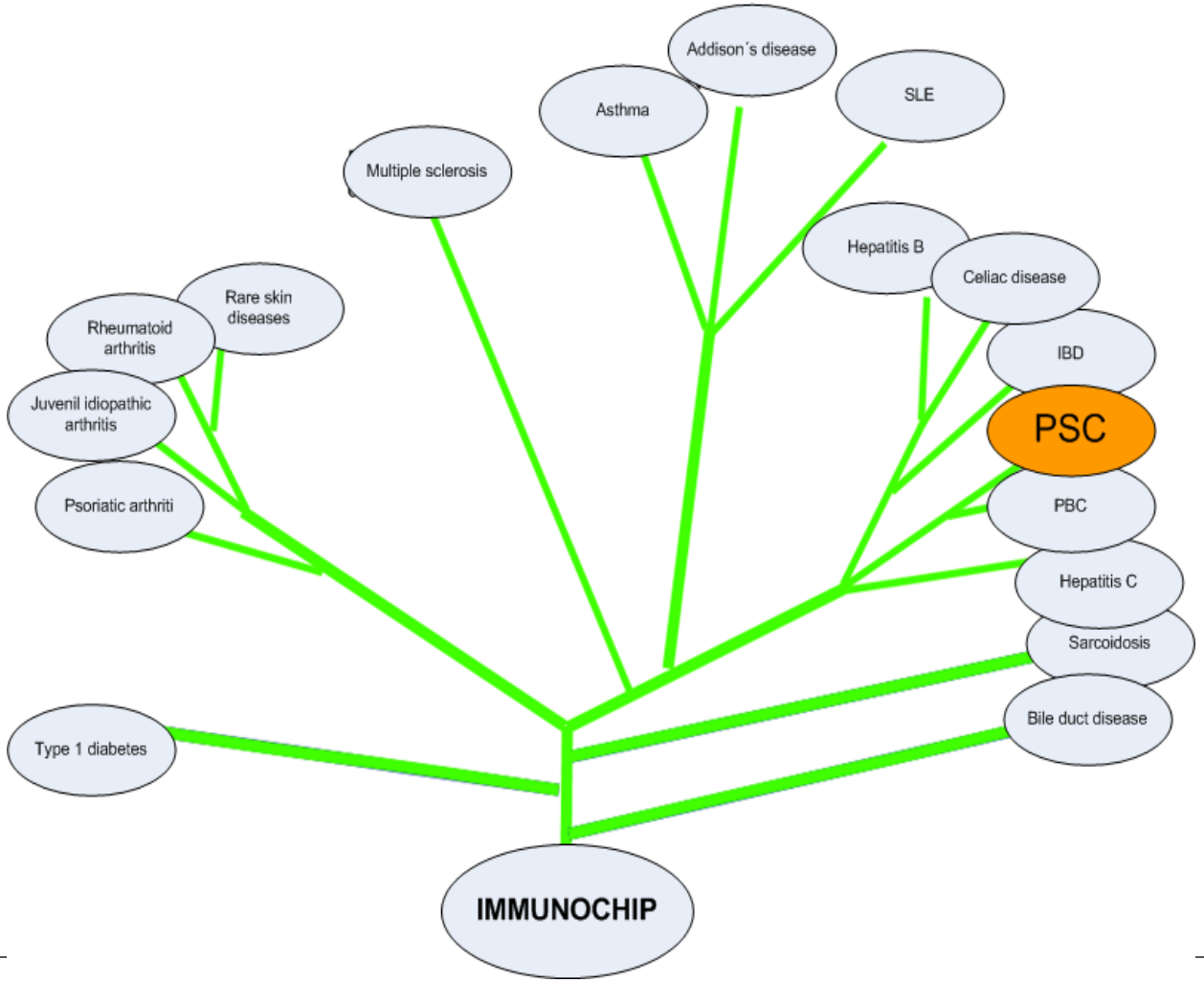


The immunochip project

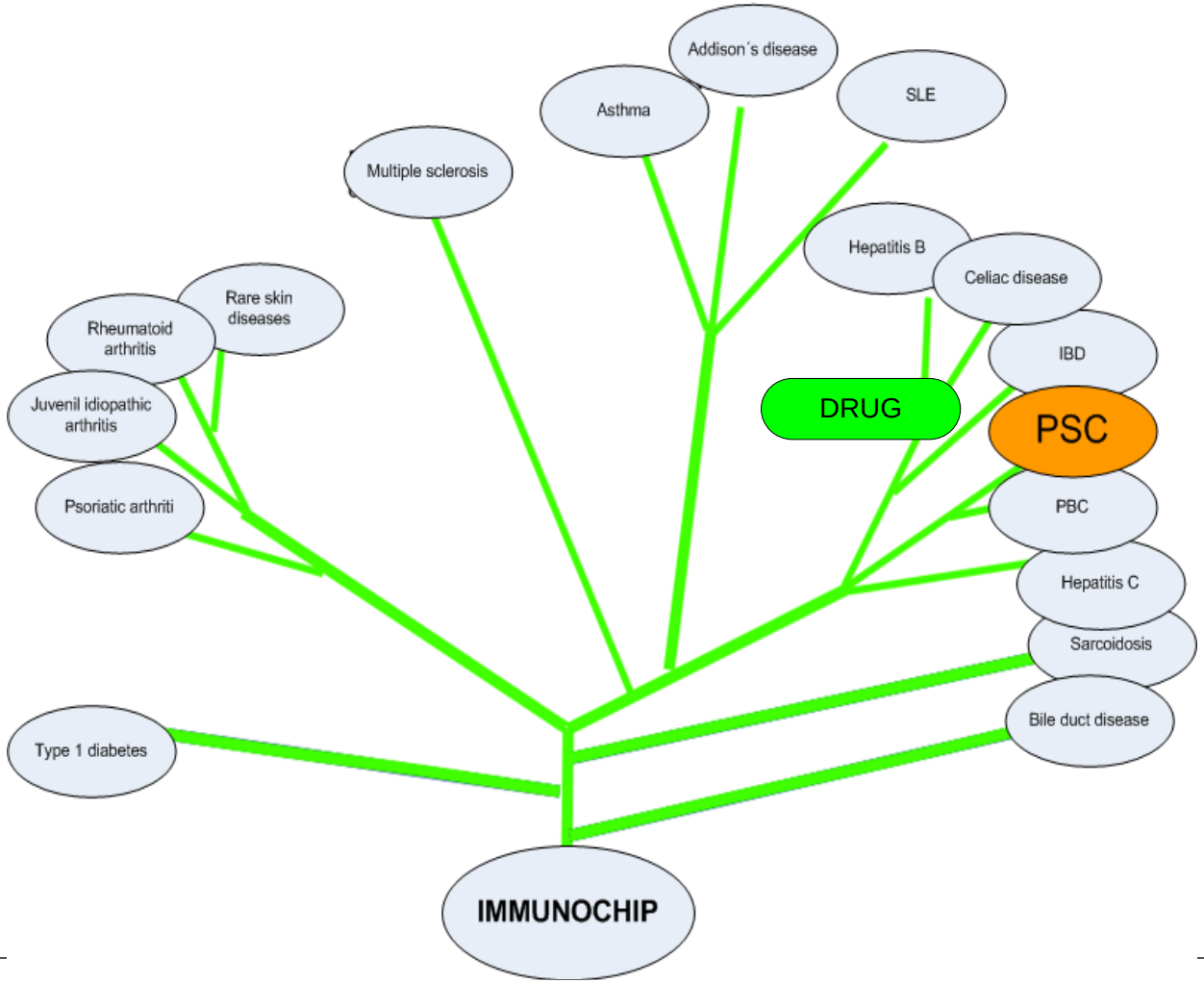
PSC:
n= 4000



The immunochip project



The immunochip project



Genes in PSC - summary

- **Genetic association studies as ”pathway-detection tools” provide clues to the pathogenesis of PSC**

- **Strong HLA association/”autoimmunity”/inflammatory pathways/”IBD” genes**