What Have We Learned from Genome-Wide Association Studies in PSC

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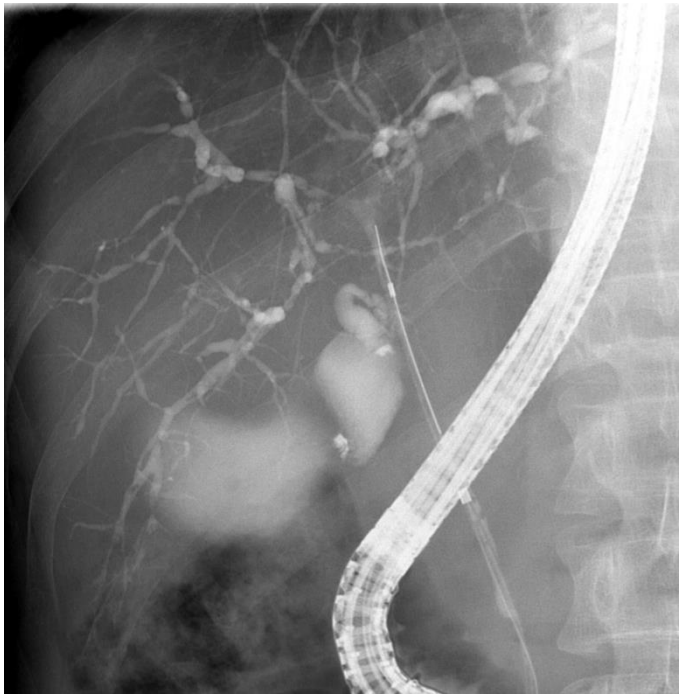
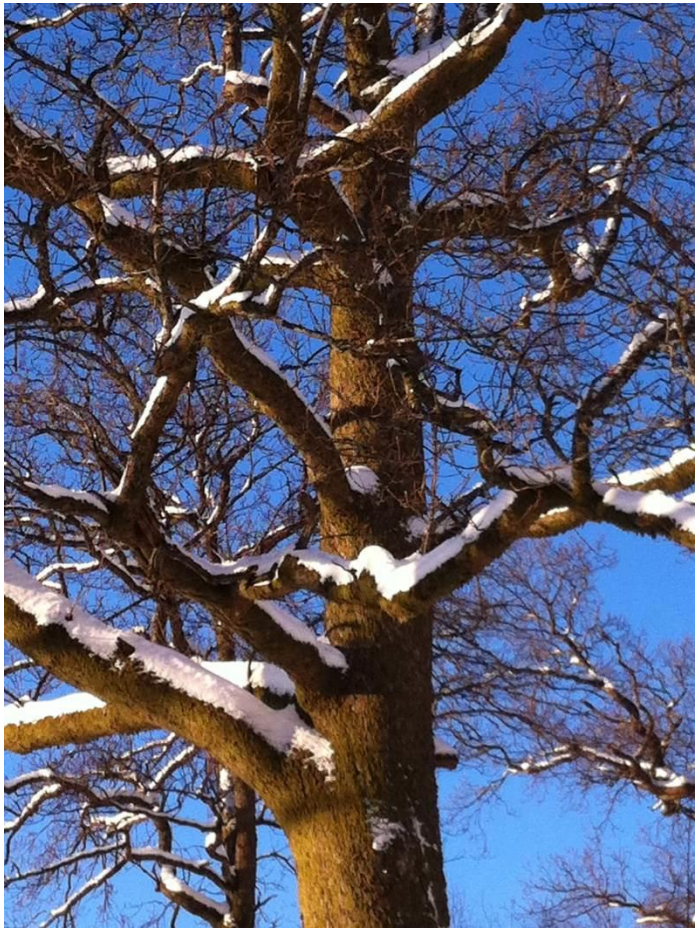
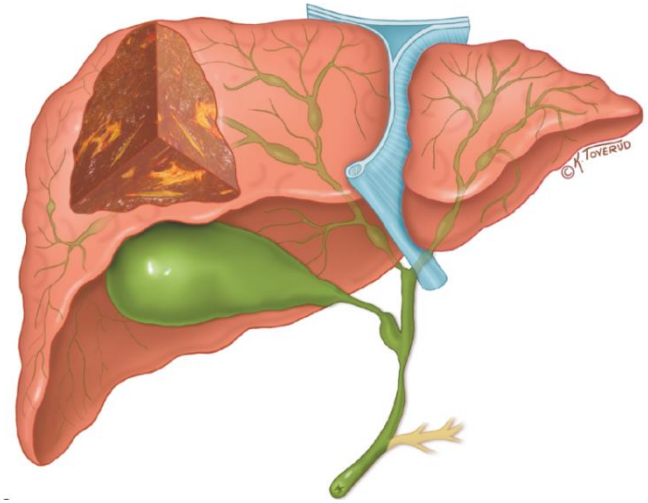
Primary sclerosing cholangitis



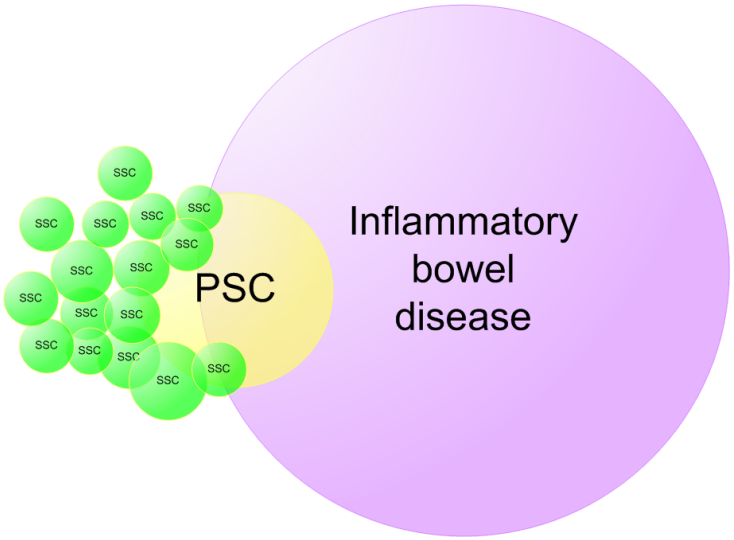


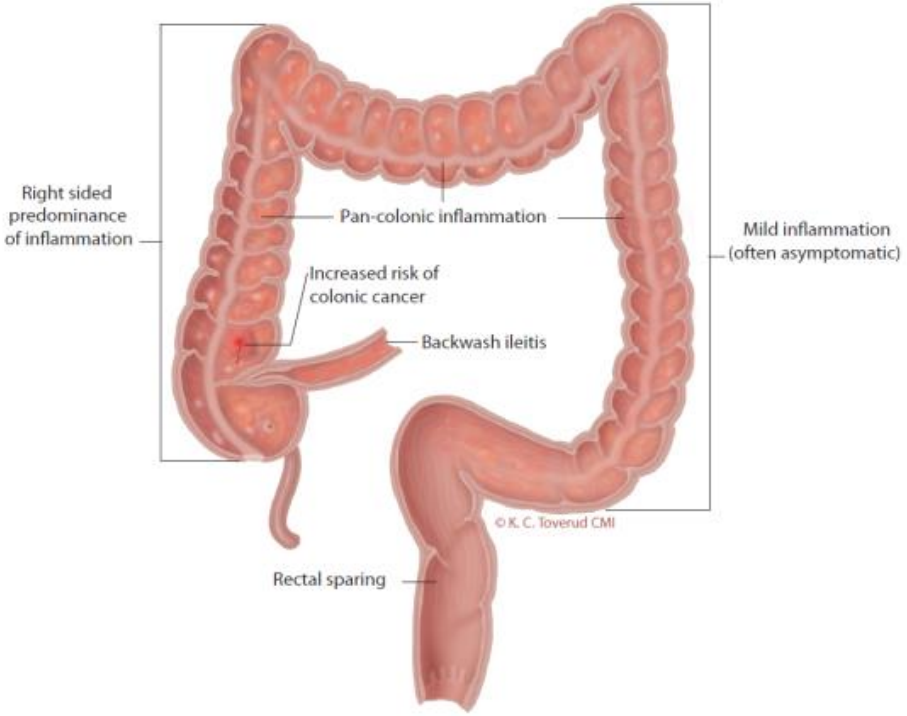
Known causes of sclerosing cholangitis



Infection	
	Bacterial/parasitic cholangitis
	Recurrent pyogenic cholangitis
Immunodeficiency related (infections)	
	Congenital immunodeficiency
	Acquired immunodeficiency (e.g. HIV)
	Combined immunodeficiencies
	Angioimmunoblastic lymphadenopathy
Mechanic/toxic	
	Cholelithiasis/choledocholithiasis
	Surgical bile duct trauma
	Intra-arterial chemotherapy
Ischaemic	
	Vascular trauma
	Hepatic allograft arterial insufficiency
	Paroxysmal nocturnal haemoglobinuria
Pancreatic disease	
	Chronic pancreatitis
	IgG4 related systemic disease
Others	
	Cystic fibrosis cholangiopathy
	ABCB4 associated cholangiopathy
	Sclerosing cholangitis of critical illness
	Hypereosinophilic syndrome
	Sarcoidosis
	Graft-versus-host disease
	Amyloidosis
	Systemic mastocytosis
	Caroli's disease
	Congenital hepatic fibrosis
	Other types of ductal plate abnormalities
	Hodgkin's disease
	Cholangitis glandularis proliferans
	Neoplastic/metastatic disease
	Langerhans cell histiocytosis
	Hepatic allograft rejection

“IBD-associated sclerosing cholangitis”

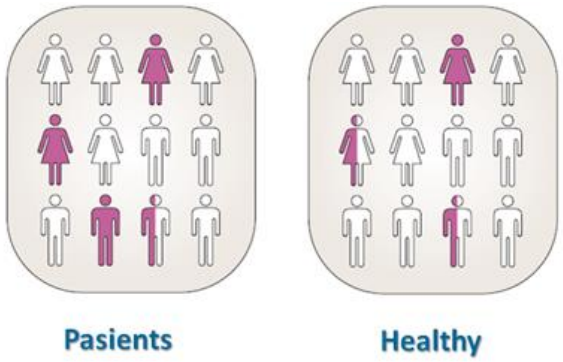


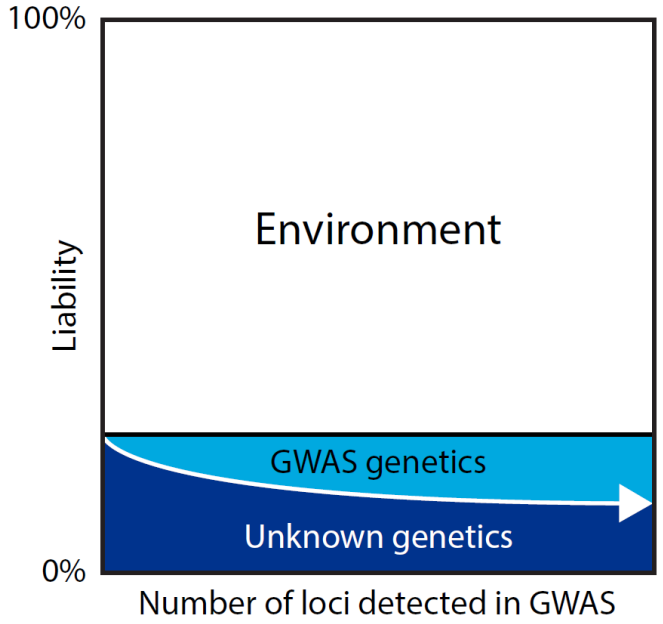


Grading the importance of genetics

- Relative sibling risk of autosomal dominant diseases >1000x
- Relative sibling risk of autosomal recessive diseases >200-500x
- Relative sibling risk of PBC 10x
- Relative sibling risk of PSC 9-39x
- Relative sibling risk of Crohn's disease 5-35x
- Relative risk in ulcerative colitis 3-9x
- Relative sibling risk of gallstones 2x

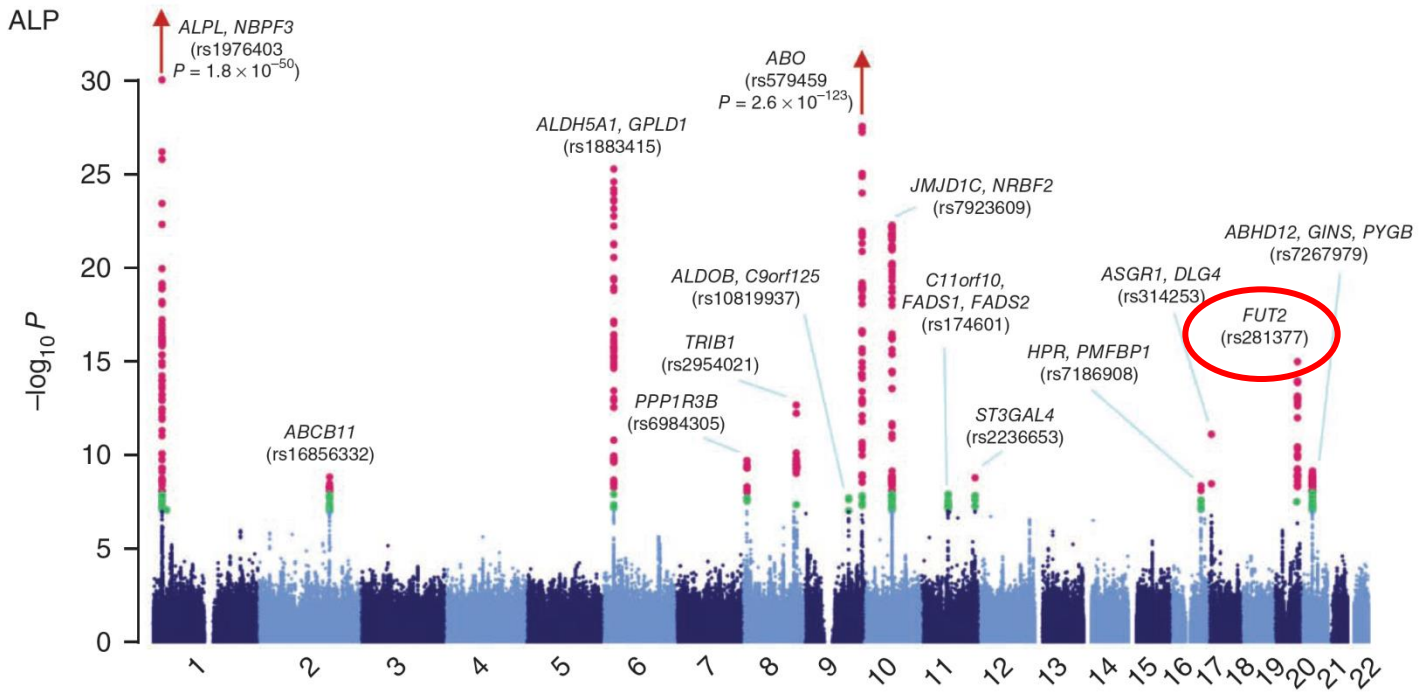
«GWAS genetics»





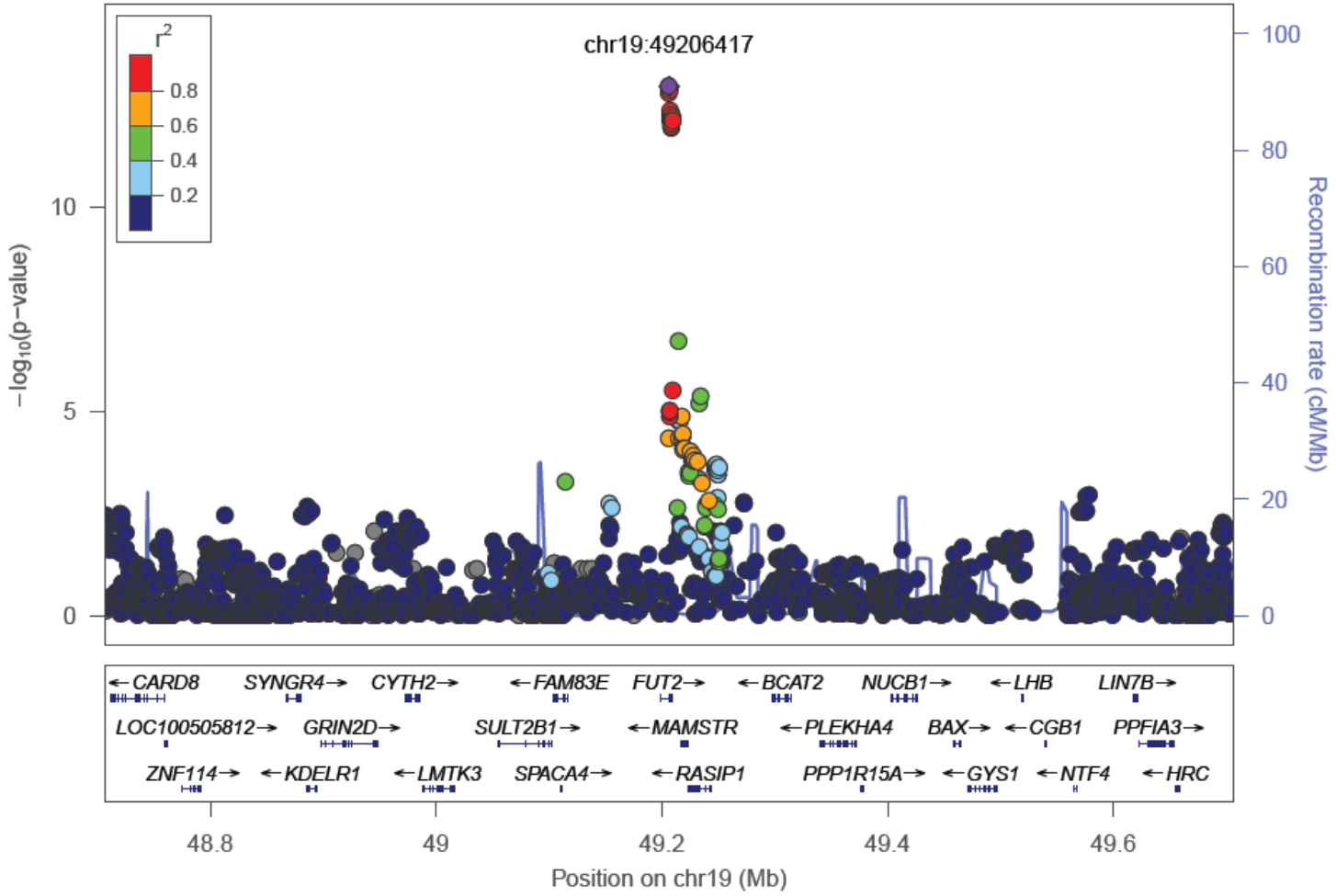
- **GWAS detect <u>common variants</u> that are >5,000-100,000 years old**
- **Rare variants are likely to lack environmental co-factors**

Alkaline phosphatase GWAS



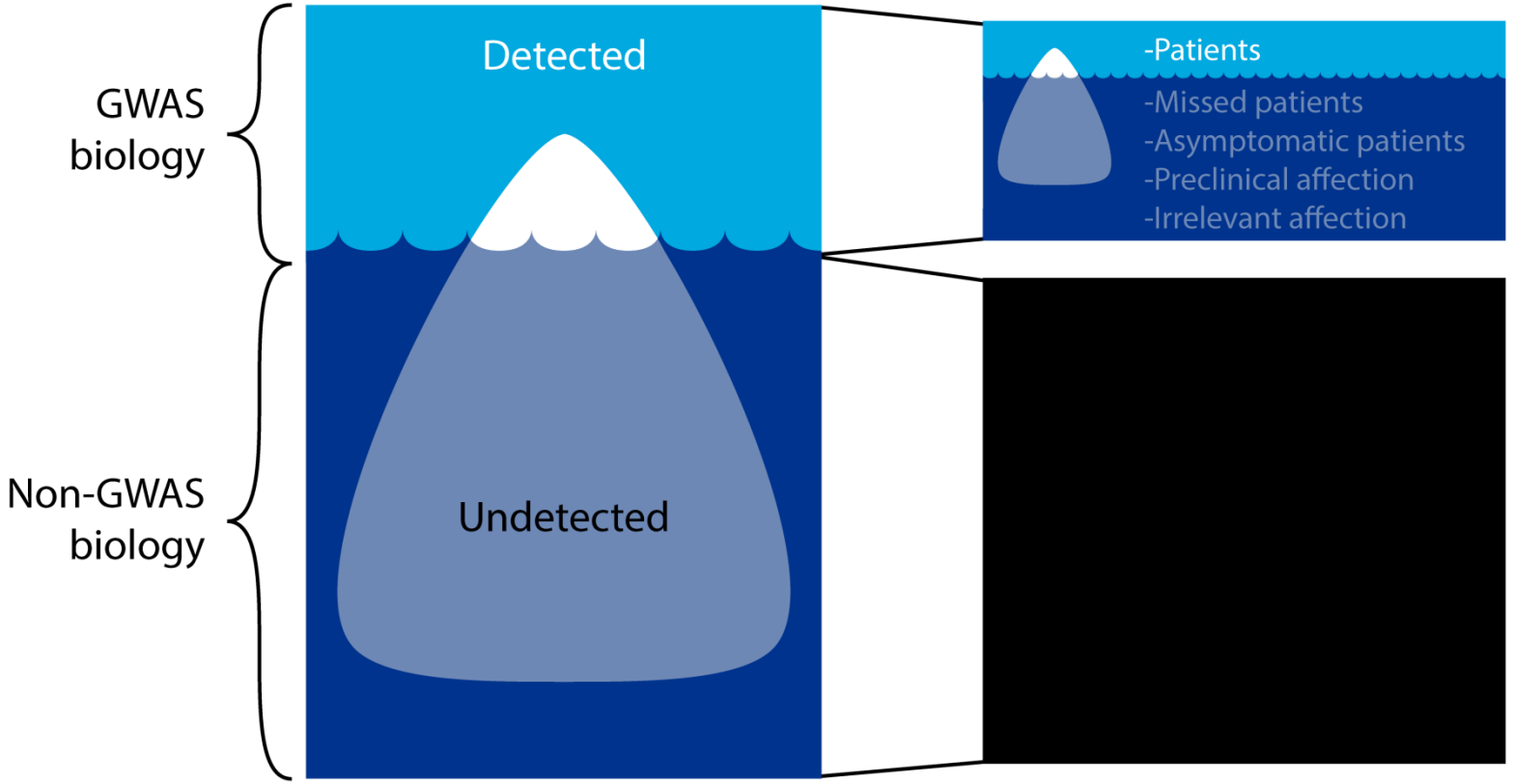
(Chambers, 2011)

FUT2 associations in PSC

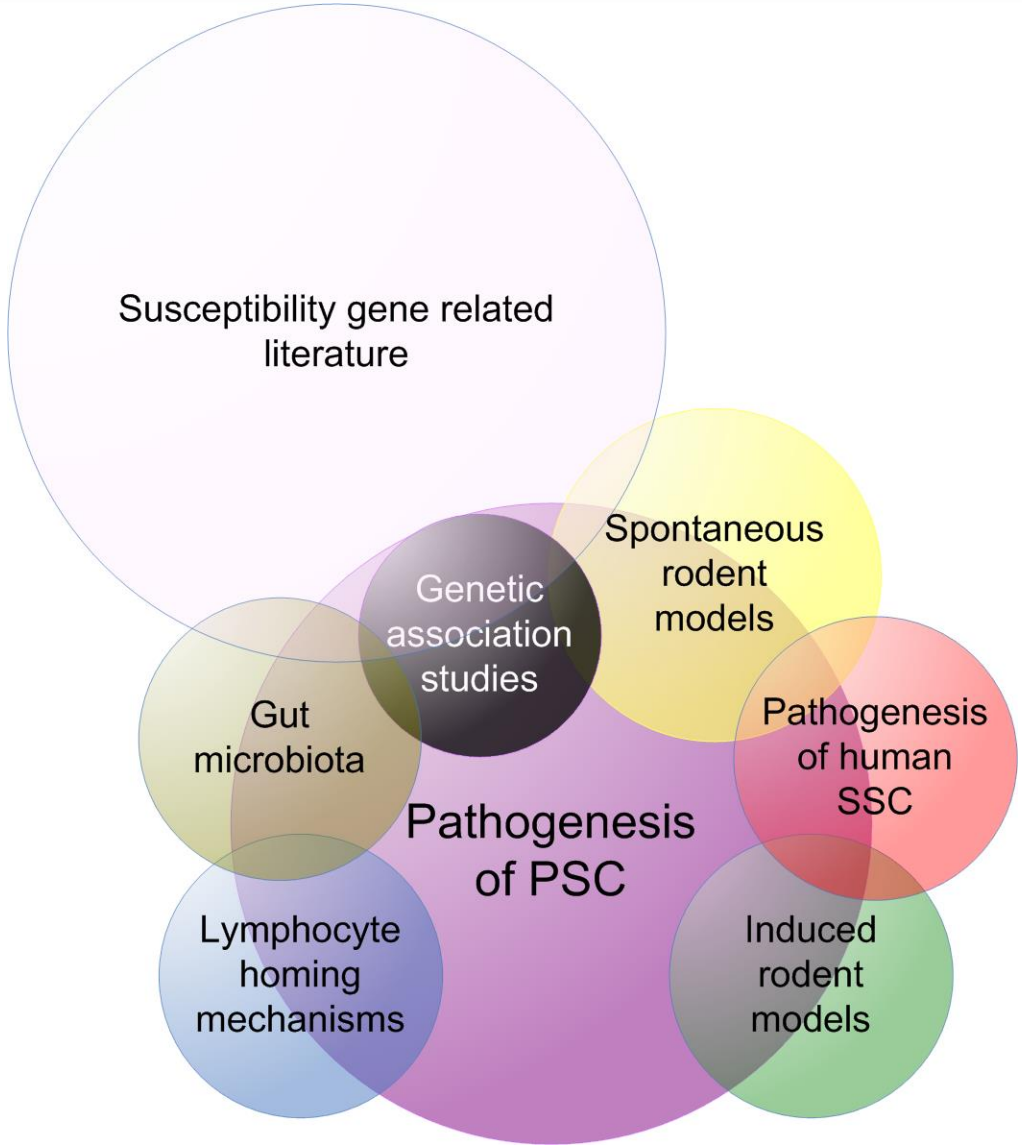


(Gou et al., in preparation)

Genetics of biology vs. disease



Genetics vs. “mechanistic” studies



Genetics of PSC – total outcome

LETTERS

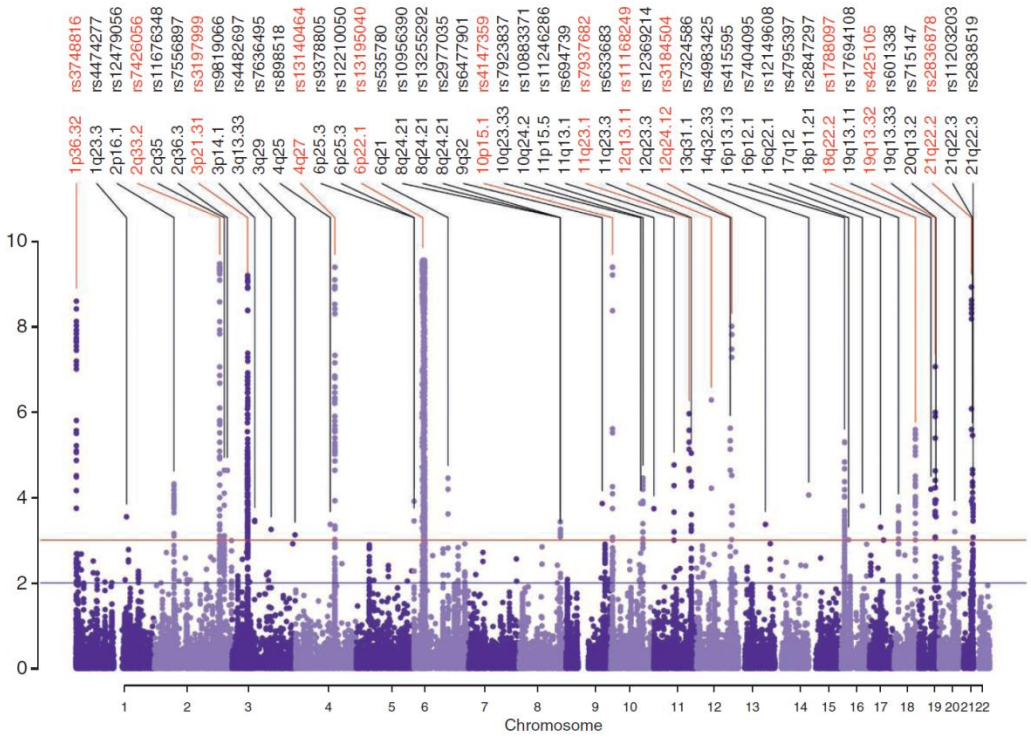
nature genetics

Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a severe liver disease of unknown etiology leading to fibrotic destruction of the bile ducts and ultimately to the need for liver transplantation[1–3]. We compared 3,789 PSC cases of European ancestry to 25,079 population controls across 130,422 SNPs genotyped using the Immunochip[4]. We identified 12 genome-wide significant associations outside the human leukocyte antigen (HLA) complex, 9 of which were new, increasing the number of known PSC risk loci to 16. Despite comorbidity with inflammatory bowel disease (IBD) in 72% of the cases, 6 of the 12 loci showed significantly stronger association with PSC than with IBD, suggesting overlapping yet distinct genetic architectures for these two diseases. We incorporated association statistics from 7 diseases clinically occurring with PSC in the analysis and found suggestive evidence for 33 additional pleiotropic PSC risk loci. Together with network analyses, these findings add to the genetic risk map of PSC and expand on the relationship between PSC and other immune-mediated diseases.

The pathogenesis of PSC is poorly understood, and, owing to the lack of effective medical therapy, PSC remains a leading indicator for liver transplantation in northern Europe and the United States[5], despite its relatively low prevalence (1 in 10,000). Affected individuals are diagnosed at a median age of 30–40 years and suffer from an increased frequency of IBD (60–80%)[5,6] and autoimmune diseases (25%)[7]. Conversely, approximately only 5% of individuals with IBD develop PSC[5,6]. Sibling relative risk of 9- to 39-fold indicates a strong genetic component to PSC risk[8]. In addition to multiple strong associations within the HLA complex, recent association studies have identified genome-wide significant loci at 1p36 (*MMEL1-TNFRSF14*), 2q13 (*BCL2L11*), 2q37 (*GPR35*), 3p21 (*MST1*), 10p15 (*IL2RA*) and 18q21 (*TCF4*)[9–13].

Several theories have been proposed to explain the development of PSC[5]. The strong HLA associations and the clinical occurrence of PSC with immune-mediated diseases suggest that autoimmunity has a role in pathogenesis. To further characterize the genetic etiology of PSC, we recruited individuals with PSC throughout Europe and North America, more than doubling the number of ascertained cases included in previous genetic studies[11]. We genotyped 196,524 SNPs in 4,228 PSC cases and 27,077 population controls (Online Methods and **Supplementary Note**) using the Immunochip[4,14], a targeted genotyping array with dense marker coverage across 186 known disease loci from 12 immune-mediated diseases. Outside these 186 loci, the Immunochip also assays thousands of SNPs of intermediate significance from multiple meta-analyses of immune-mediated diseases.

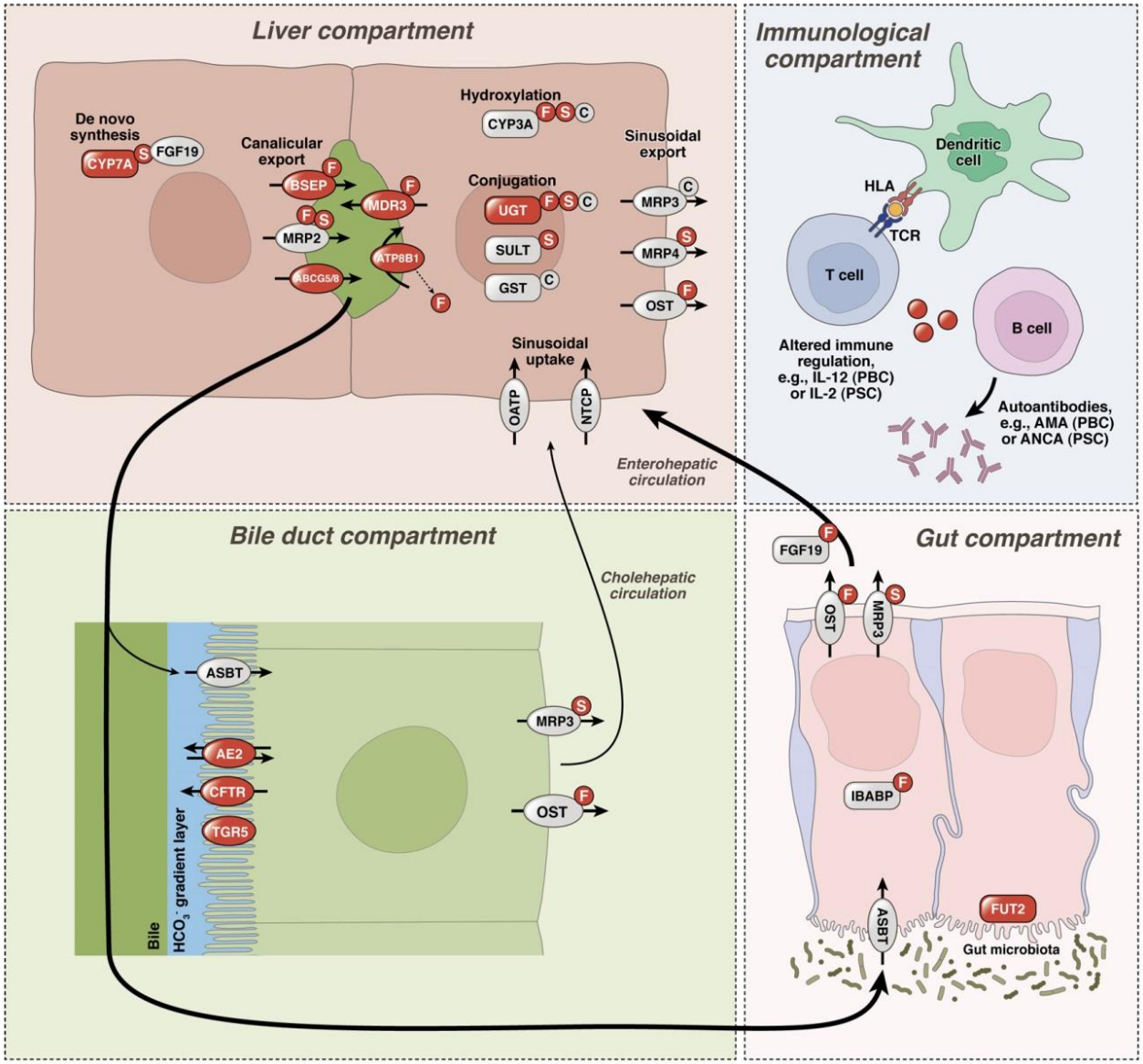


- **Ongoing study: Immunochip cross-phenotype analysis**
- **Ongoing study: US/UK/German/Scandinavian GWAS meta-analysis**
- **Ongoing study: PSC & PBC pruritus GWAS**

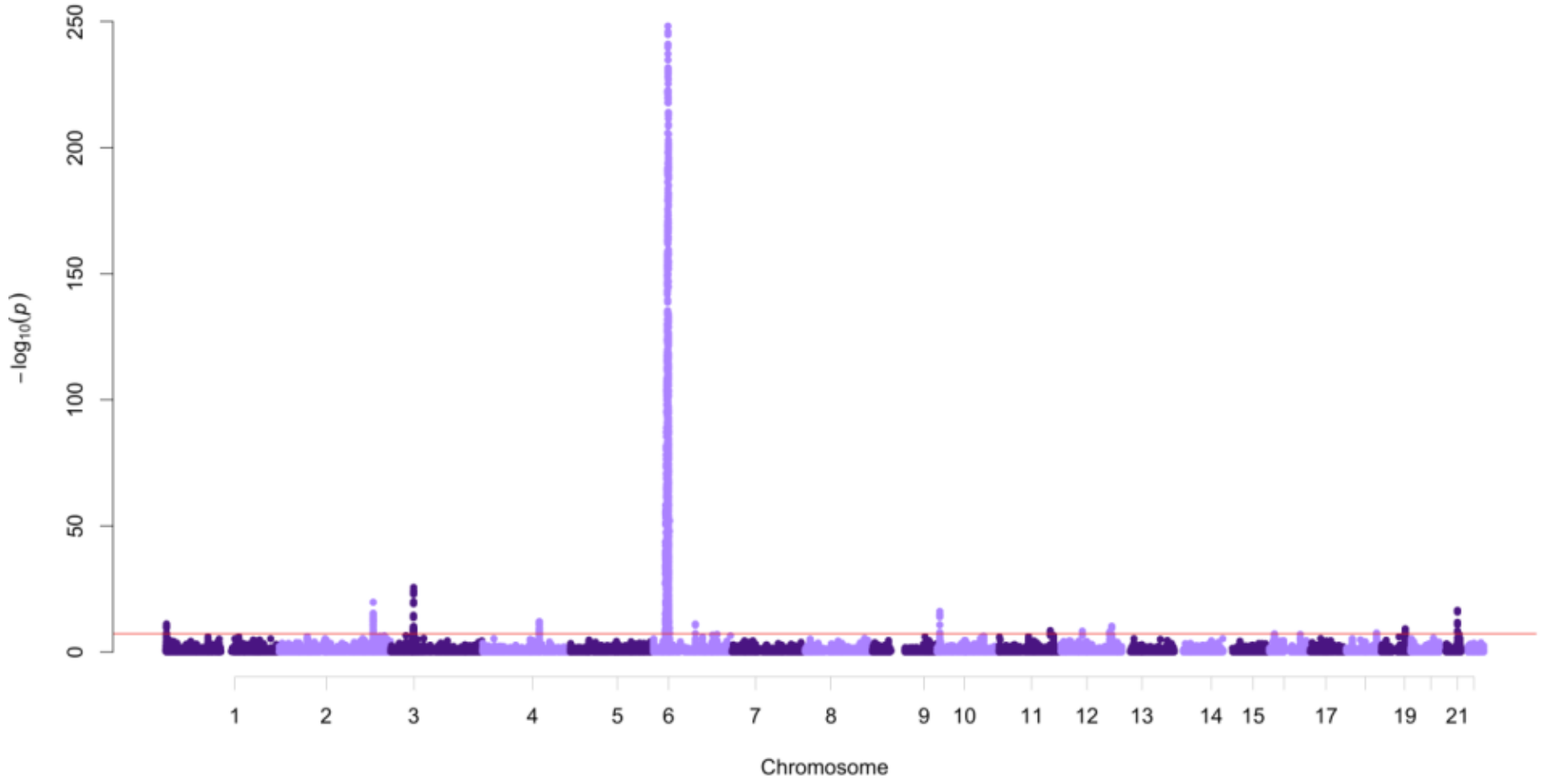
The 16 main genes in PSC

Locus	Gene	PSC	UC	CD	DM	CeD	RA	AITD	MS	PBC	VIT	AS	PS	SLE	SSc	SARC
01p36.32	*TNFRSF14*	1	1	0	0	1	1	1	1	1	0	0	0	0	0	0
02q13	*BCL2L11*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
02q33	*CD28*	1	0	0	1	1	1	1	0	0	0	0	0	0	0	0
02q37.3	*GPR35*	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
03p21.31	*MST1*	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
04q27	*IL2,IL21*	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
06p21	*HLA*	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
06q15	*BACH2*	1	0	1	1	1	0	1	1	0	1	0	0	0	0	0
10p15.1	*IL2RA*	1	0	1	1	0	1	0	1	0	1	0	0	0	0	0
11q23	*SIK2*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12q13	*HDAC7*	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
12q24	*SH2B3*	1	0	0	1	1	0	1	0	1	0	0	0	0	0	0
18q21	*TCF4*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18q22	*CD226*	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0
19q13	*PRKD2, STRN4*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21q22	*PSMG1*	1	1	1	0	0	0	0	0	0	0	1	0	0	0	0
Number of shared loci		**NA**	**7**	**7**	**7**	**6**	**5**	**5**	**4**	**3**	**3**	**2**	**1**	**1**	**1**	**1**

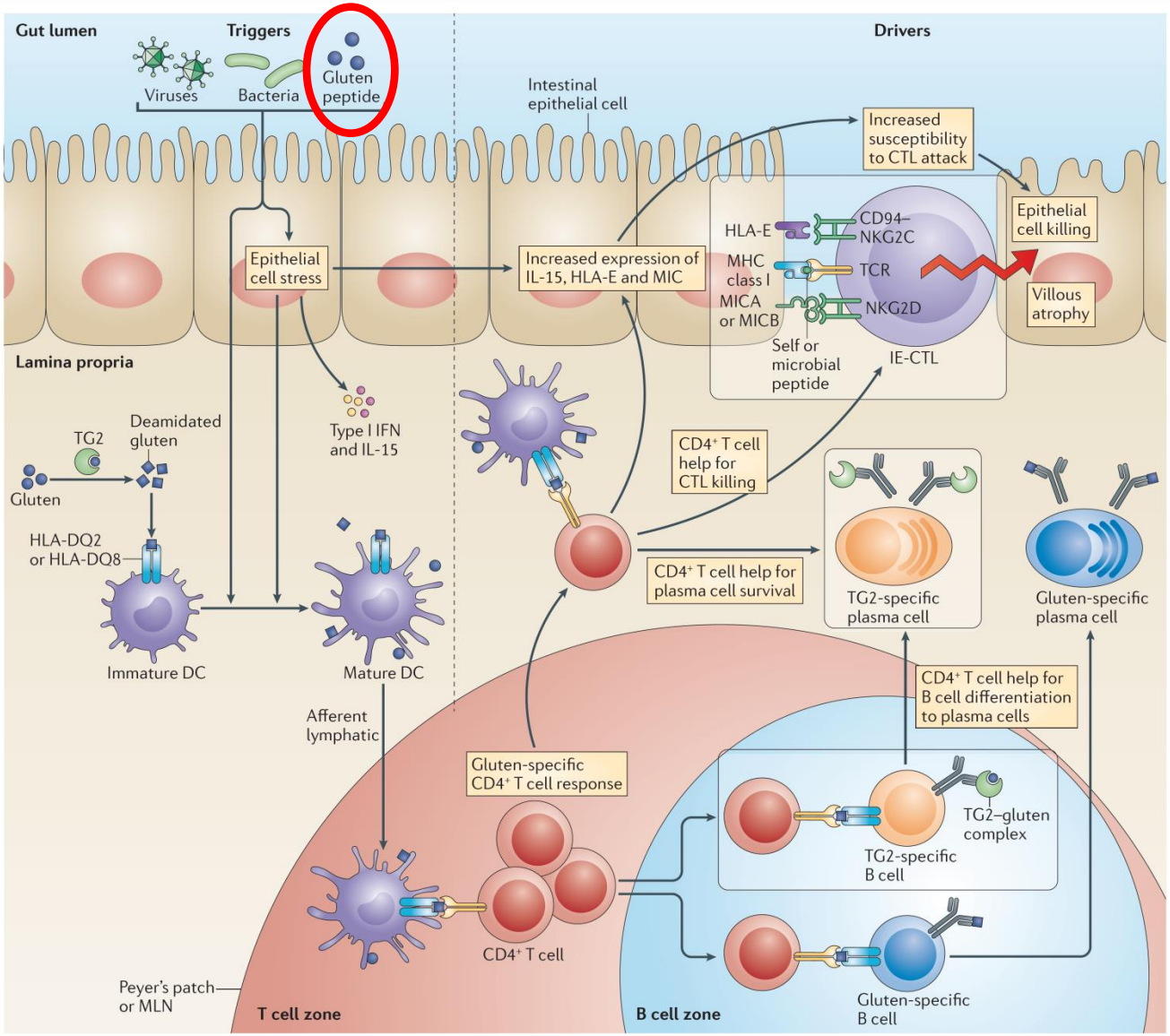
PSC genes = immunology



…is there (another) elephant in the room?



Modeling autoimmunity from celiac disease



(Sollid and Jabri, 2013)

Modeling autoimmunity from celiac disease

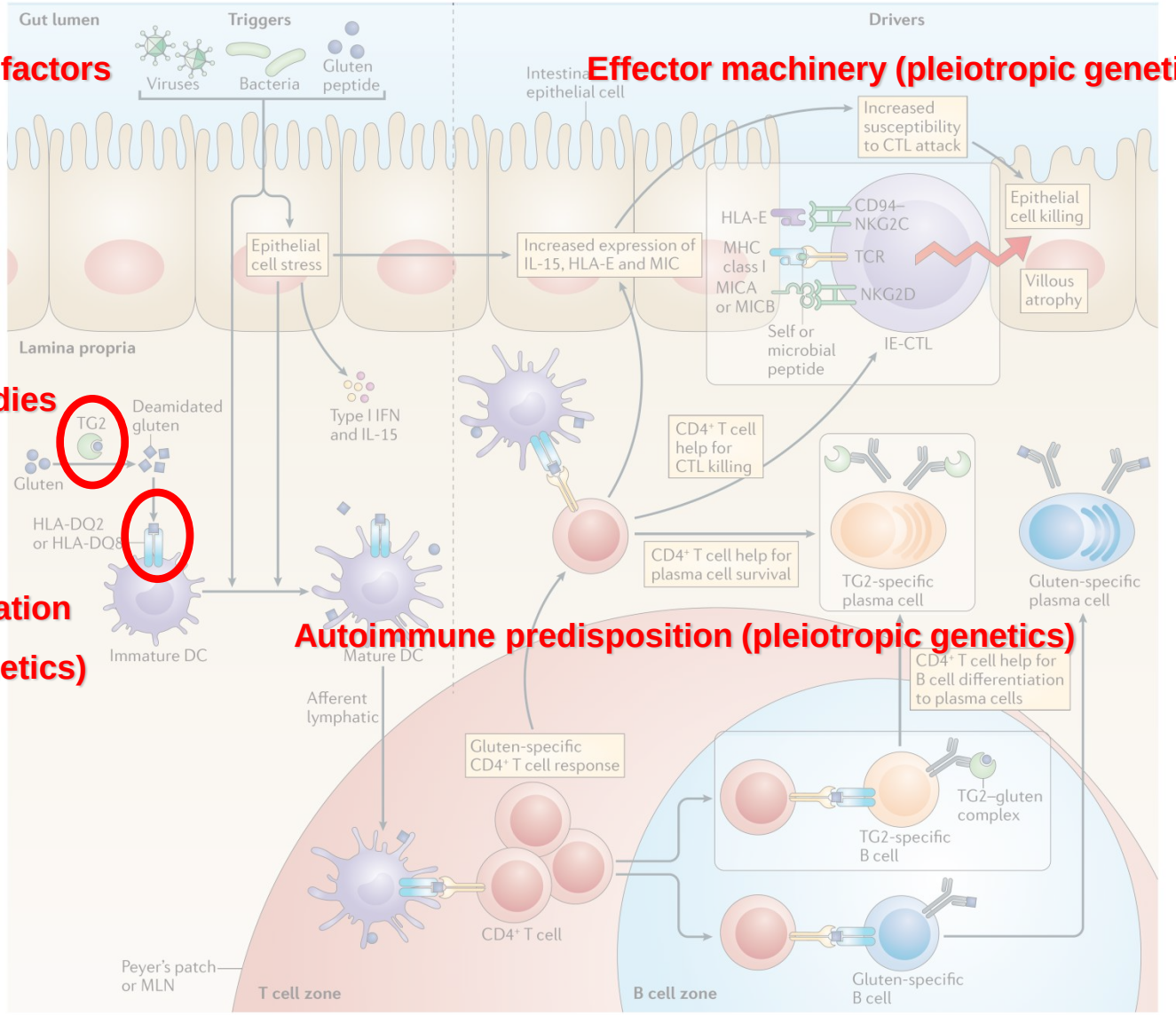
Environmental factors

Effector machinery (pleiotropic genetics)

Autoantibodies

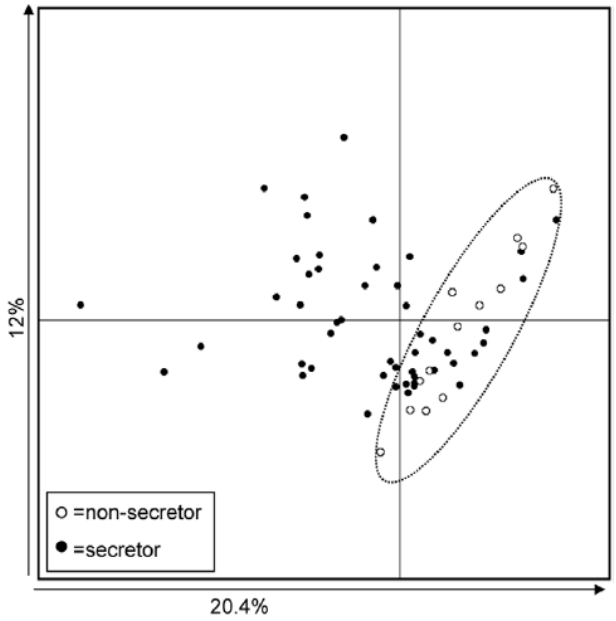
HLA association (specific genetics)

Autoimmune predisposition (pleiotropic genetics)

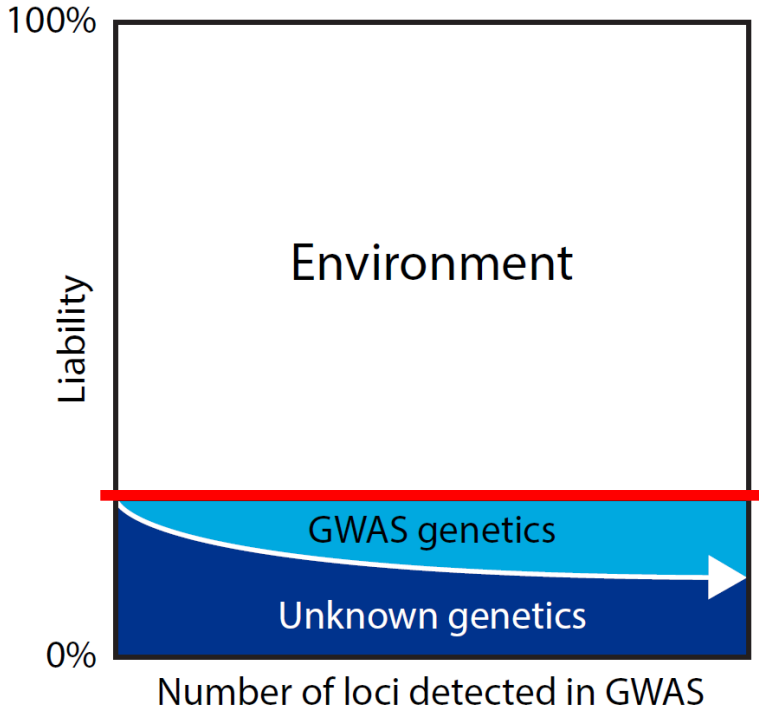


(Sollid and Jabri, 2013)

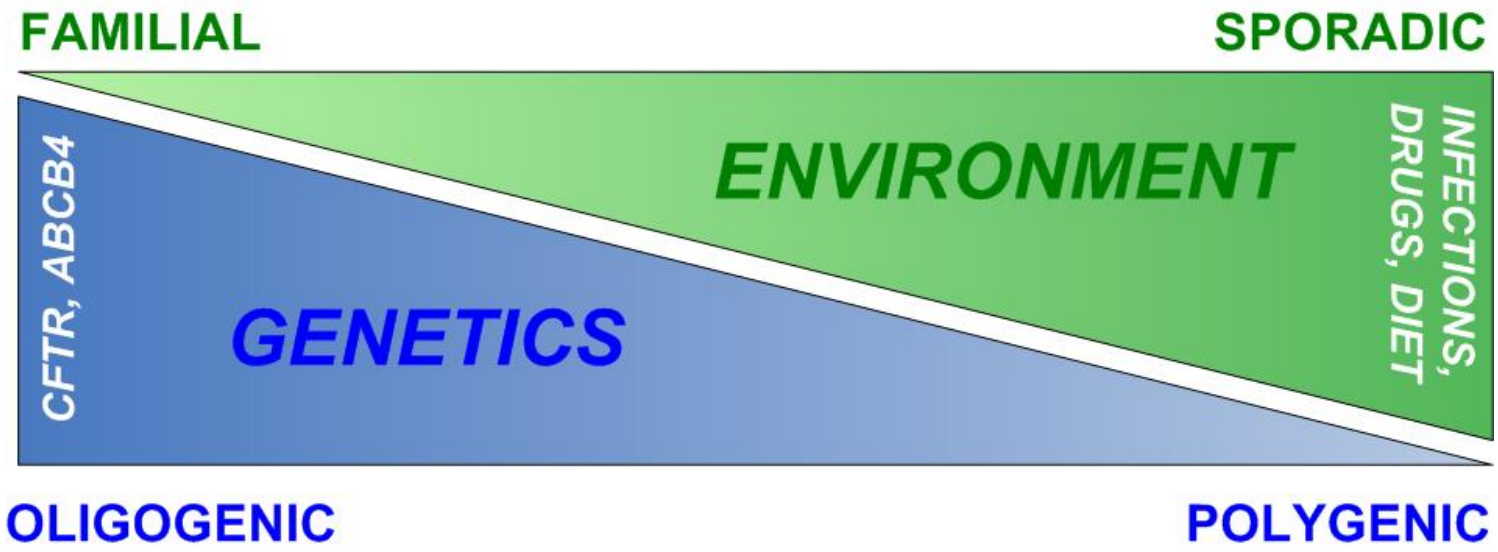
Gene-environment interaction – *FUT2*



(Wacklin et al. 2011)

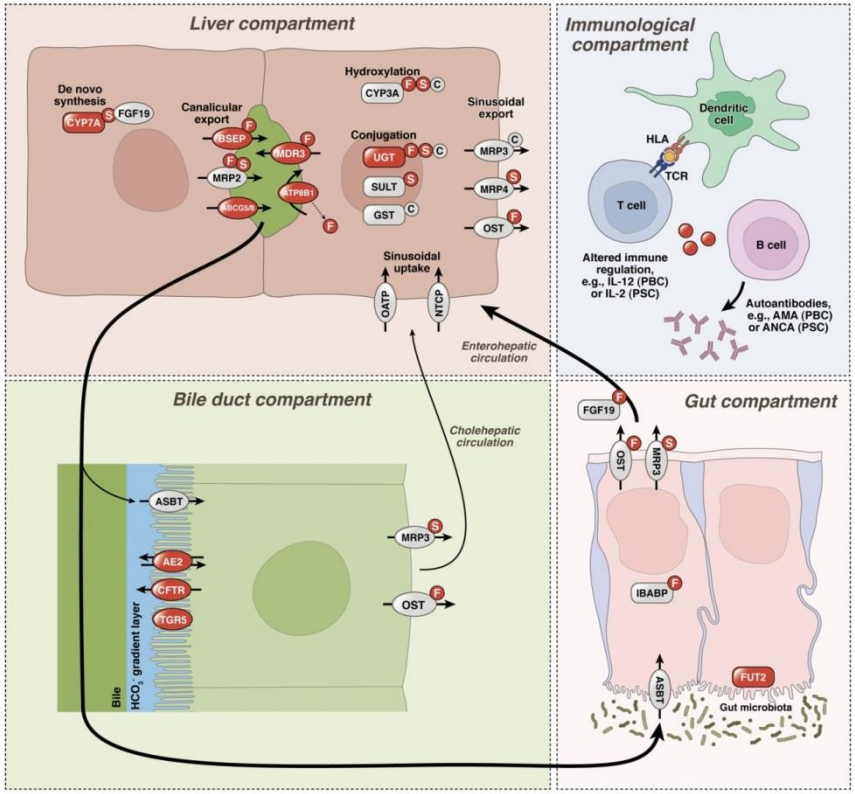


Genetics and «sclerosing cholangitis»



Genetic “compartments” vs. therapy

Bile acid therapy



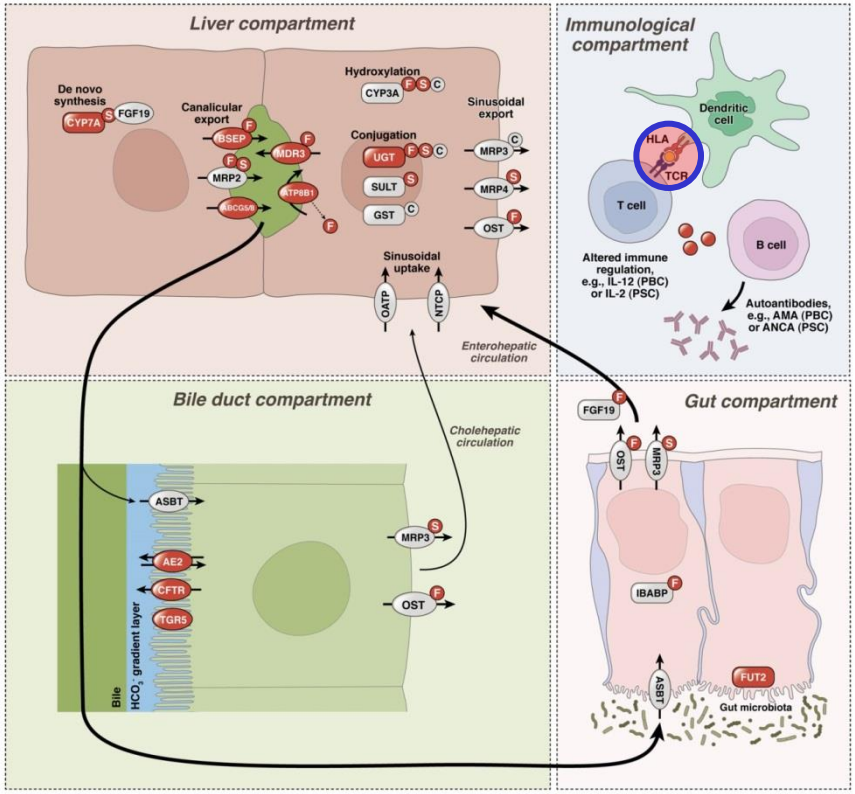
Immuno-suppression/ anti-fibrotics

Lymphocyte traficking blockade

Antibiotics/ prebiotics/ probiotics

Genetic “compartments” vs. therapy

Bile acid therapy



Immuno-suppression/ anti-fibrotics

Lymphocyte trafficking blockade

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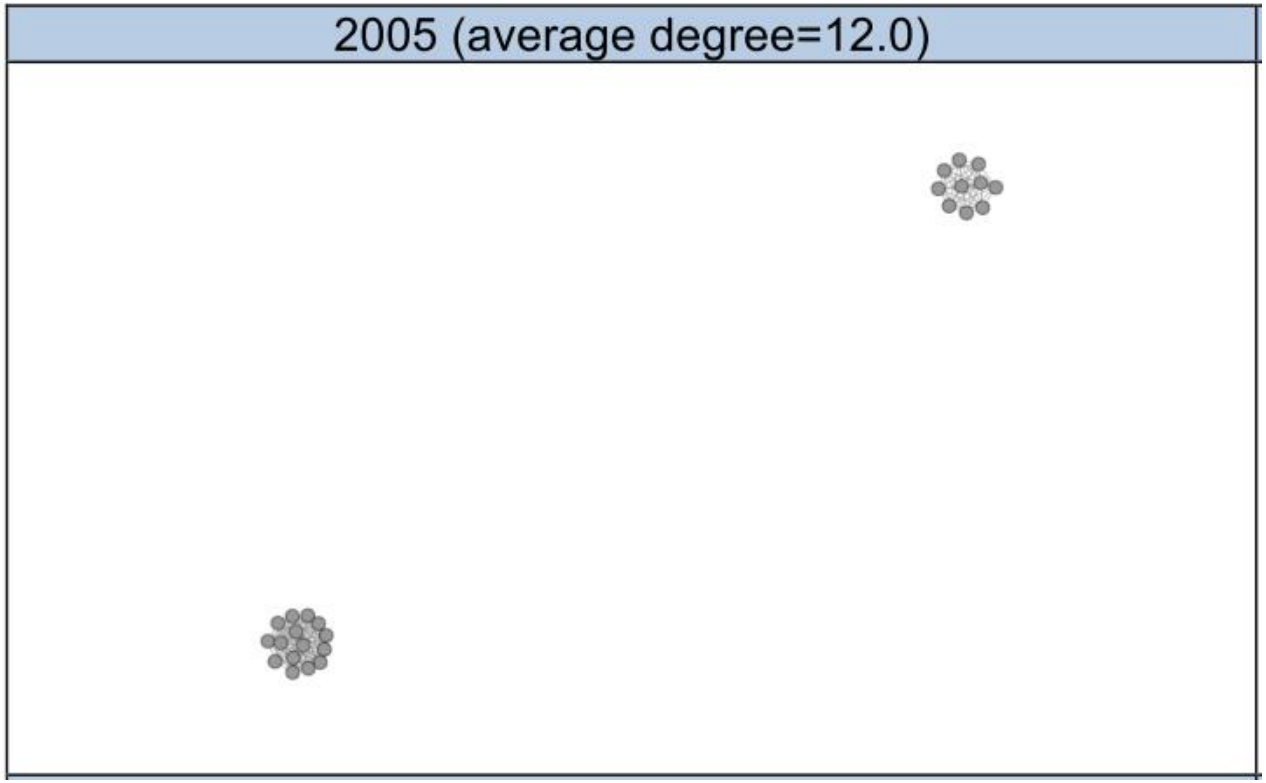
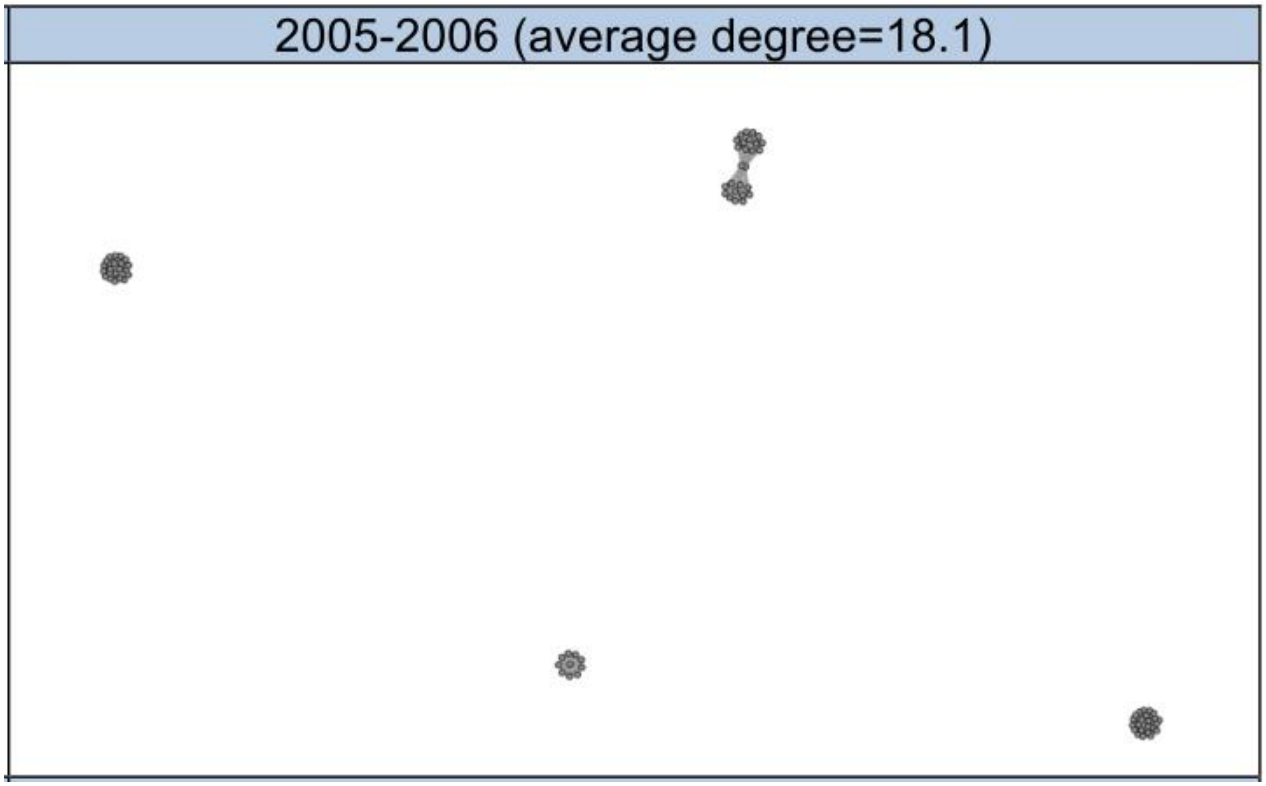
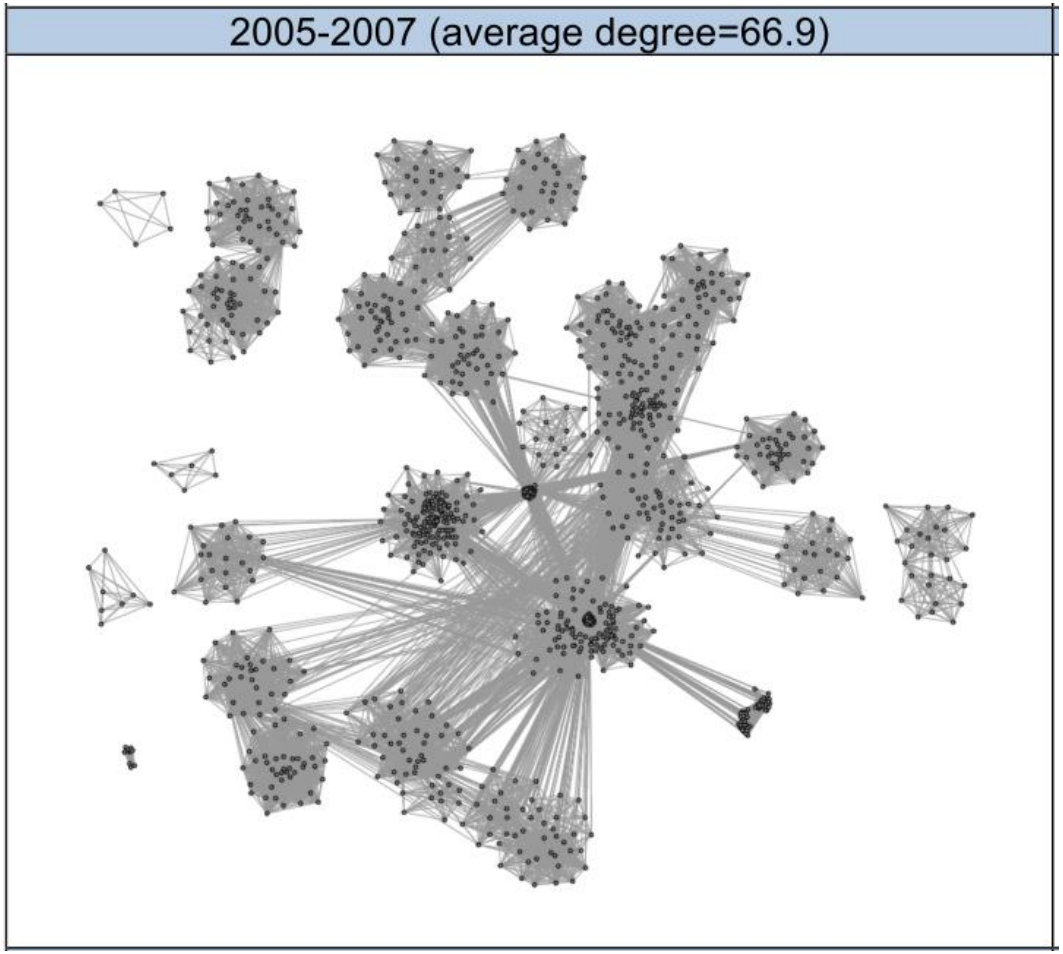


(Sulliman, 2012)



(Sulliman, 2012)



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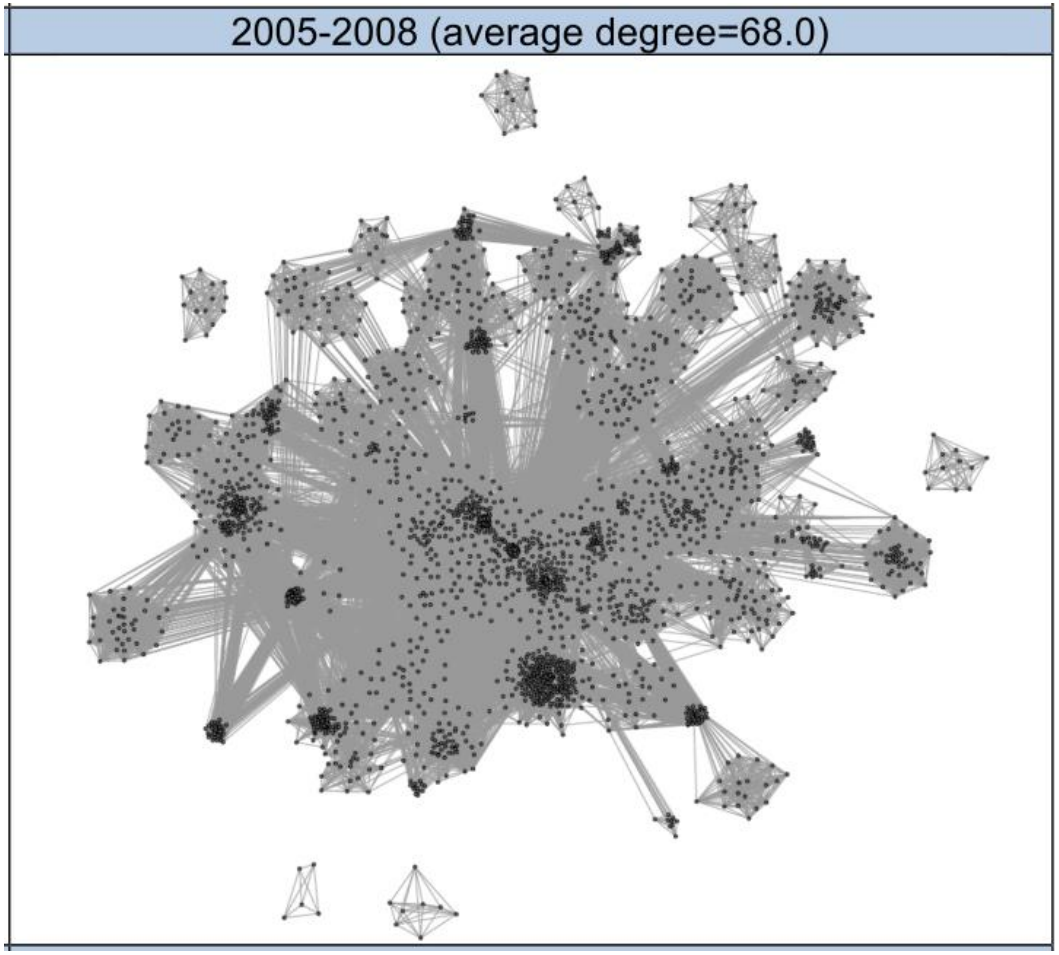

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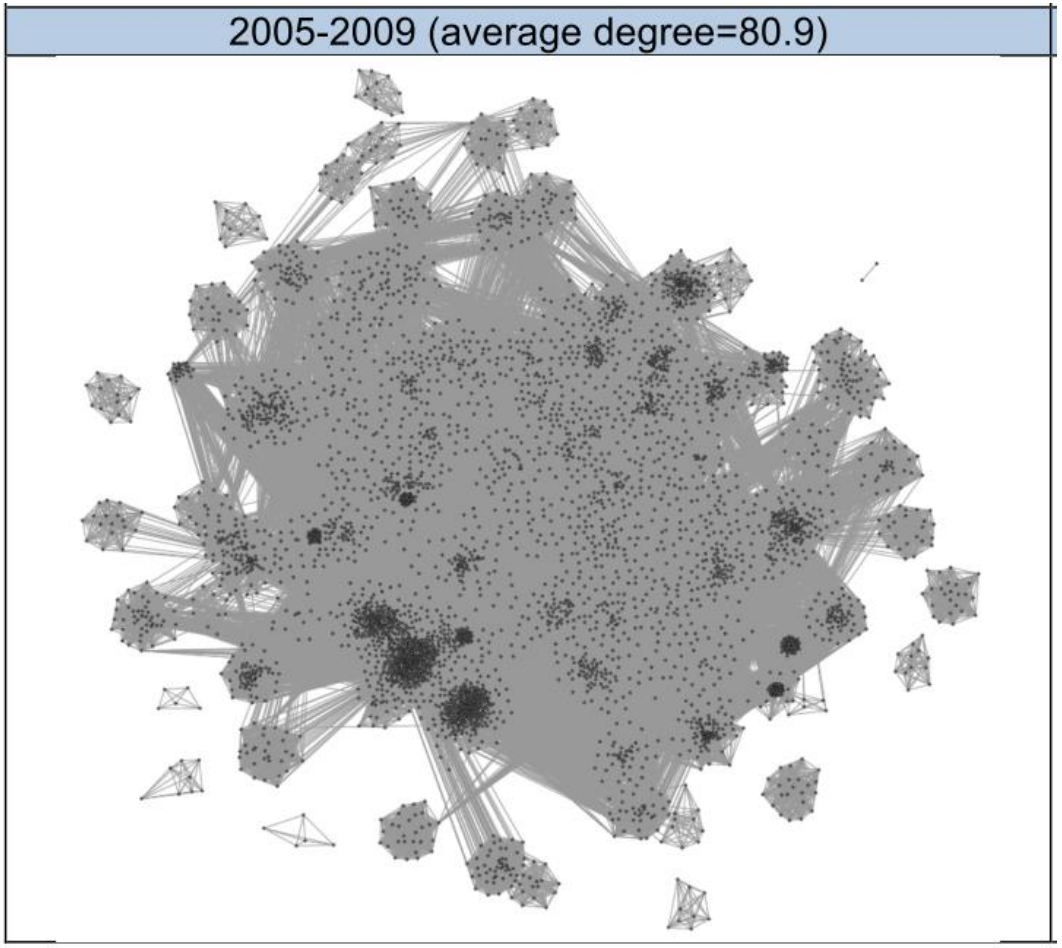

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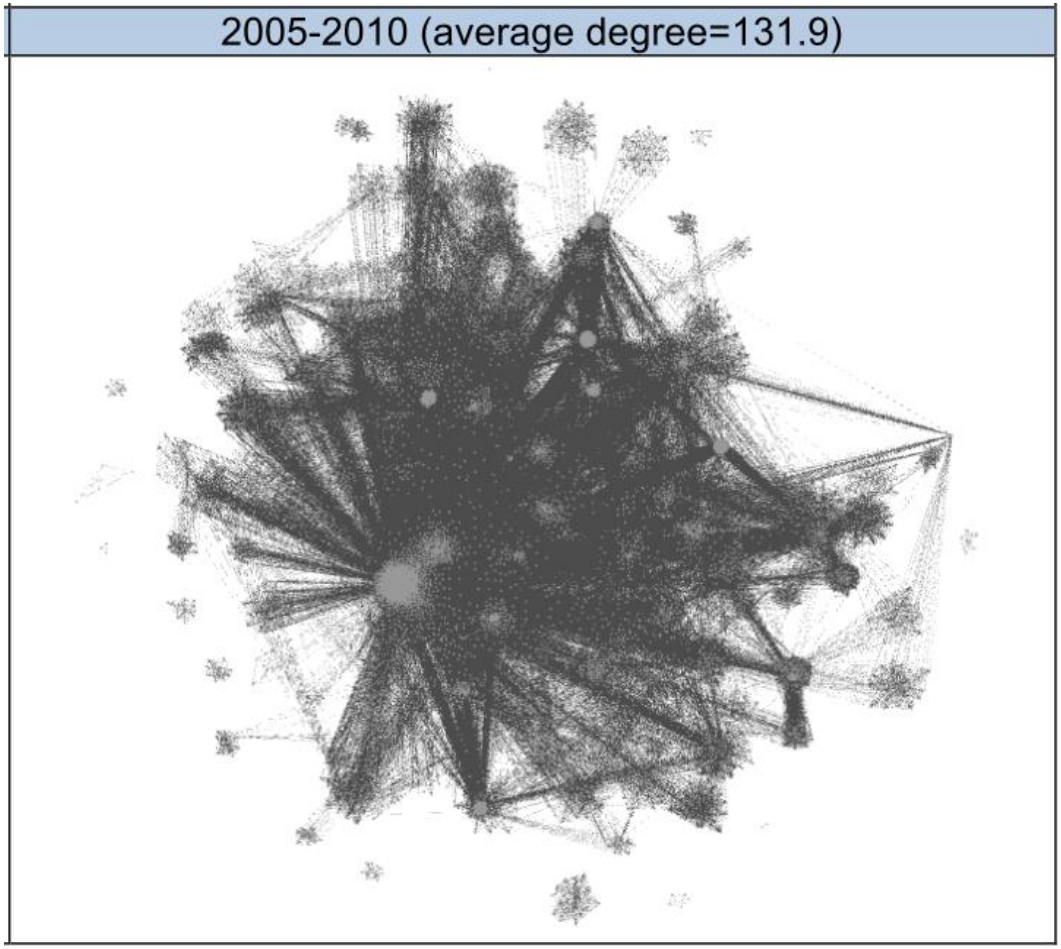
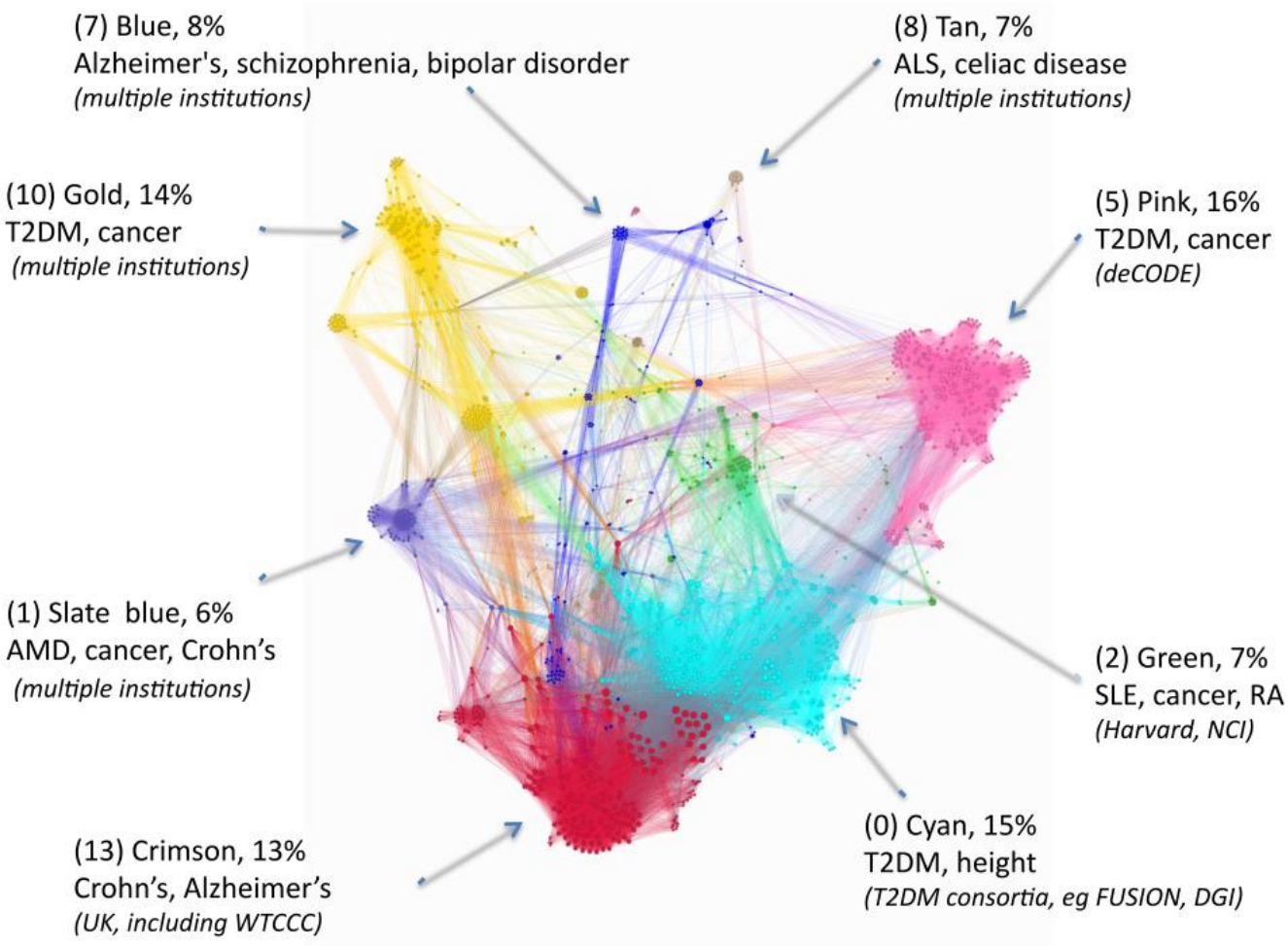


(Sulliman, 2012)



(Sulliman, 2012)

The International PSC study group

Welcome to the International PSC Study Group (IPSCSG) Home Page

- Home
- IPSCSG network
- Projects
- Database and biobanking protocols
- Oslo 2010
- Boston 2010
- Berlin 2011
- San Francisco 2011
- EASL Barcelona 2012
- Hamburg 2012
- Grants

IPSCSG
International PSC Study Group

The International PSC study group (IPSCSG) was founded in Oslo in 2010. The aim of the IPSCSG is to coordinate PSC research projects between leading institutions worldwide. More than 17 countries are represented (see map) and an alignment of important research topics in PSC means that rather than competition and redundancy, projects are run efficiently and are of a size that allows for robust conclusions to be drawn. Both basic and clinical research groups are represented, allowing for translational research that would otherwise not be feasible. A joint database for registering patient data has been established, and several studies are presently being performed.

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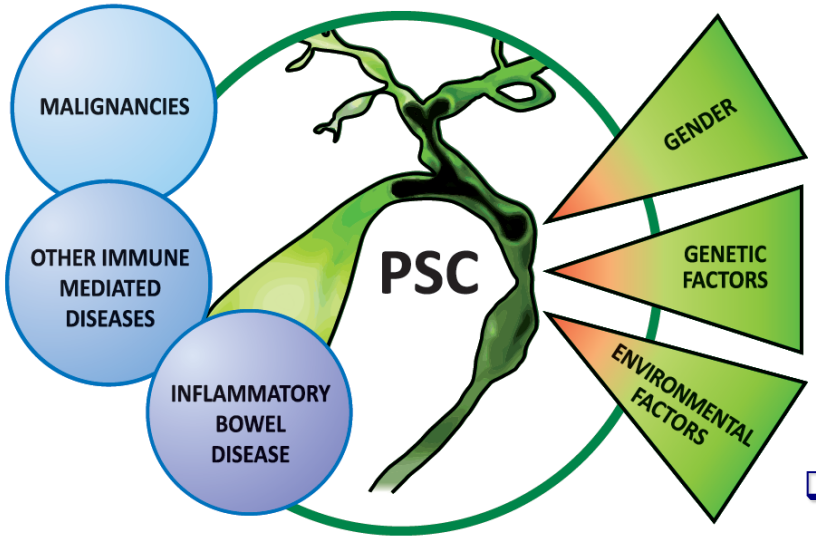
Dr. Tom Hemming Karlsen, Oslo, Norway (coordinator/secretary)

For further information, please contact t.h.karlsen@medisin.uio.no

- **Established 2010 (in Oslo)**
- **>20 countries**
- **Meets twice annually**
- **Two-day meeting biennially**
- **Common database**
- **Biobank protocols**
- **Project driven → publications**
- **Basis for grant applications**

Genetics and PSC - summary



- 16 robust and 33 suggestive genes
- More genes to come…
- PSC genetics = immunology
- Is there an environmental trigger?
- Study the genes in the context of PSC