Genetikk ved PSC –
og andre autoimmune sykdommer

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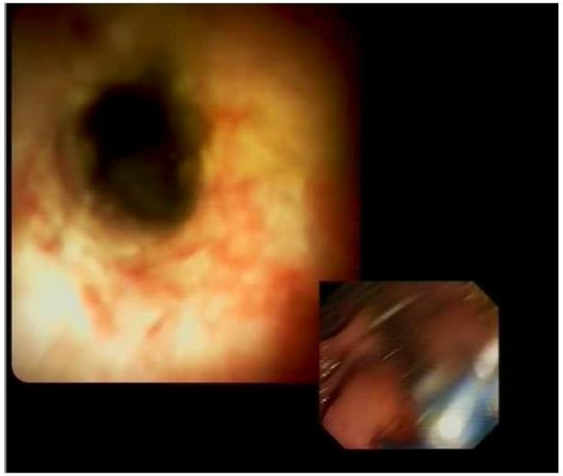
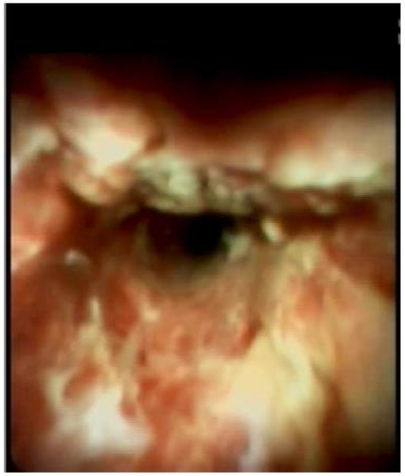
International PSC Study Group

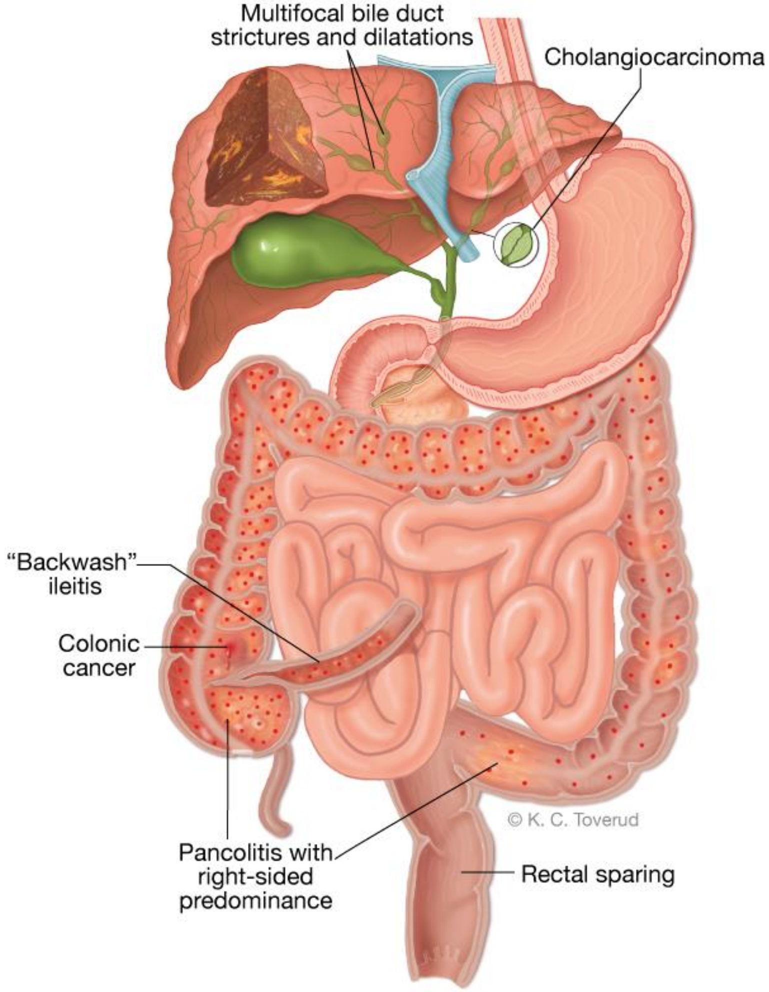
ous-research.no/nopsc

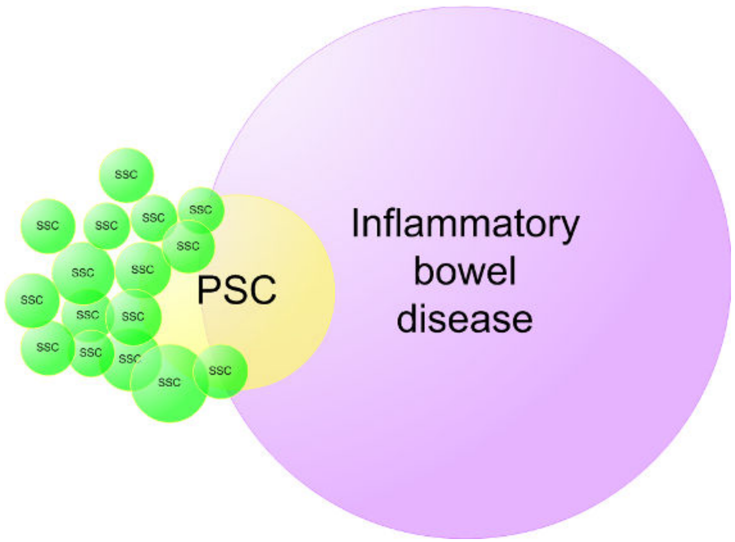
www.ipscsg.org

Primær skleroserende cholangitt

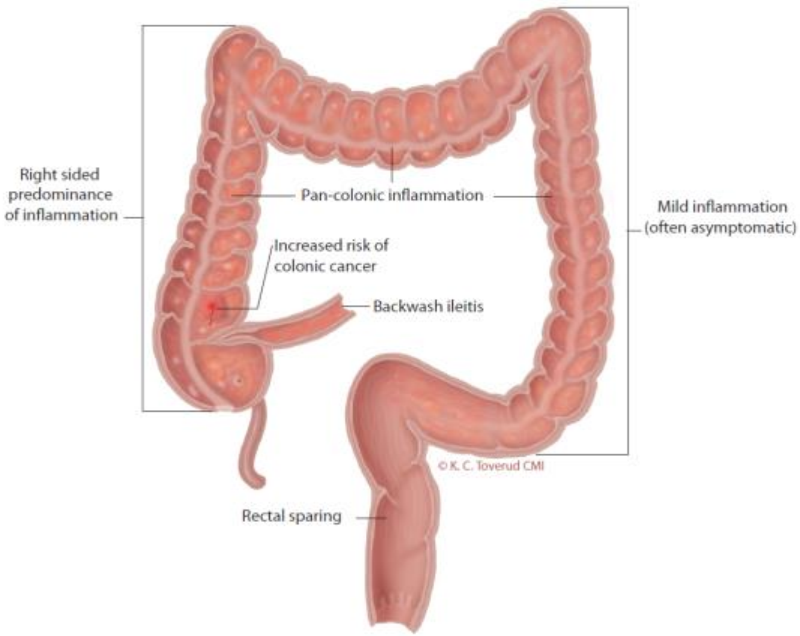




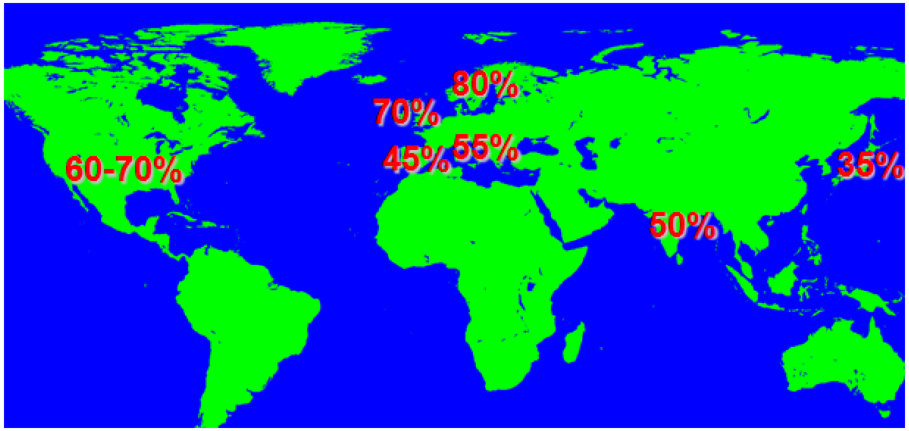
Primær skleroserende cholangitt



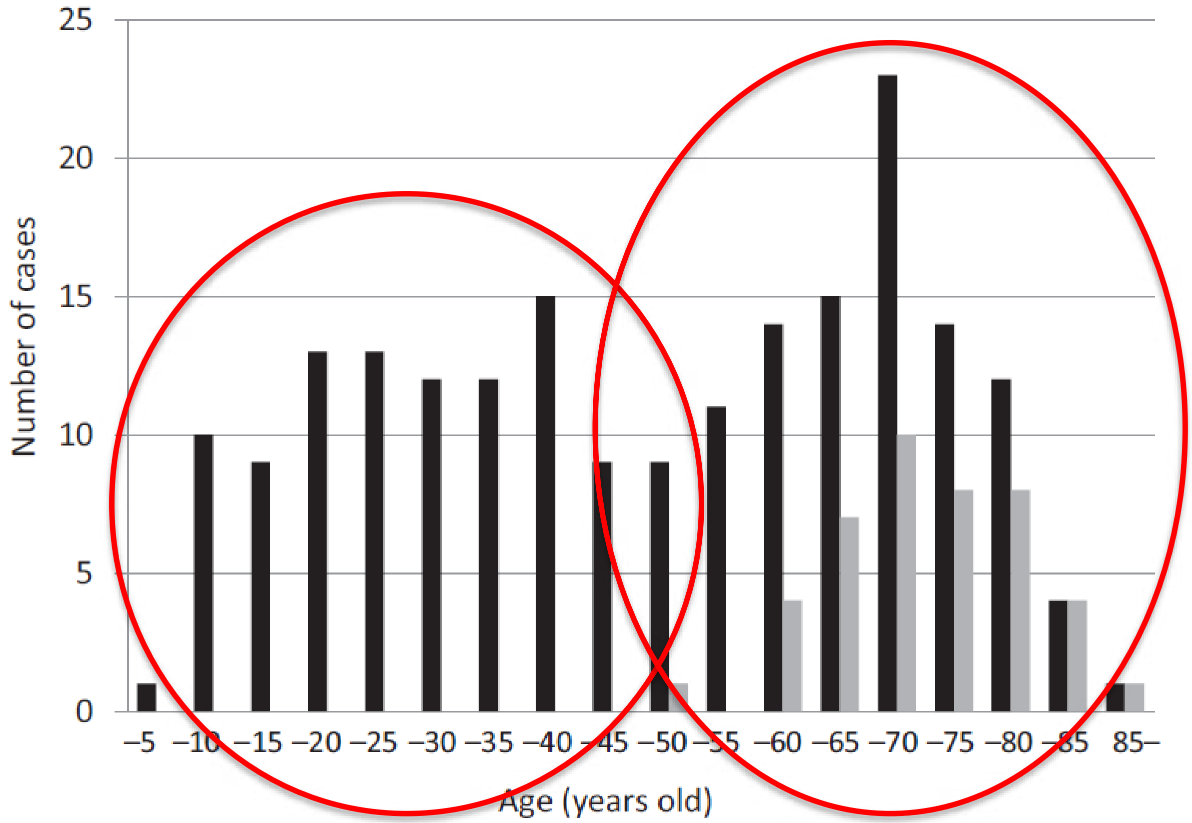


Tarmsykdommen ved PSC - geografi



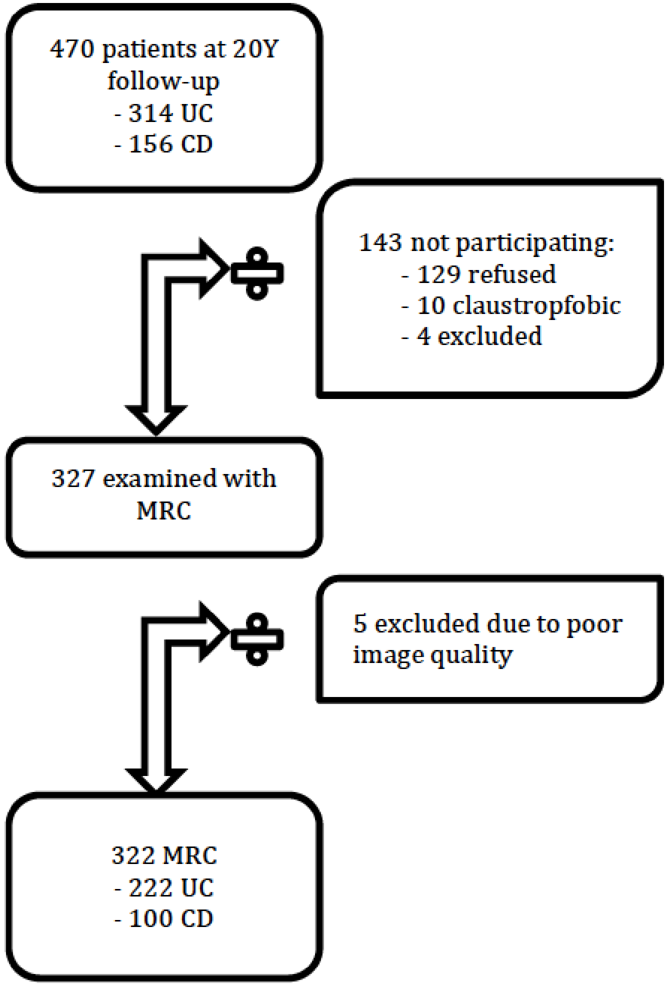


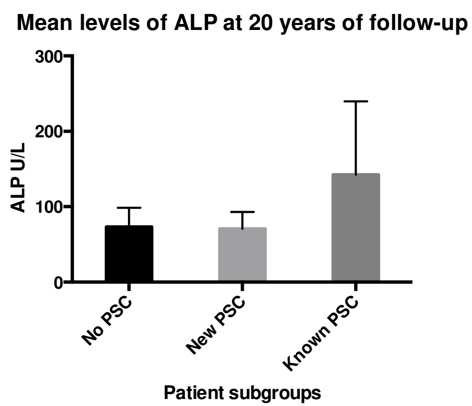
Tarmsykdommen ved PSC - geografi



(Tanaka et al., 2014)

PSC ved tarmsykdom

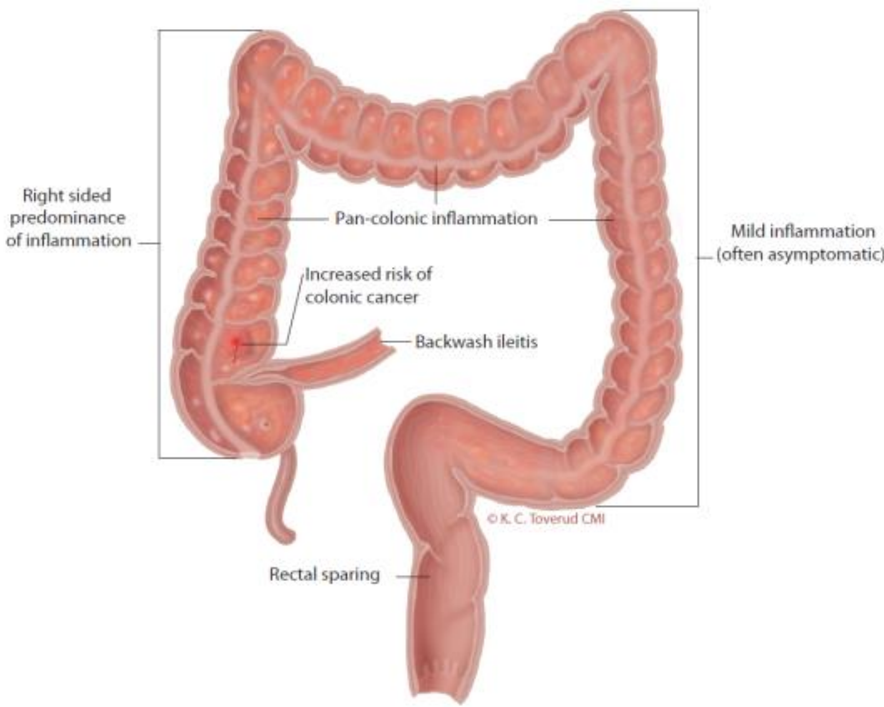


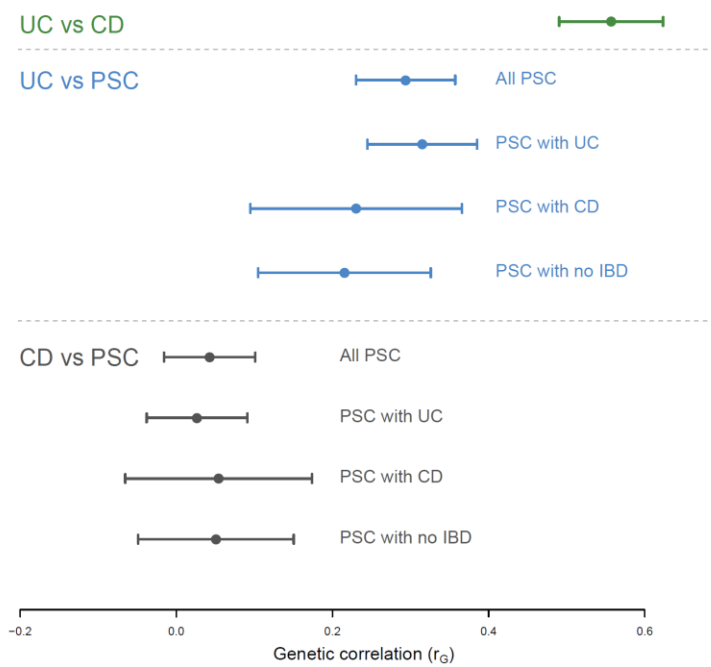


- Kjent PSC forekomst 2.2%
- Ekte PSC forekomst 8.1%
  - UC 6.8%, CD 9.1%
- Ukjente PSC pasienter ♀ 71%

(Lunder et al., Gastroenterology early online)

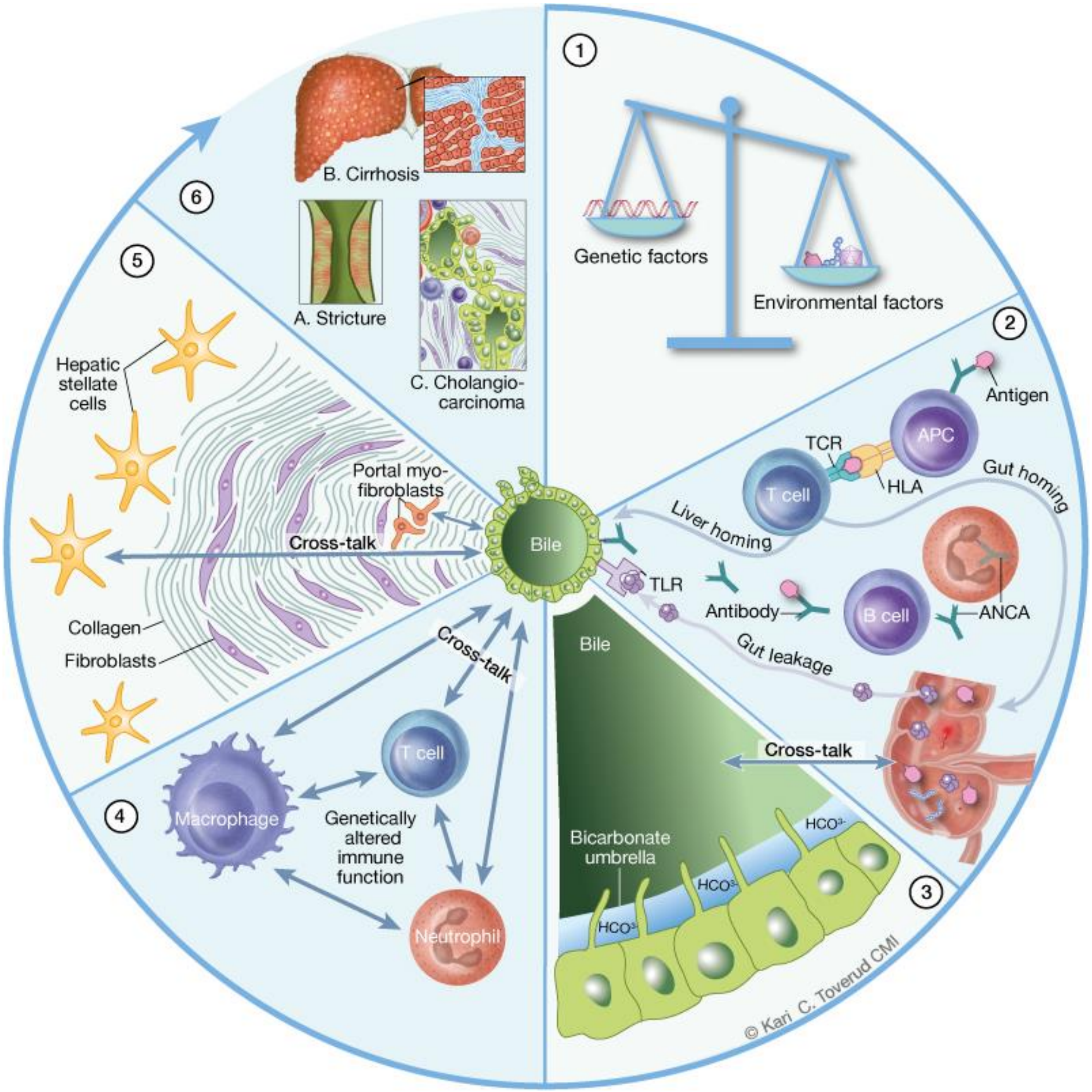
“PSC-IBD”





(Gou et al., in submission)

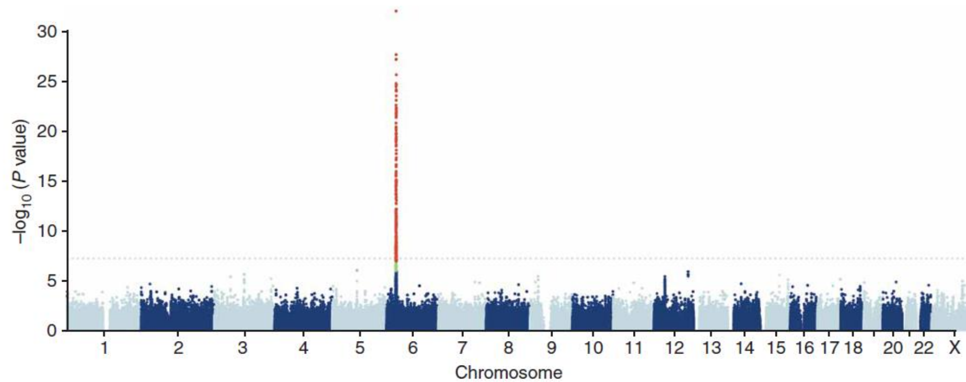
Hvor kommer genene inn i bildet?



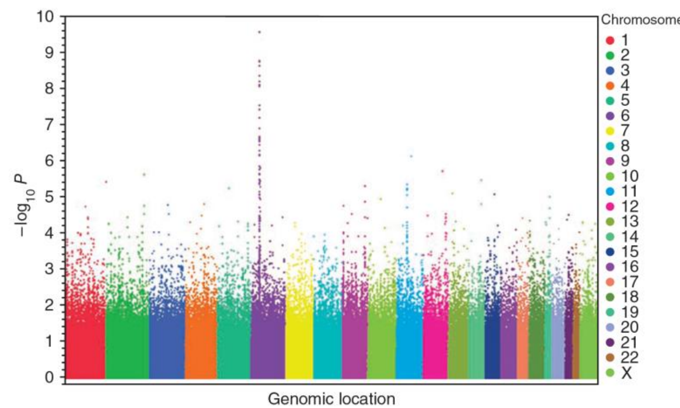
(Karlsen et al., in submission)

GWAS eksempler – «drug-induced liver injury»

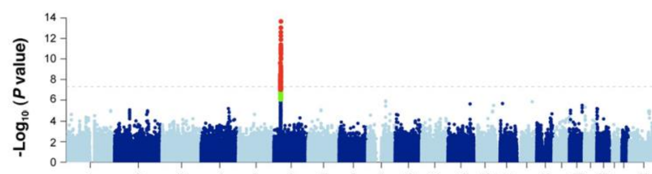
Flucloxacillin



Lumiracoxib



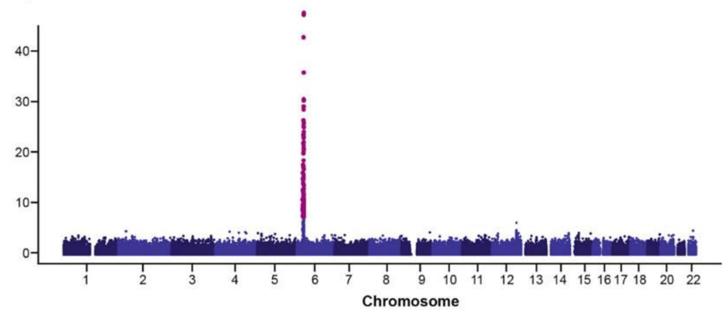
Amoxicillin-clavulunate



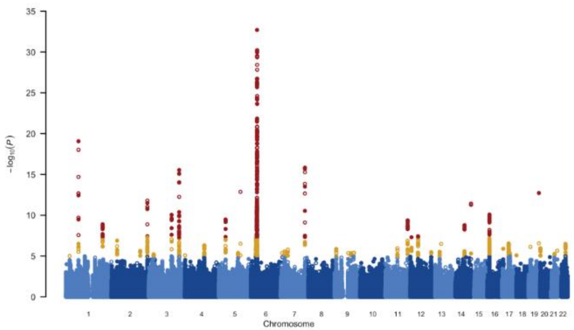
(For references to studies, see https://www.genome.gov/26525384)

GWAS eksempler – AIH, PBC og PSC

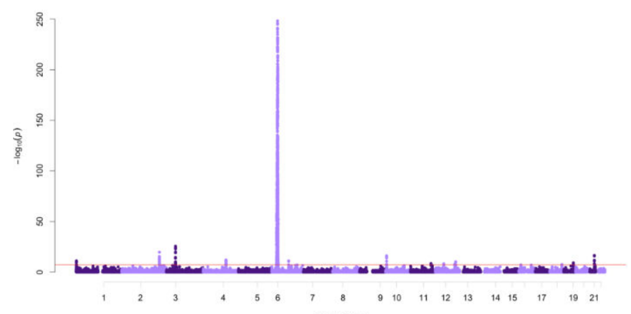
Autoimmun hepatitt



Primær biliær cirrhose

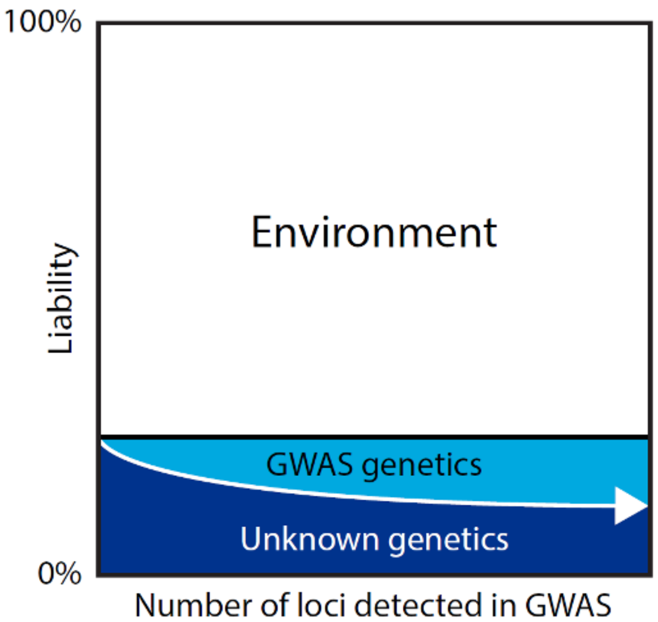


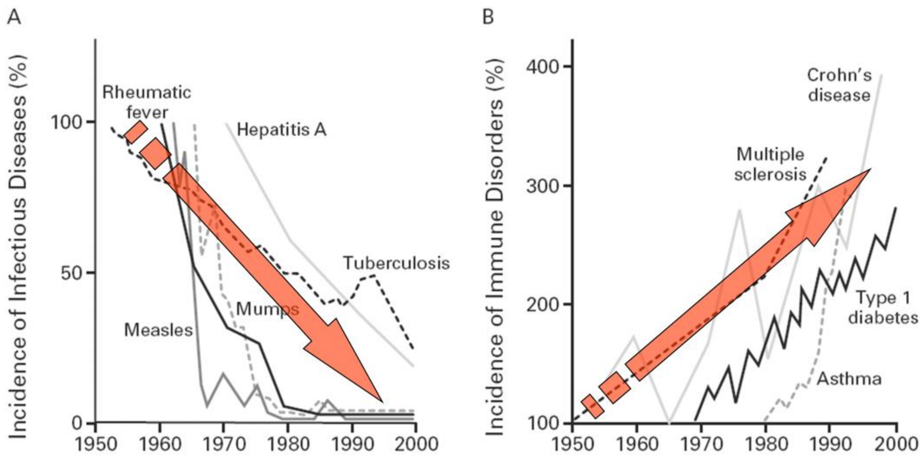
Primær skleroserende cholangitt



(For references to studies, see https://www.genome.gov/26525384)

«GWAS genetikk»

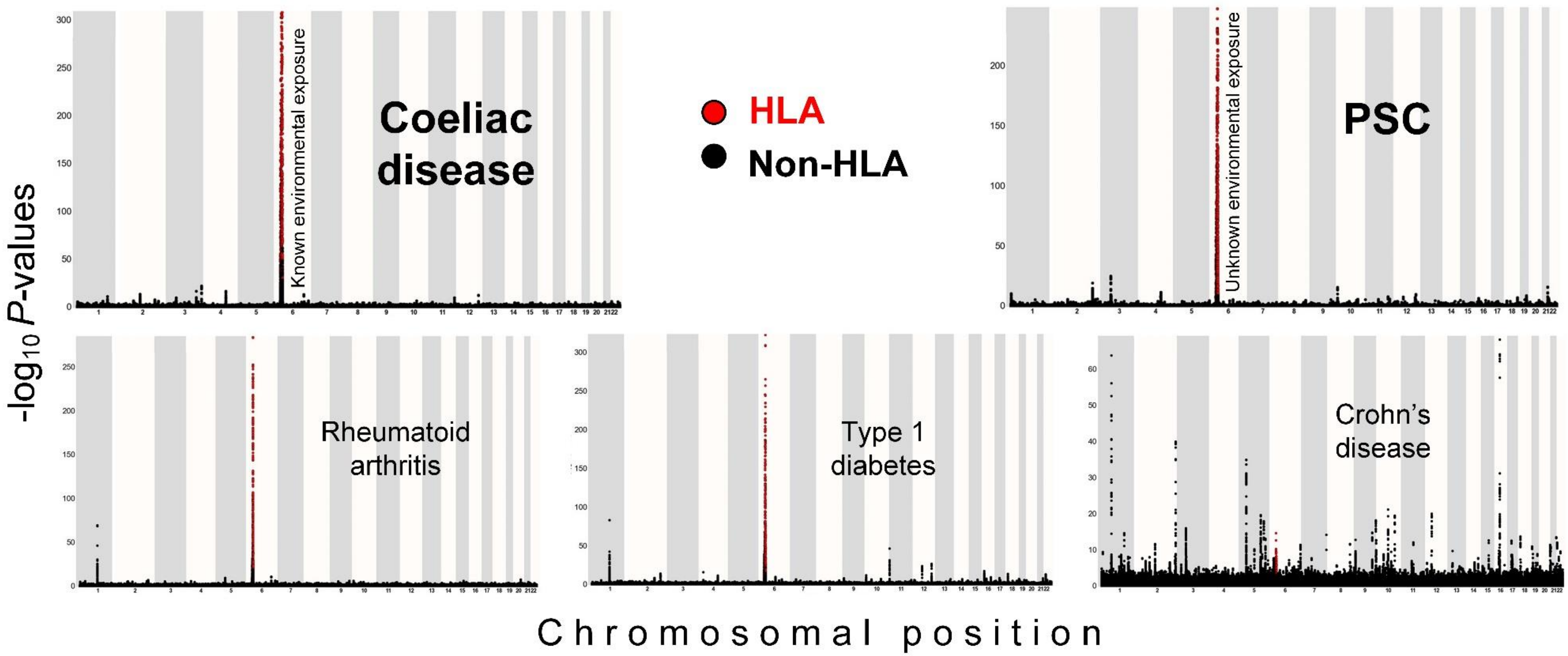




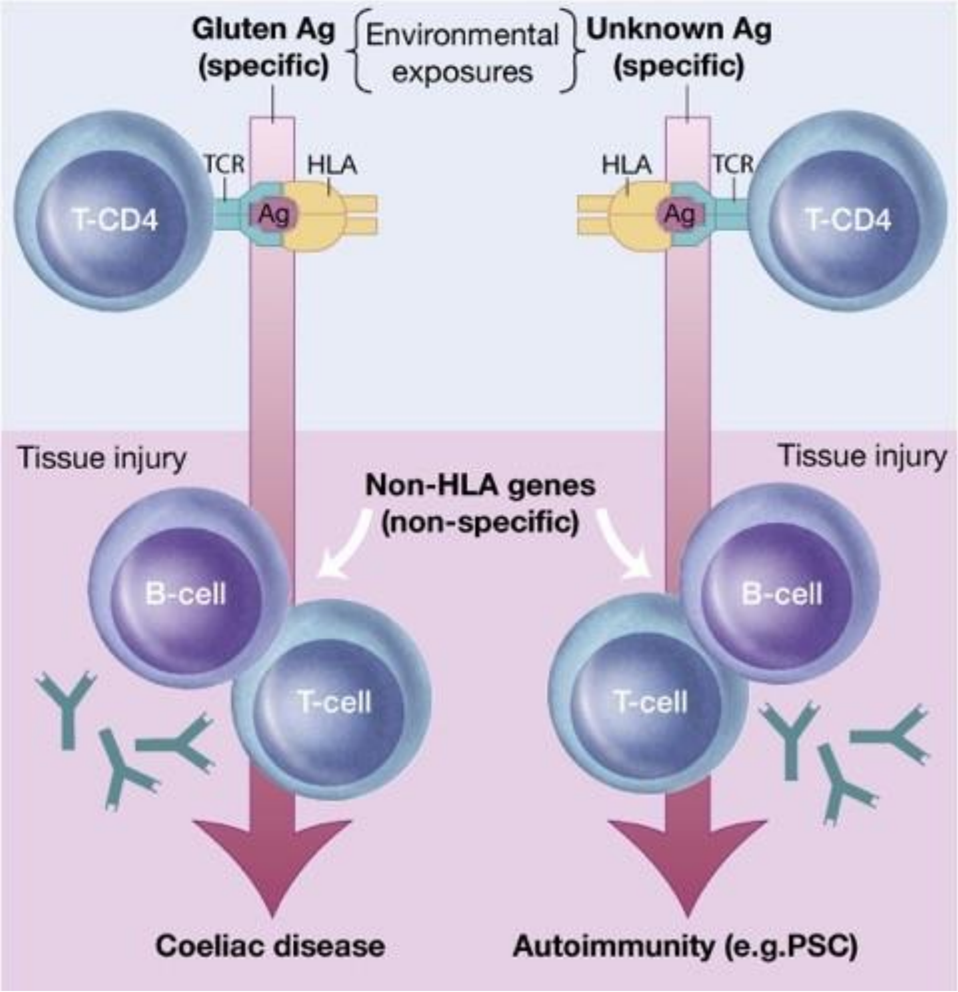
(Bach, 2002)

- Mye vi fortsatt ikke vet om genetikken ved PSC
- Miljøfaktorer som påvirker PSC utvikling er lite kjent

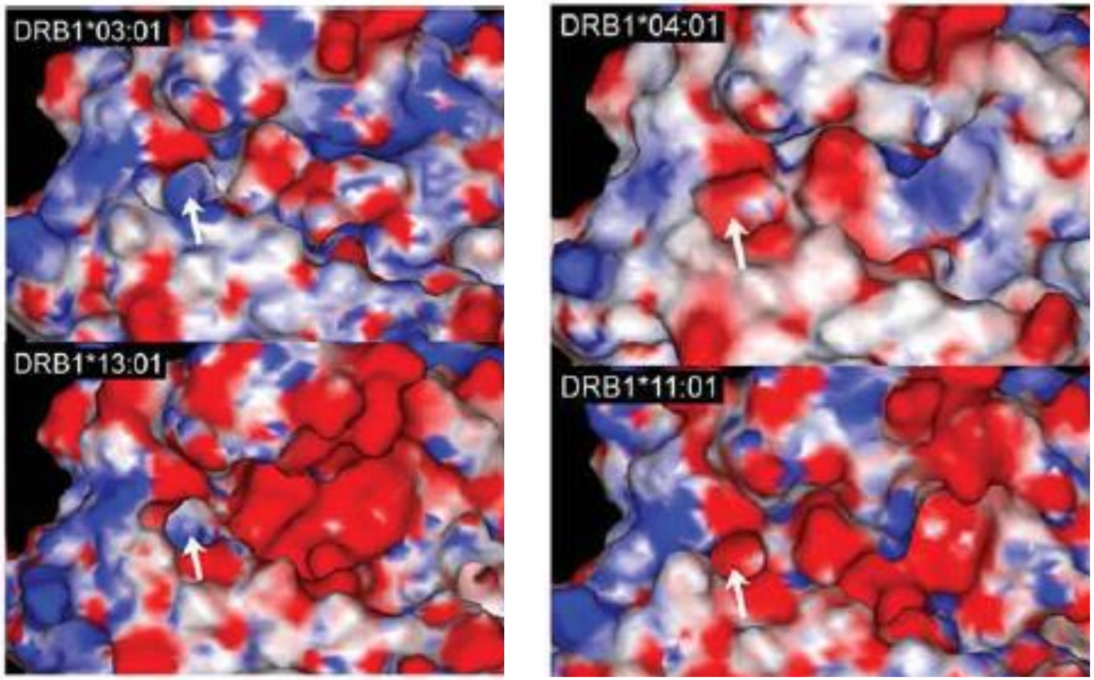
HLA funnene i PSC



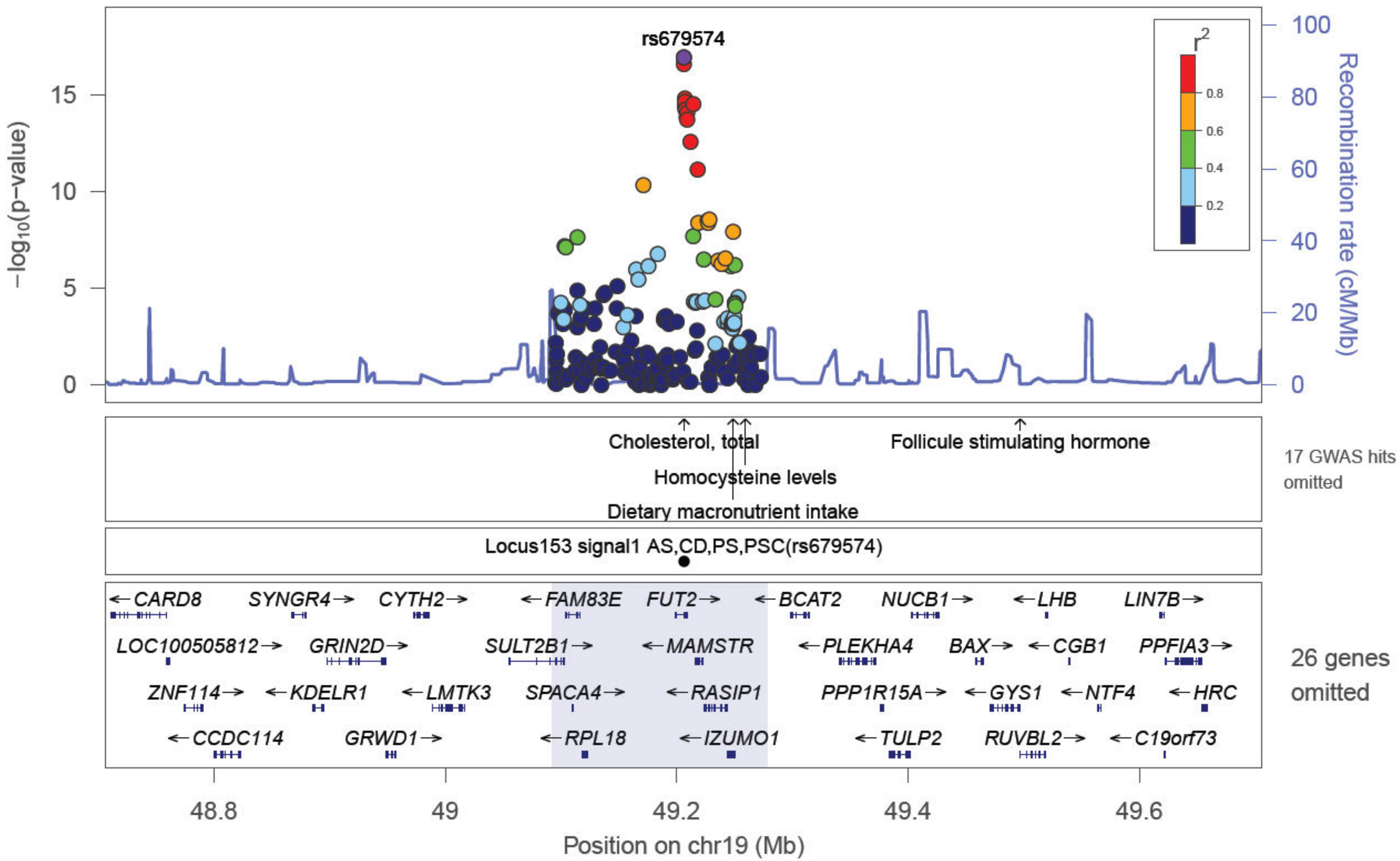
Et fundamentalt biologisk problem



Hva er det som binder til HLA?

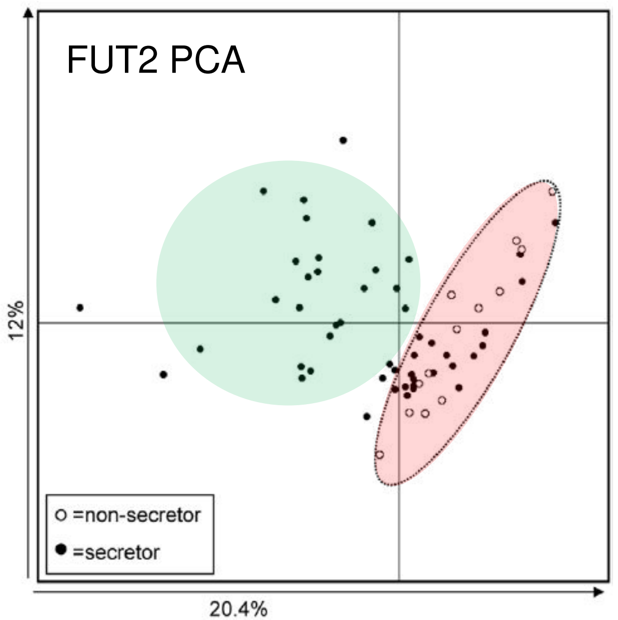


Genetikk og tarmen

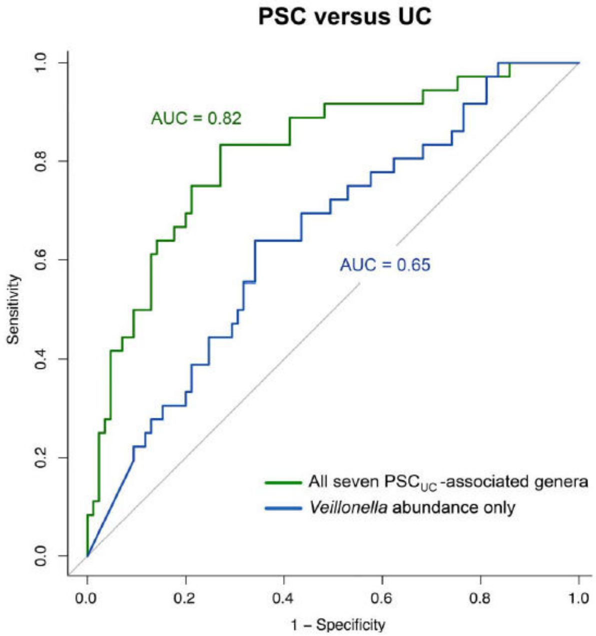


(Ellinghaus et al., Nature Genetics 2016)

«Mikrobiota» og gener

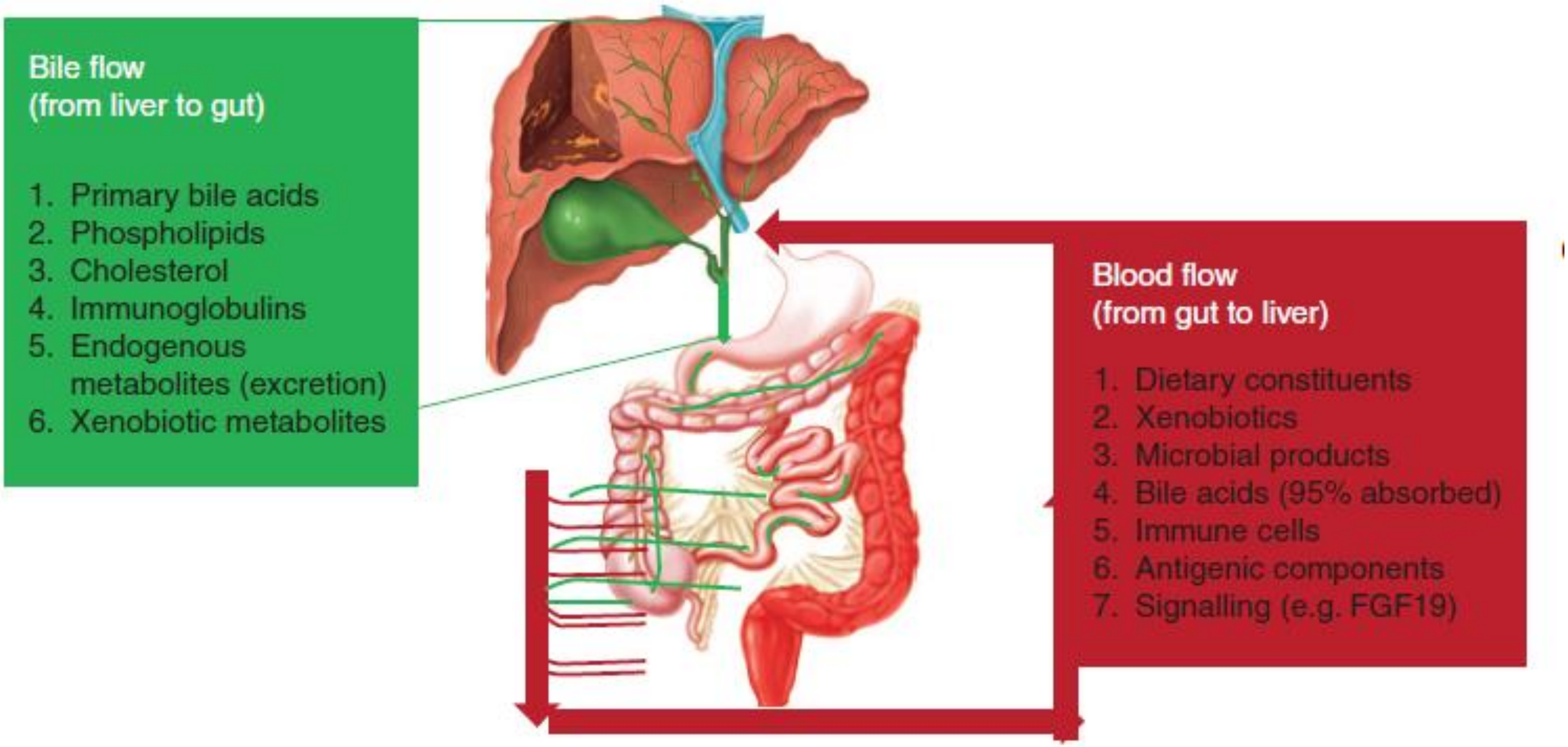


(Wacklin et al. 2011)

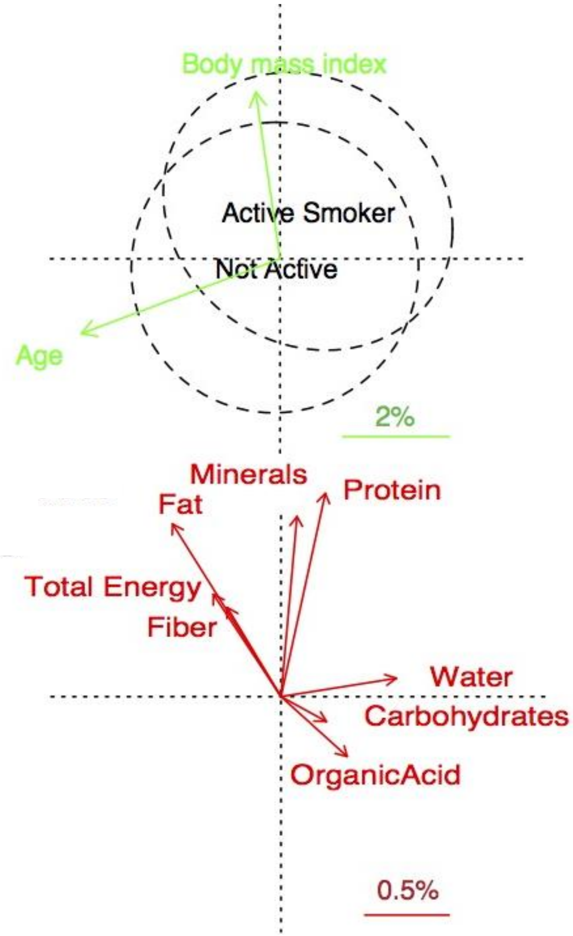


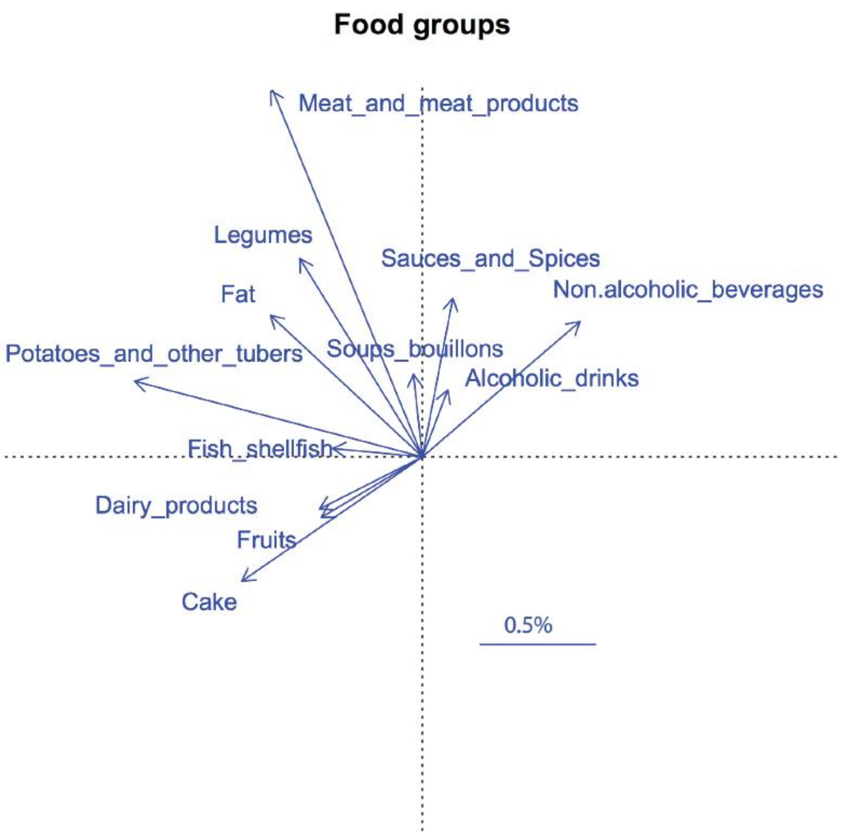
(Kummen et al, Gut 2016)

Tarm-lever relasjonen går to veier



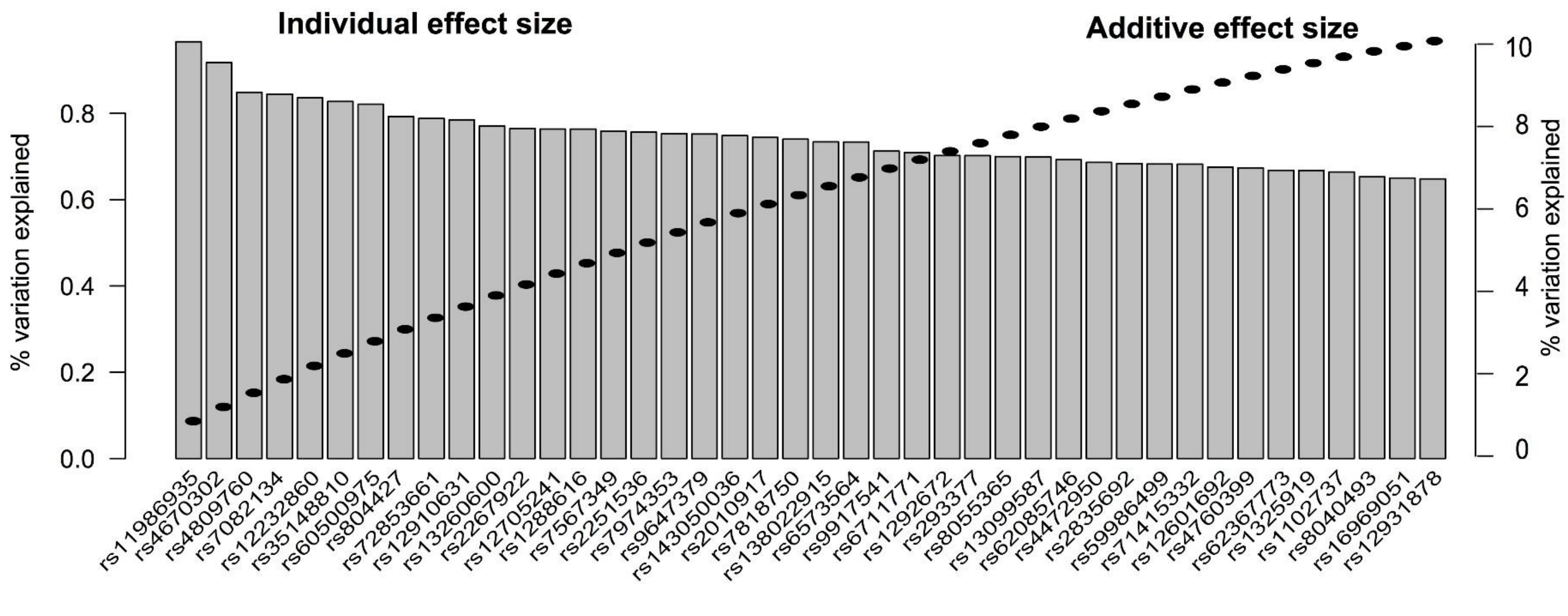
Hvor sterkt kan vi påvirke mikrobiota?





(Wang et al., in revisions)

Genetikken er omtrent like sterk…



(Wang et al., in revisions)

Mikrobiota ved PSC

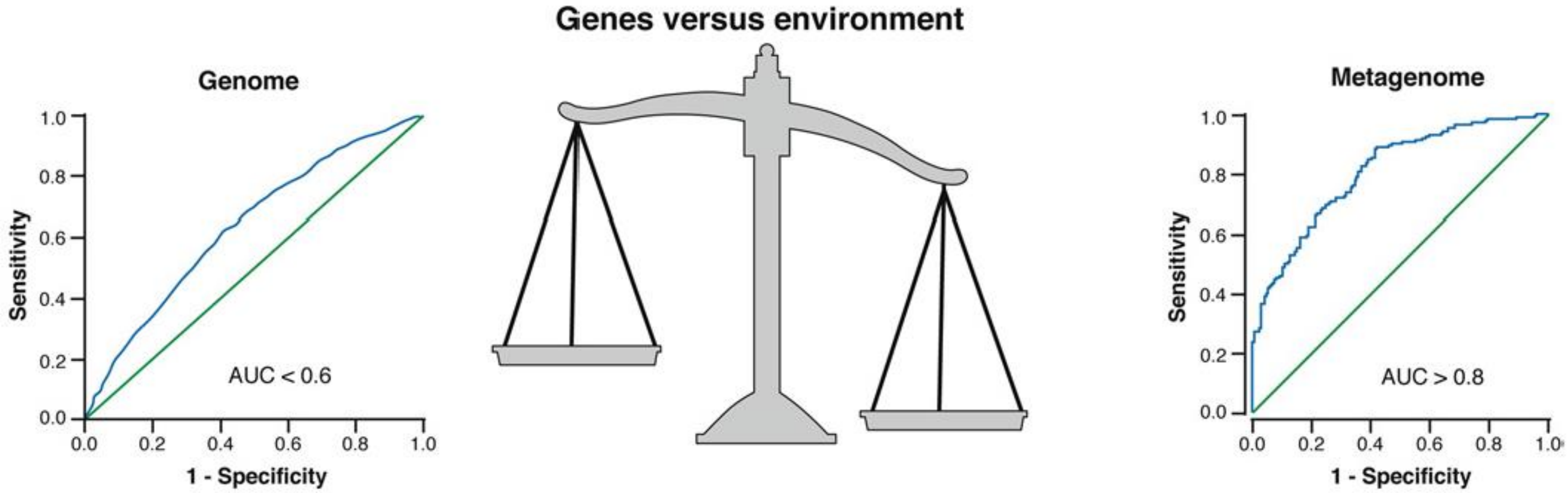
Table 1 Studies of the gut microbiota in primary sclerosing cholangitis (PSC)

Study	Year (reference number)	Material	n PSC	Diversity	Top indicator findings	Novelty
Rossen *et al*	2015 (18)	Mucosa	12	Reduced	*Clostridiales*↓	First report on the gut microbiota in PSC
Kevans *et al*	2016 (17)	Mucosa	31	No change*	No consistent indicator found	Highlighted bias from patient origin
Torres *et al*	2016 (20)	Mucosa	20	No change	*Barnesiellaceae* and *Blautia*↑	Microbiota consistency across different sampling sites
Kummen *et al*	2016 (19)	Stool	85	Reduced	*Veillonella*↑	Biomarker utility of the gut microbiota in PSC
Quaraishi *et al*	2016 (21)	Mucosa	11	NA	*Escherichia, Lachnospiraceae* and *Megasphera*↑	Discussion on metabolic effects from indicator findings
Sabino *et al*	2016 (22)	Stool	52	Reduced	*Enterococcus, Lactobacillus* and *Fusobacterium*↑	*Streptococcus* and *Veillonella*↑ in patients with cirrhosis
Rühlemann *et al*	2016 (23)	Stool	73	NA	*Veillonella*↑ (but not PSC specific)	Validation of biomarker utility of the gut microbiota in PSC

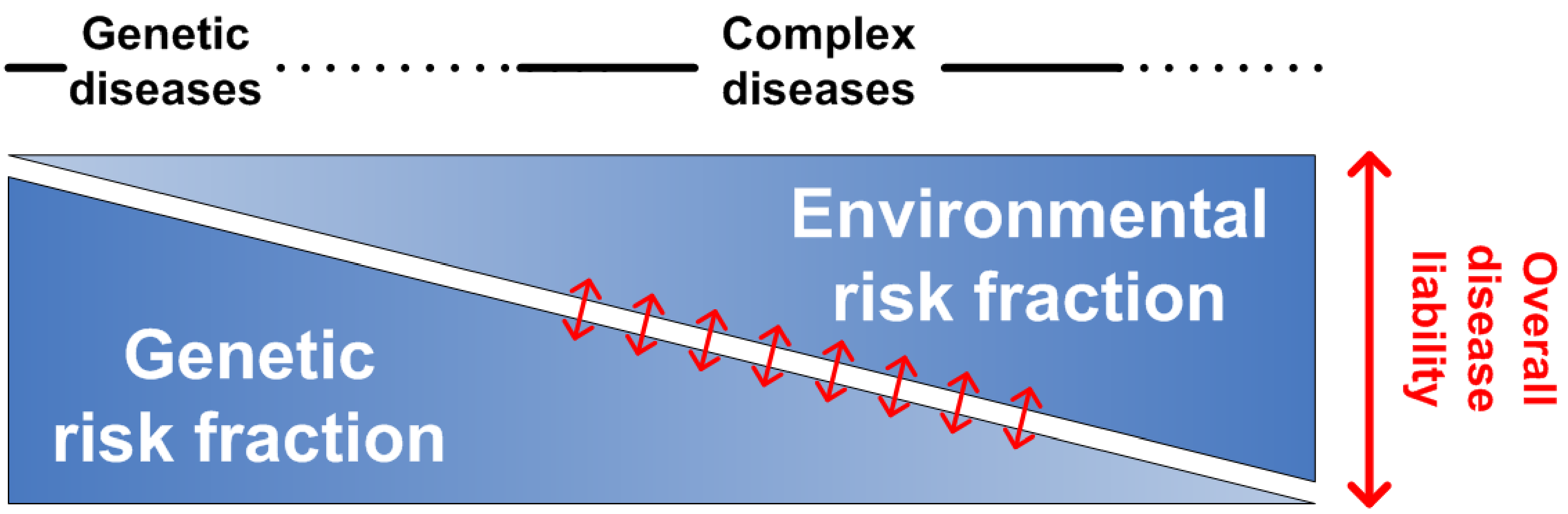
*A significant decrease in Chao1 was detected in the Oslo patients (n=19) whereas no significant change in diversity measures was found in the Calgary patients (n=12).
NA, not available.

(Karlsen, in press Gut)

Gener versus mikrobiota



Andre gener

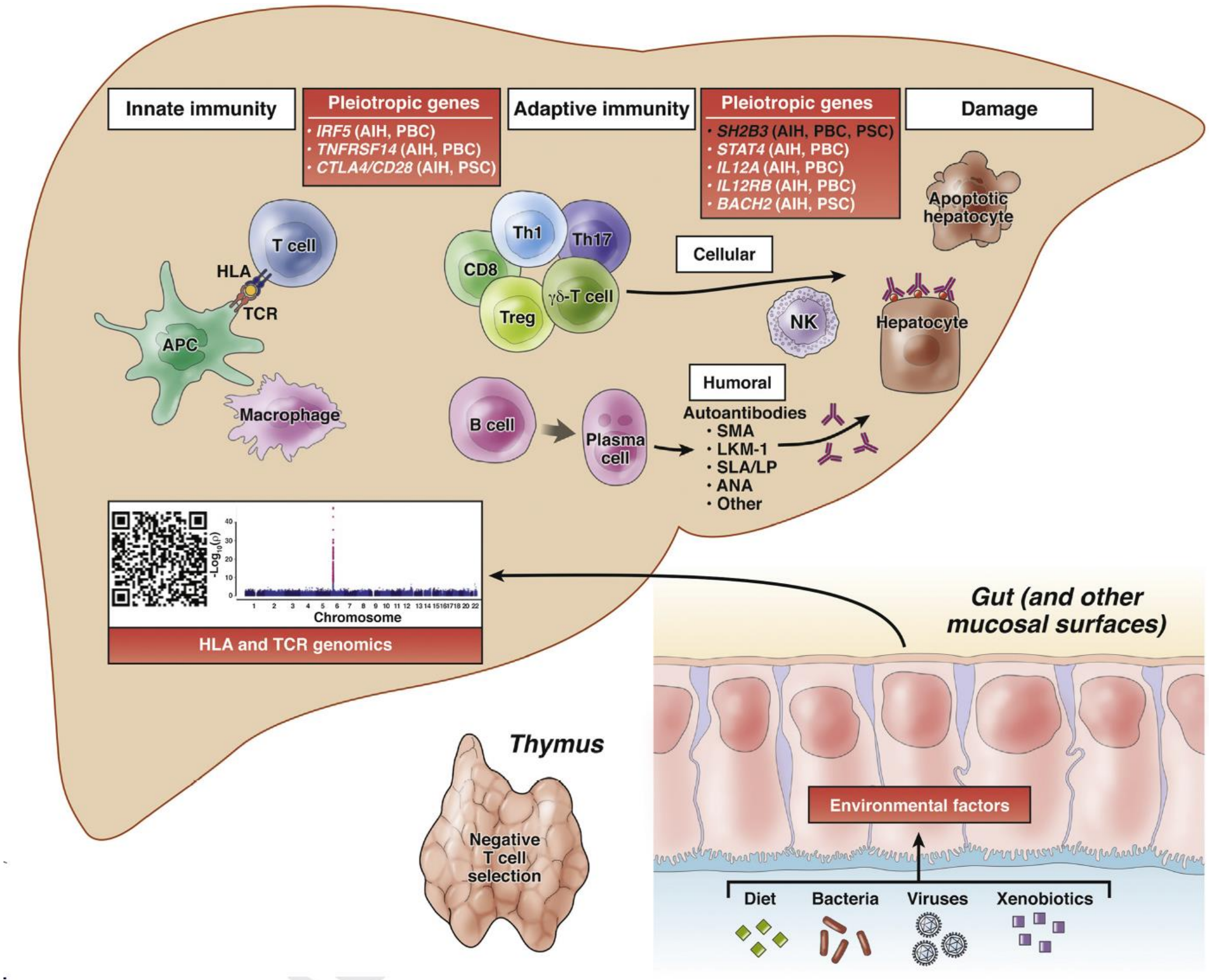


Genetic diseases
Complex diseases
Environmental risk fraction
Genetic risk fraction
Overall disease liability

Mange flere gener…

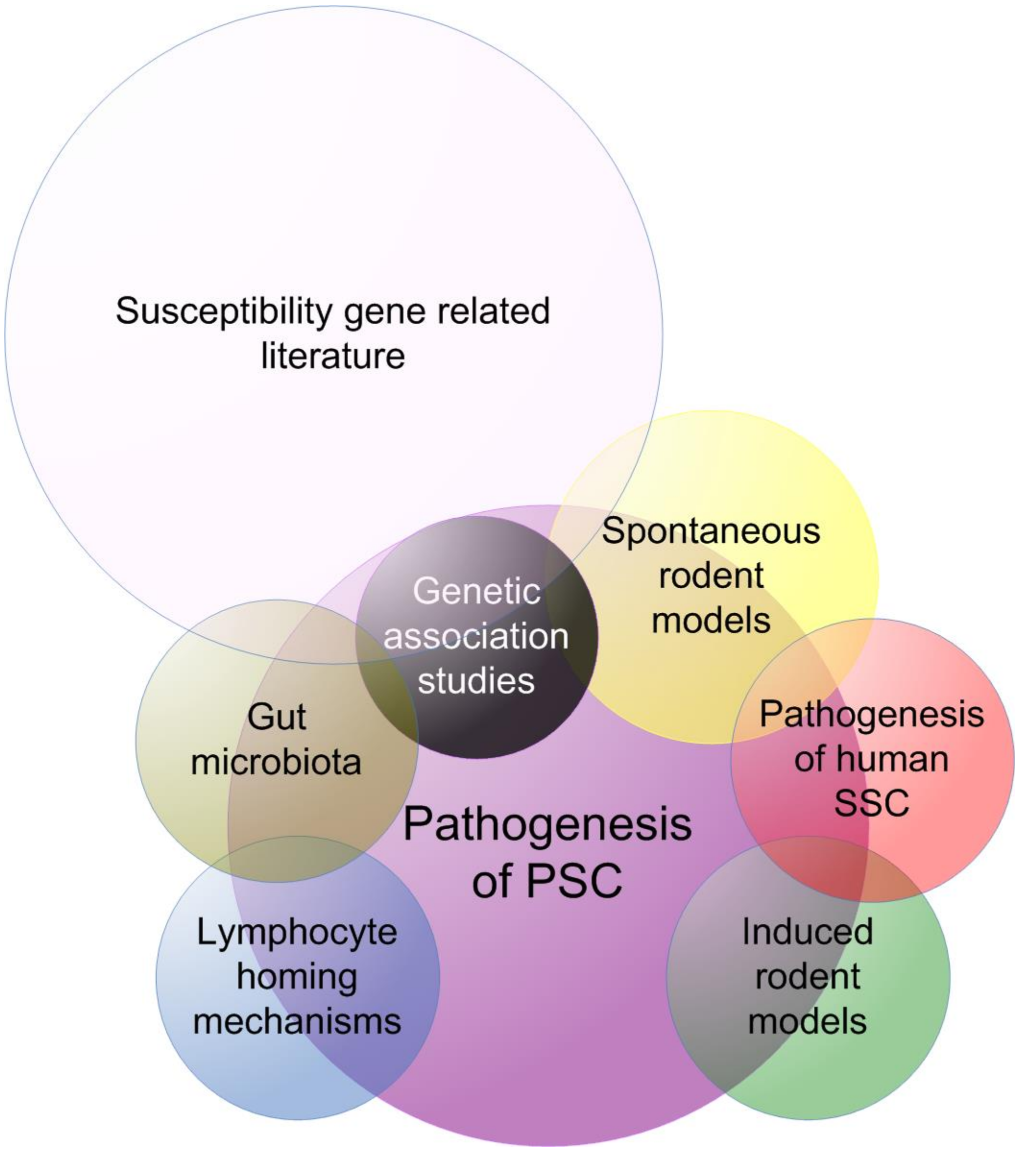
Locus	Chr.	lead SNP	Gene	Study (year)
1	1	rs3748816	*MMEL1, TNFRSF14*	Folseraas et al. 2012
2	2	rs6720394	*BCL2L11*	Melum et al. 2011
3	2	rs7426056	*CD28, CTLA4*	Liu et al. 2013
4	2	rs7556897	*CCL20*	Ellinghaus et al. 2016
5	2	rs3749171	*GPR35*	Ellinghaus et al. 2013
6	3	rs3197999	*MST1*	Melum et al. 2011
7	4	rs3774937	*NFKB1*	Ellinghaus et al. 2016
8	4	rs13140464	*IL2, IL21*	Liu et al. 2013
9	6	rs56258221	*BACH2*	Liu et al. 2013
10	10	rs4147359	*IL2RA*	Srivastava et al. 2012
11	11	rs7937682	*SIK2*	Liu et al. 2013
12	12	rs11168249	*HDAC7*	Liu et al. 2013
13	12	rs12369214	*RFX4, RIC8B*	Ellinghaus et al. 2016
14	12	rs3184504	*SH2B3, ATXN2*	Liu et al. 2013
15	16	rs11649613	*CLEC16A, SOCS1*	Ellinghaus et al. 2016
16	18	rs1452787	*TCF4*	Ellinghaus et al. 2013
17	18	rs1788097	*CD226*	Liu et al. 2013
18	19	rs60652743	*PRKD2, STRN4*	Liu et al. 2013
19	21	rs2836883	*PSMG1*	Liu et al. 2013

Hva betyr genfunnene?

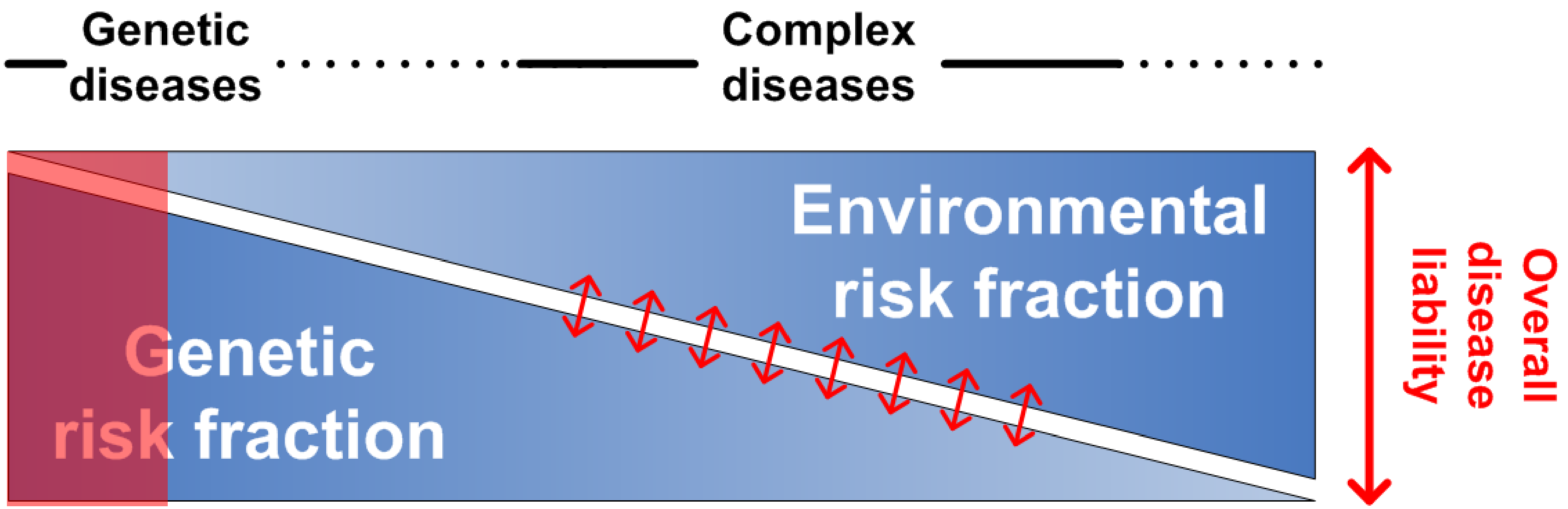


(Karlsen/Hirschfield, 2014)

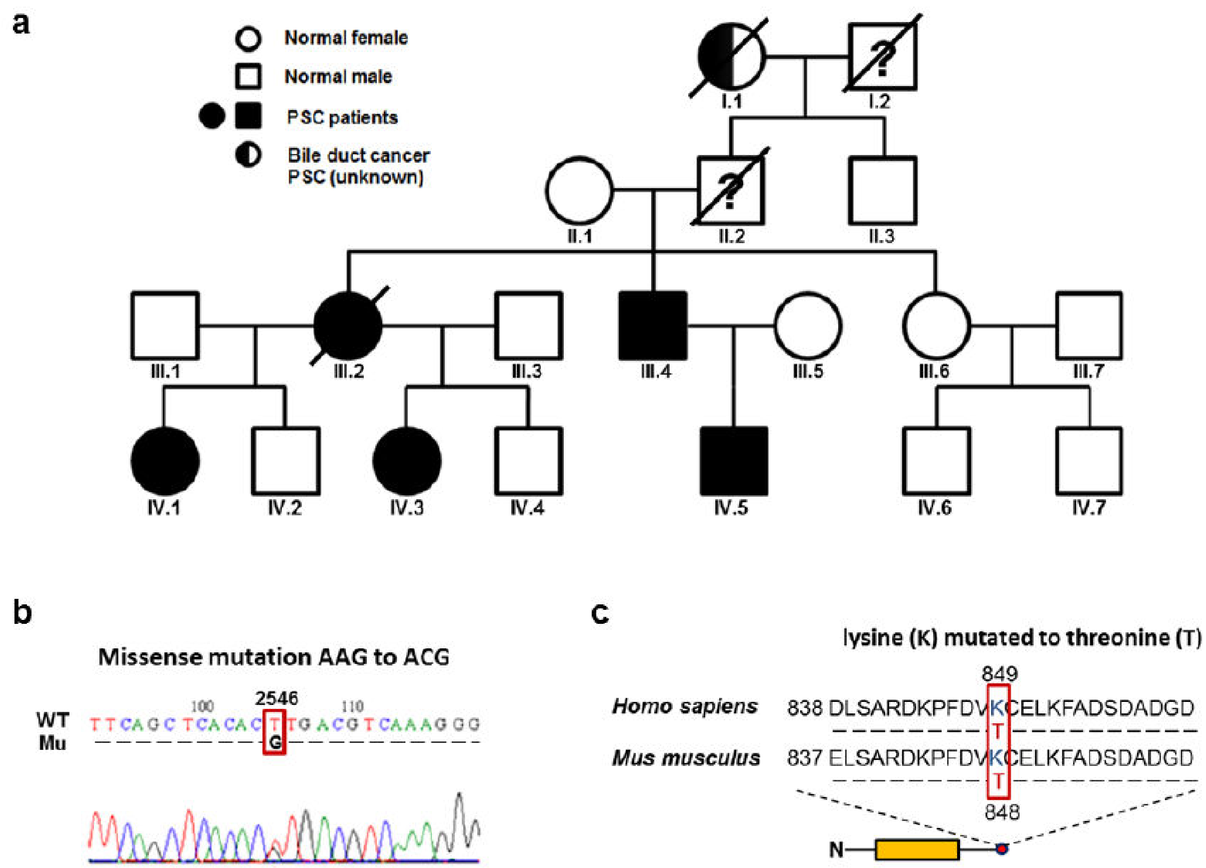
Vi trenger forskning for å forstå genene



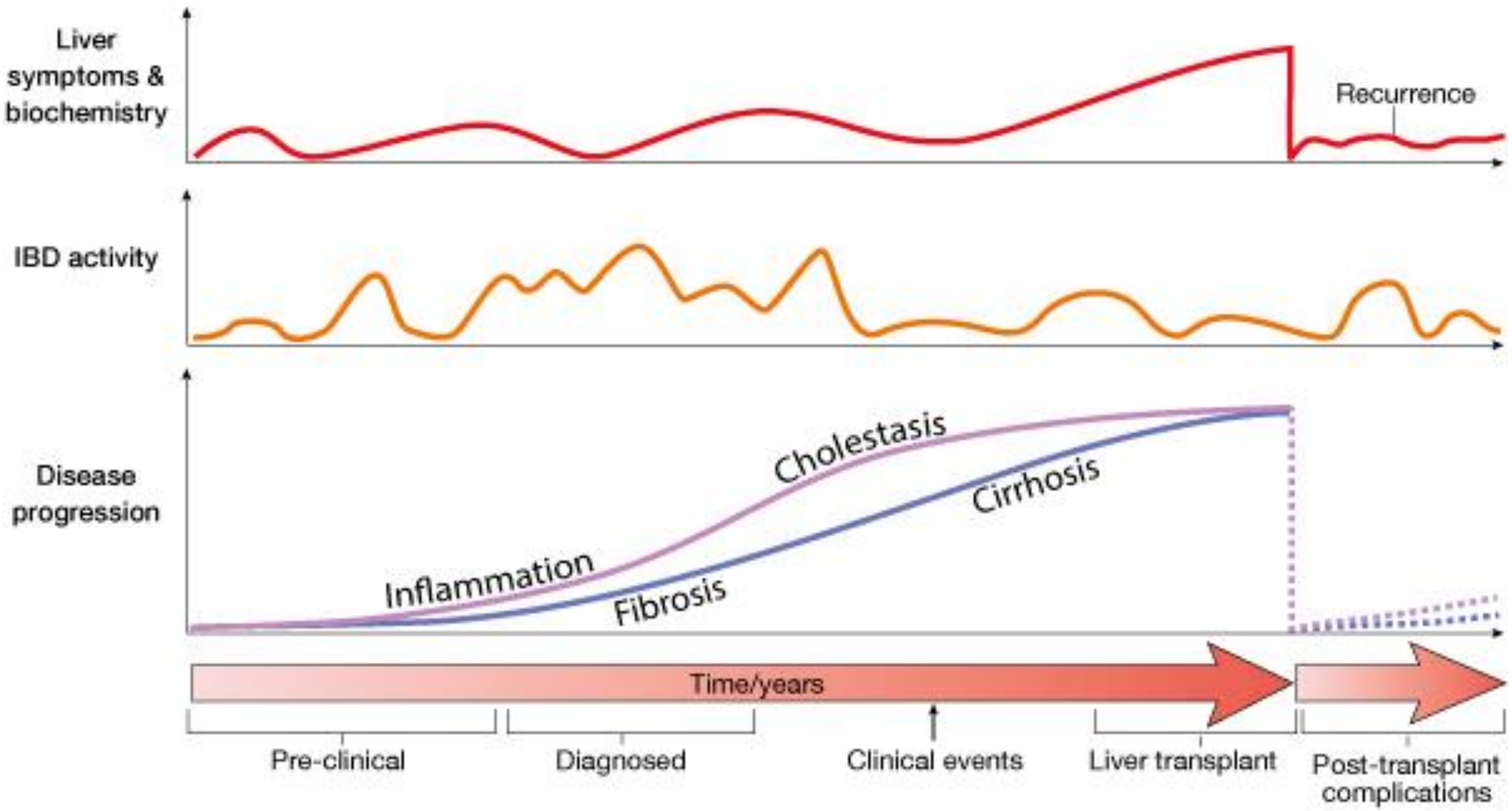
Famliær PSC (>2-3 slektninger)



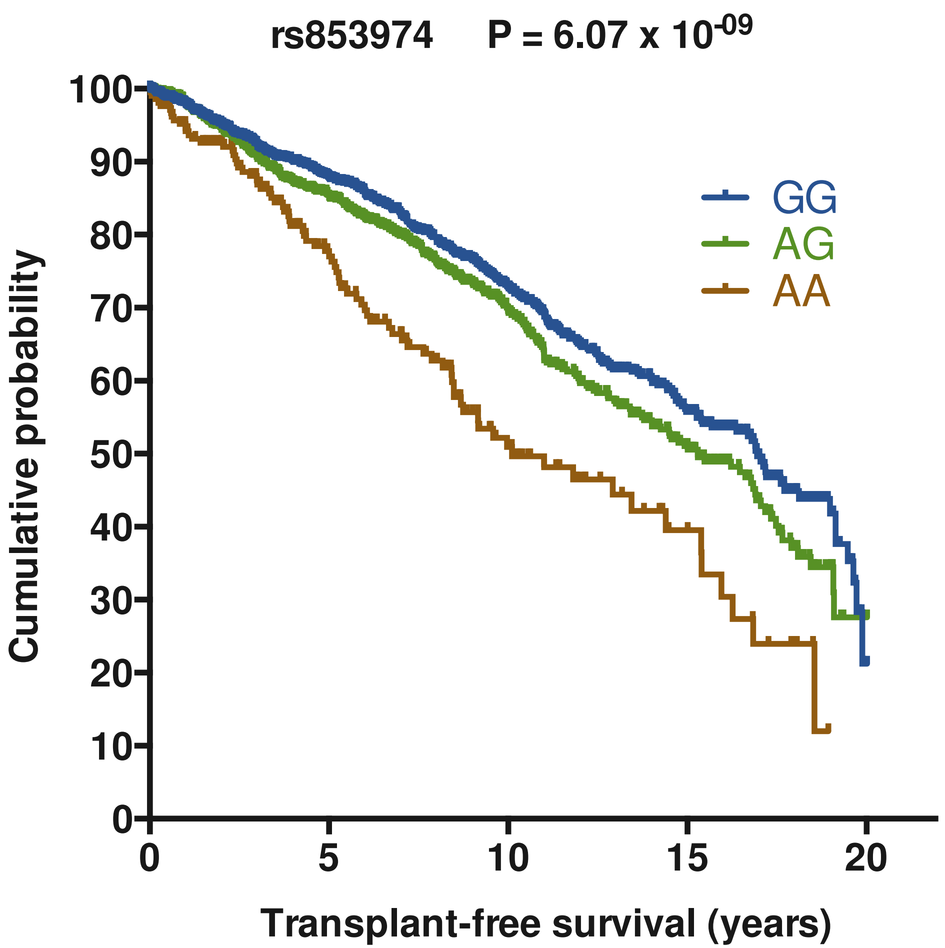
Eksempel på familieforekomst av PSC



Modifier genes

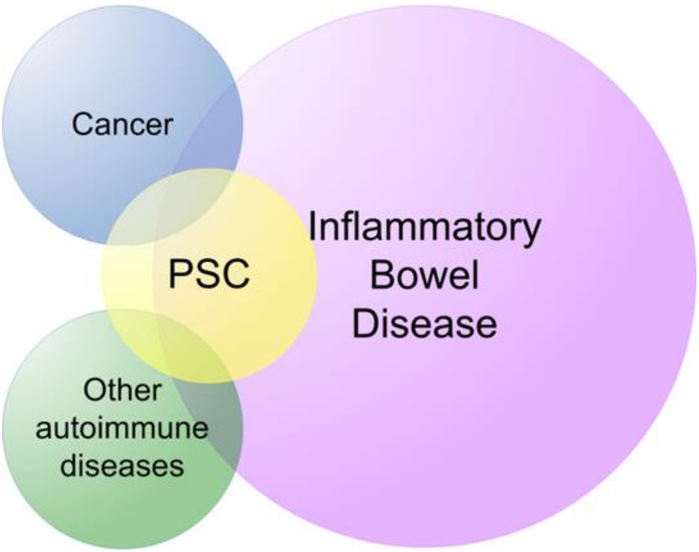


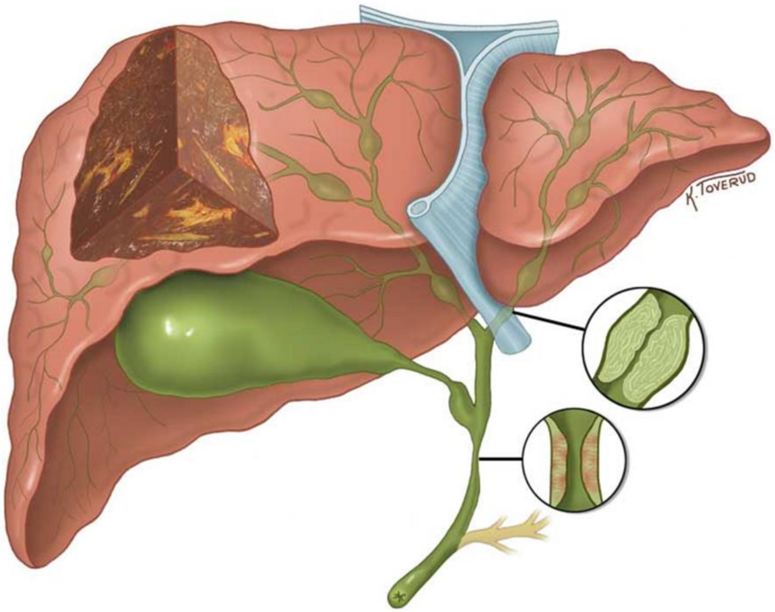
Modulatorgener (eks. *RSPO3*)



(Alberts et al, EASL 2016)

Cholangiocarcinom og genetikk





Spennende nye funn som gir håp

Gene	Chromosome	Frequency (%)	Potential therapeutics for further study
KRAS	ch12	38%	Refametinib (phase II in HCC)
CDKN2A	chr9	20%	Ilorasertib (phase II in solid tumors)
SMAD4	chr18	18%	TGFβ receptor inhibitor (phase I, i.e. LY2157299 (Galunisertib))
ERBB2	chr17	8%	Trastuzumab, Pertuzumab
BRAF V600	chr7	6%	Vemurafenib, Encorafenib
EGFR	chr7	6%	Gefitinib, Erlotinib, Afatinib, (Cetuximab)
TGFBR2	chr3	2%	TGFβ receptor inhibitor
FGF23	chr12	2%	FGFR4 inhibitor (phase I, i.e. BLU-554, FGF401)
FGFR2	chr10	2%	BGJ398 (phase II study),
PIK3CA	chr3	4%	Everolimus (RAD001)
Total		**66%**	(patients with one or more „druggable“ targets)

(Goeppert et al, EASL 2016)

Concluding statements

- Mer enn 30 sykdomsgener funnet så langt
- Genene samspiller med miljøet, der vet vi mye mindre
- Familiær PSC er sjelden, tenk på det hvis 3 eller flere og ikke IBD
- Oppmuntrende genfunn i pågående studier av cholangiocarcinom