Genetics in PSC and UC

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NOTHING TO DISCLOSE

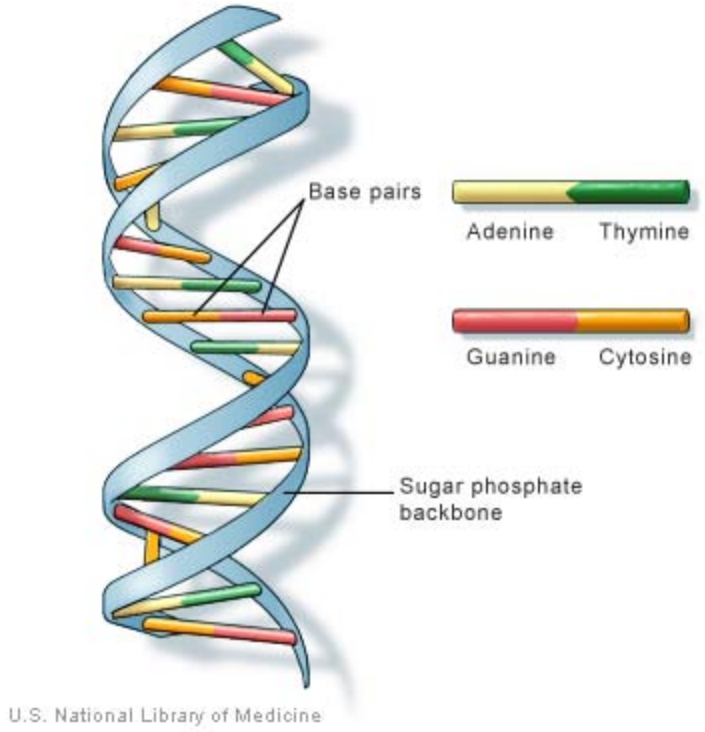
Outline

- What is genetics?
- What is the association beteween genetics and disease – genotype vs phenotype?
- What do we know about genetics in PSC and UC?
- How does PSC and UC genetics help us understand the disease?
- Inheritance in PSC?
- Summary and conclusions

What is genetics?

- Ancient Greek *genesis*, "origin“
- The branch of biology that deals with the science of genes and heredity, especially the mechanisms of hereditary transmission and the variation of inherited characteristics
- The hereditary material is DNA

DNA is a double helix formed by base pairs attached to a sugar- phosphate backbone



- Nearly every cell in a person's body has the same DNA
- The information in DNA is stored as a code made up of four chemical bases
- A base, sugar, and phosphate are called a nucleotide
- Human DNA: 3 billion bases > 99 % are the same in all people.

What is a SNP? (single nucleotide polymorphism)

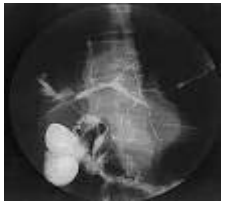
- SNPs are the most common type of genetic variation
- Each SNP represents a difference in a nucleotide (ex C→ A)
- 10 million SNPs in the human genome
- Most SNPs have no effect on health or development.
- Function
  - → Biological markers, helping scientists locate genes that are associated with disease.
  - → May play a more direct role in disease by affecting the gene's function
    - Response to drugs
    - Risk for development of disease in families
    - Association to complex diseases such as IBD and PSC

GWAS (genome-wide association studies) - scanning of DNA to find SNPs

- Computerized databases that contain the reference human genome sequence (ex Human Genome Project)
- New technologies that can quickly and accurately analyze whole-genome samples for genetic variations
- Two groups: people with and without the disease being studied
- DNA from each participant (blood sample)
- DNA is placed on tiny chips and scanned on automated laboratory machines that identify SNPs.
- If certain genetic variations are found to be significantly more frequent in people with the disease compared to people without disease, the variations are said to be "associated" with the disease.

Genotype vs Phenotype

- Genotype is the internally coded, inheritable information
- Phenotype is the outward, physical manifestation



What are the PSC phenotypes? One disease – many diseases?

- Slow progression – fast progression
- IBD - no IBD
- Small duct- large duct
- Asymptomatic - symptomatic disease
- No dysplasia/cancer - development of cancer/dysplasia
- Primary causes – secondary causes

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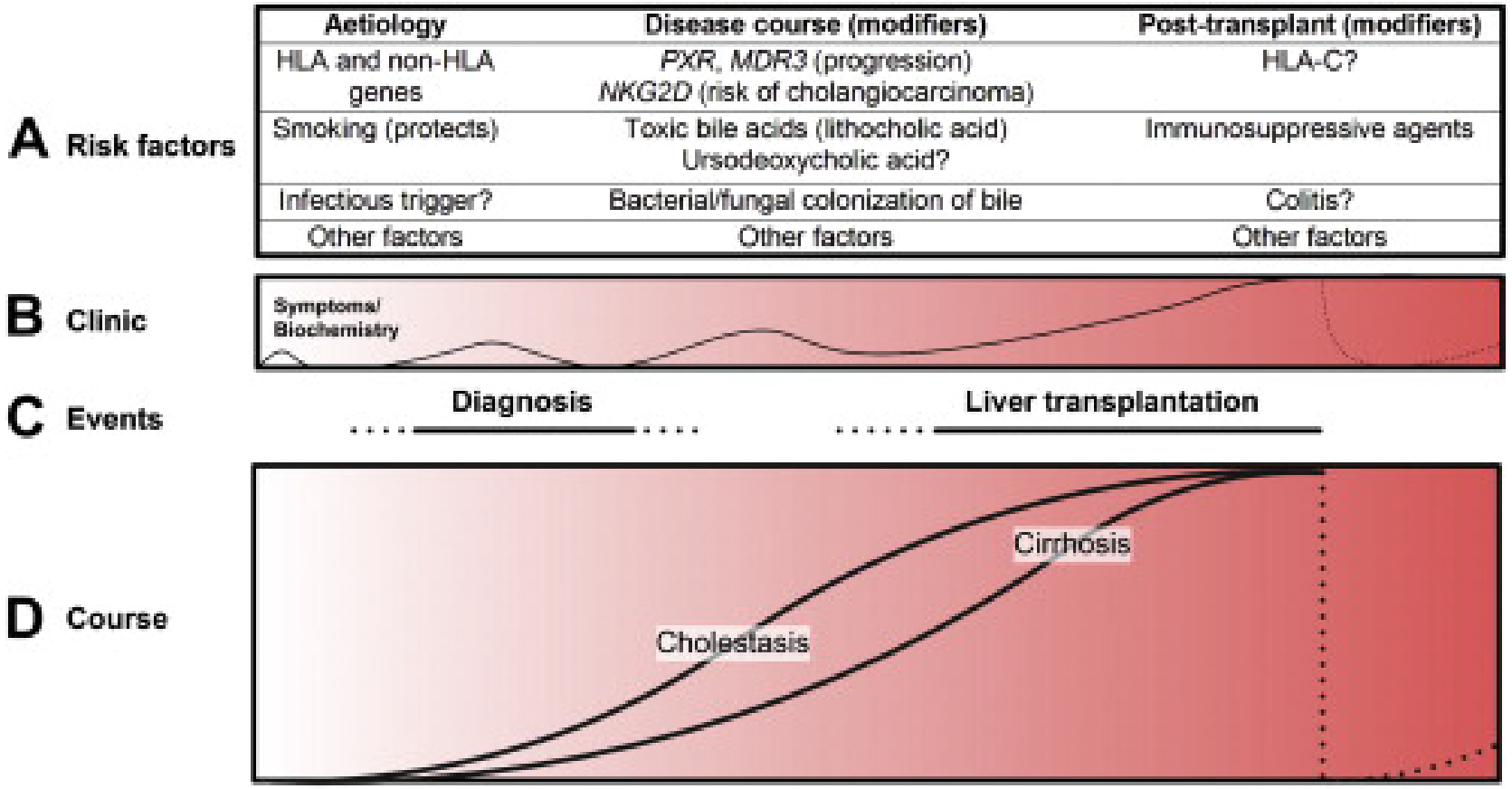

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Prevalence of PSC around the world

Study, [Ref.] Country	Period	No. of patients	Population	Case-finding	Case-ascertainment[a]	Incidence[§] (95% CI)	Prevalence[§] (95% CI)	IBD (%)	Male (%)
Escorsell *et al.*, [31] Spain	1984-1988	43	19,230,000	Personal registry gastroenterologists and hepatologists	I + II + III + IV	0.07	0.22	47	60
Berdal *et al.*, [24] Akershus, Norway	1985-1994	12	180,000	ICD-9	III	0.7	5.6	n.a.	58
Byron *et al.*, [35] Winnipeg, Canada	1987-1994	39	650,000	All clinical records referral center	II + III + VI or II + IV + VI	n.a.	6.5	n.a.	n.a.
Boberg *et al.*, [27] Oslo, Norway	1986-1995	17	130,000	Prospective registration	II + III + IV	1.3 (0.8-2.1)	8.5 (2.8-14.2)	71	71
Ang *et al.*, [44] Changi, Singapore	1989-1998	10	750,000	10 consecutive patients	III + IV	n.a.	1.3	20	90
Bambha *et al.*, [39] Olmsted County, US	1976-2000	22	?	Medical records linkage system, pathology reports, laboratory reports, IBD research records	I + II + III + V or I + II + IV + V	0.9	13.6	73	68
Hurlburt *et al.*, [37] Alaska, US	1984-2000	0	100,312	All clinical records, ICD-9	III	0	0	n.a.	n.a.
Card *et al.*, [32] UK	1987-2002	223	2,027,909	General Practice Research Database	n.a.	0.41 (0.34-0.48)	3.85 (3.04-4.80)	48	63.5
Kingham *et al.*, [33] Swansea, UK	1984-2003	46	251,000	Prospective registration	I + II + III + IV	0.91	12.7	62	62
Lindkvist *et al.*, [34] Västra Götaland, Sweden	1992-2005	199	1,492,000	ICD-9 and ICD-10	II + III + V	1.22	16.2	76	71
Kaplan *et al.*, [40] Alberta, Canada	2000-2005	49	1,112,521	ERCP database, review of MRCPs, pathology database, ICD-9, ICD-10	II + III + V or II + IV + V	0.92	n.a.	67	55

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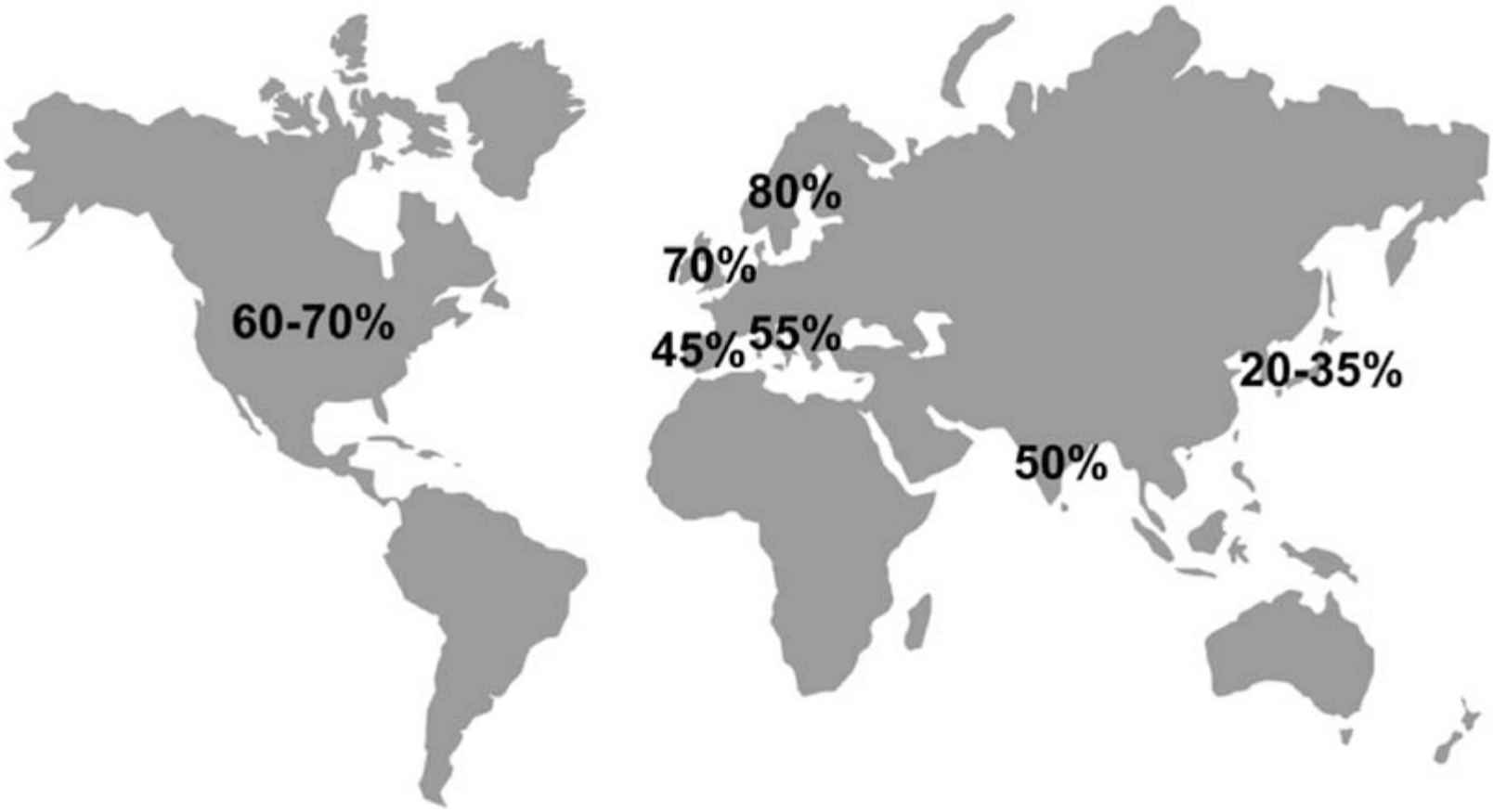
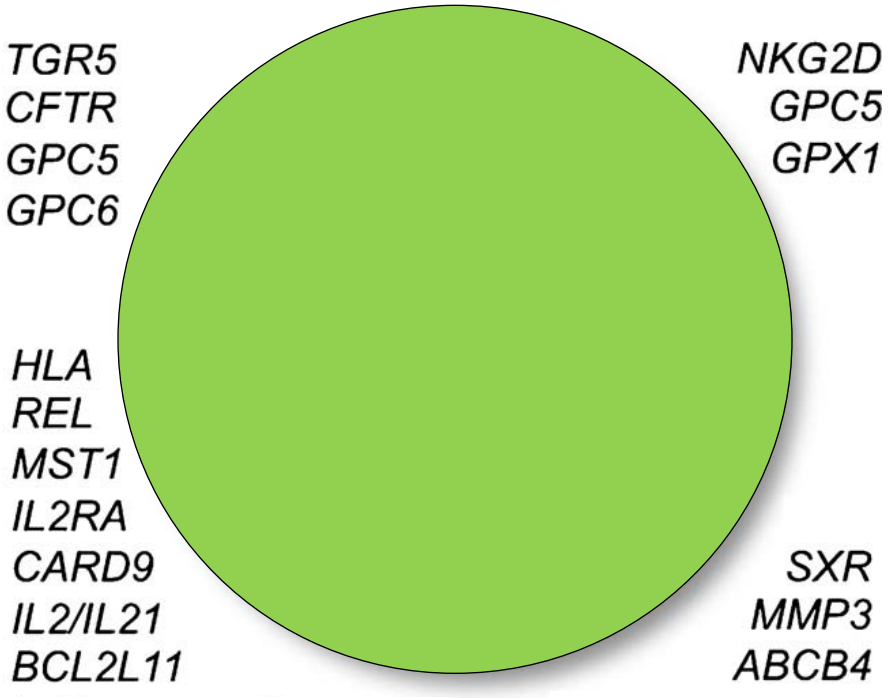
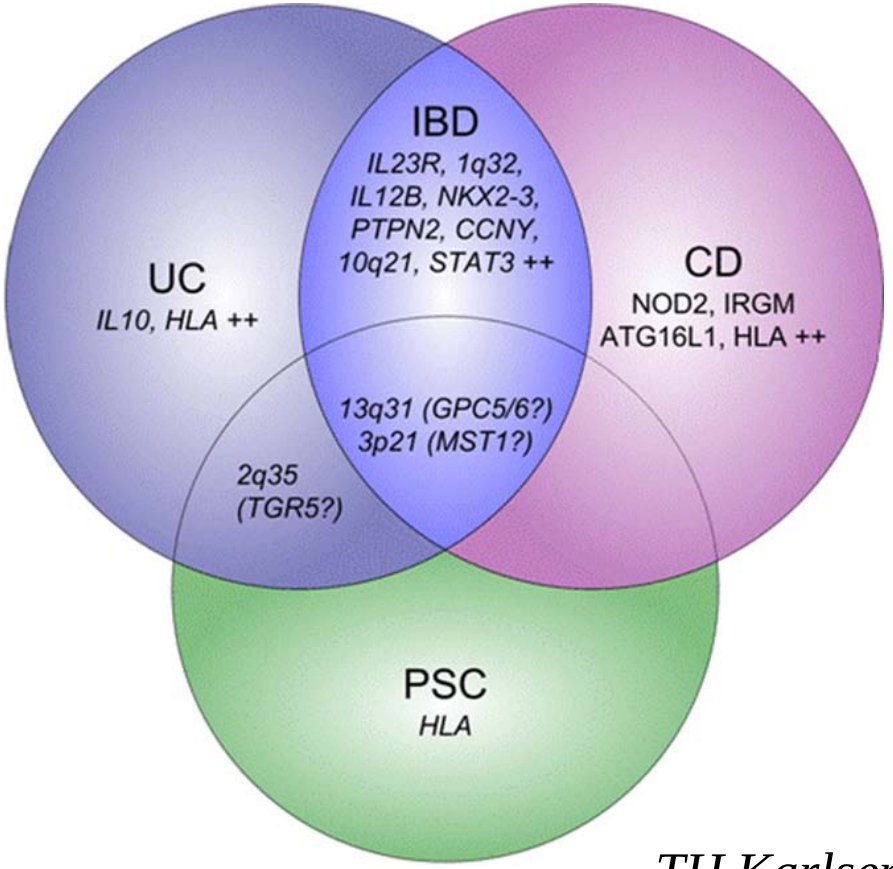
Association between PSC and IBD



Genetic variations in genes from studies including GWAS (SNPs associated with PSC)



There is a genetic overlap between PSC and IBD



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Genetic associations are shared with other autoimmune diseases

- 100 susceptibility locus in IBD explains 25% of the heredity in IBD
- Less in PSC?

Phenotype Overlap Map for Primary Sclerosing Cholangitis (PSC) Associated Loci

Phenotype	6p21	3p21.3	2q35	IL2RA	BCL2L11	IL2/ IL21	GPC5/ GPC6	REL
UC	X	X	X			X		X
CD	X	X		X				
PBC	X							
Type1 Diab	X			X		X		
RA	X			X		X		X
Celiac dis	X					X		X
MS	X			X			X	
NH Lymphoma	X				X			
SLE	X			X				X
Other	X			X		X		X

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Genetics help us to understand the pathogenesis of PSC

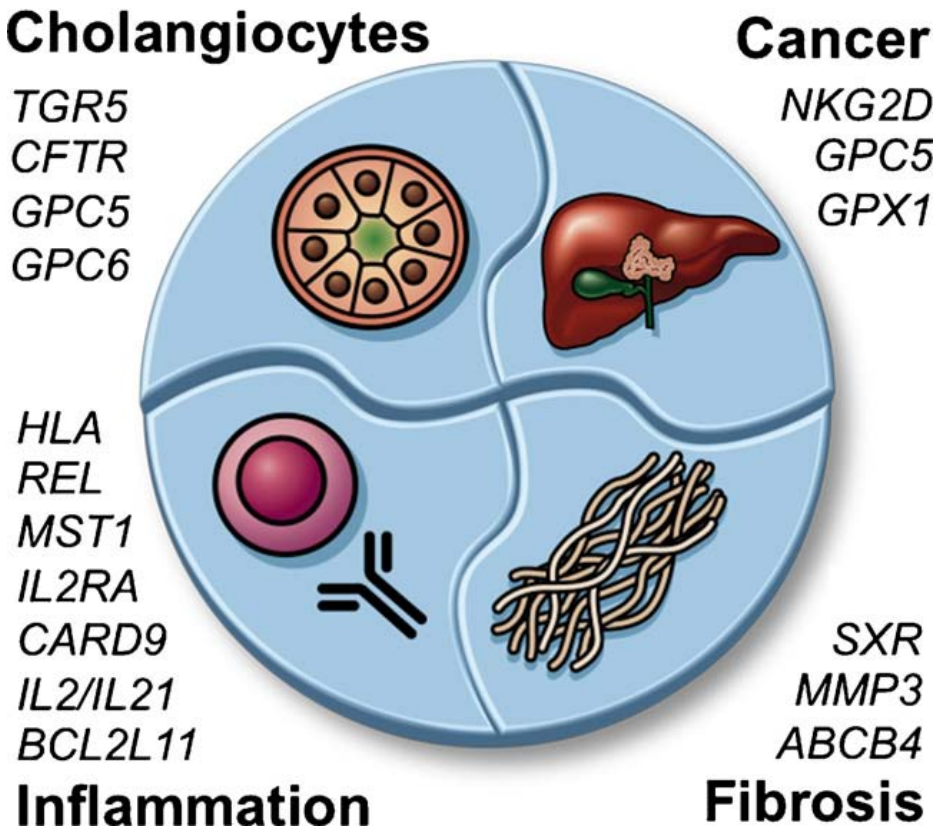
- Theories on the pathogenesis of PSC

  → Leaky gut hypothesis

  → Autoimmune disease

  → Homing of lymphocytes

  → Toxic bile



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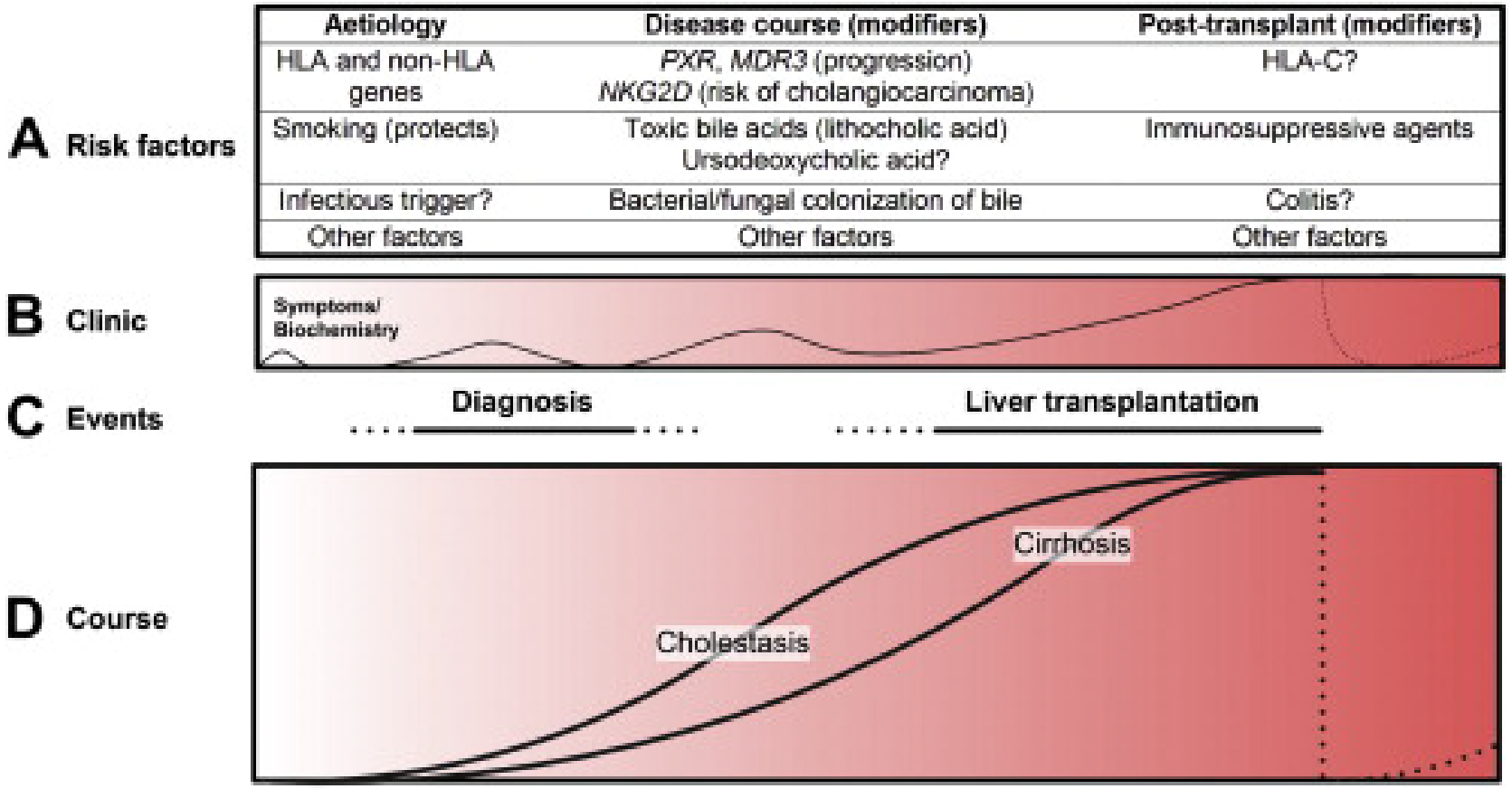

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Can PSC susceptibility genes be utilized for predicting disease or disease behavior?

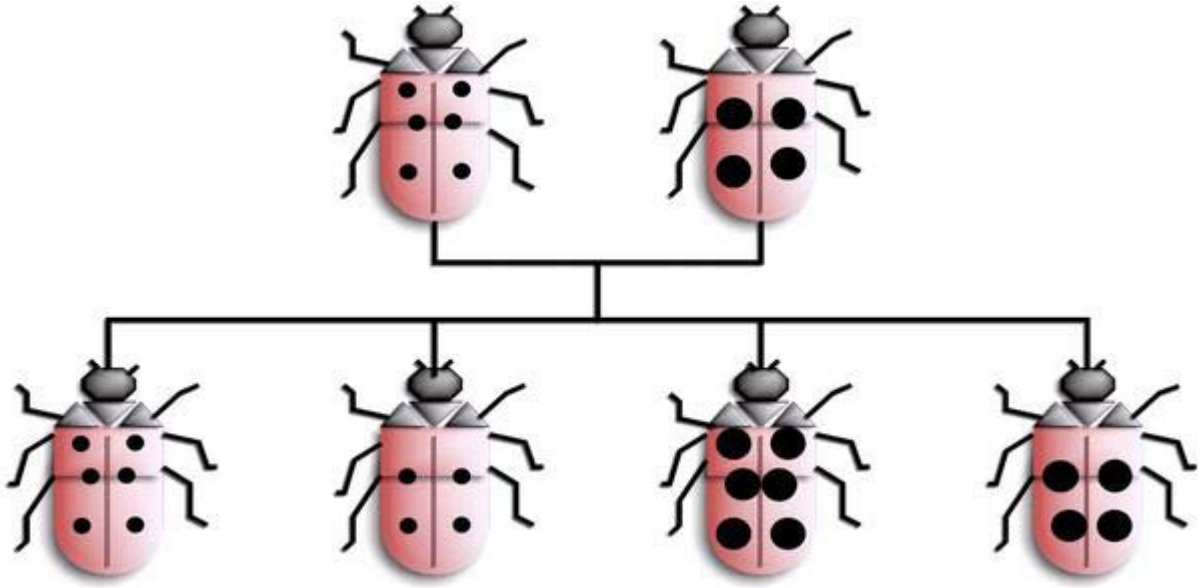
- Personalized medicine?

→ Complex and rare disease

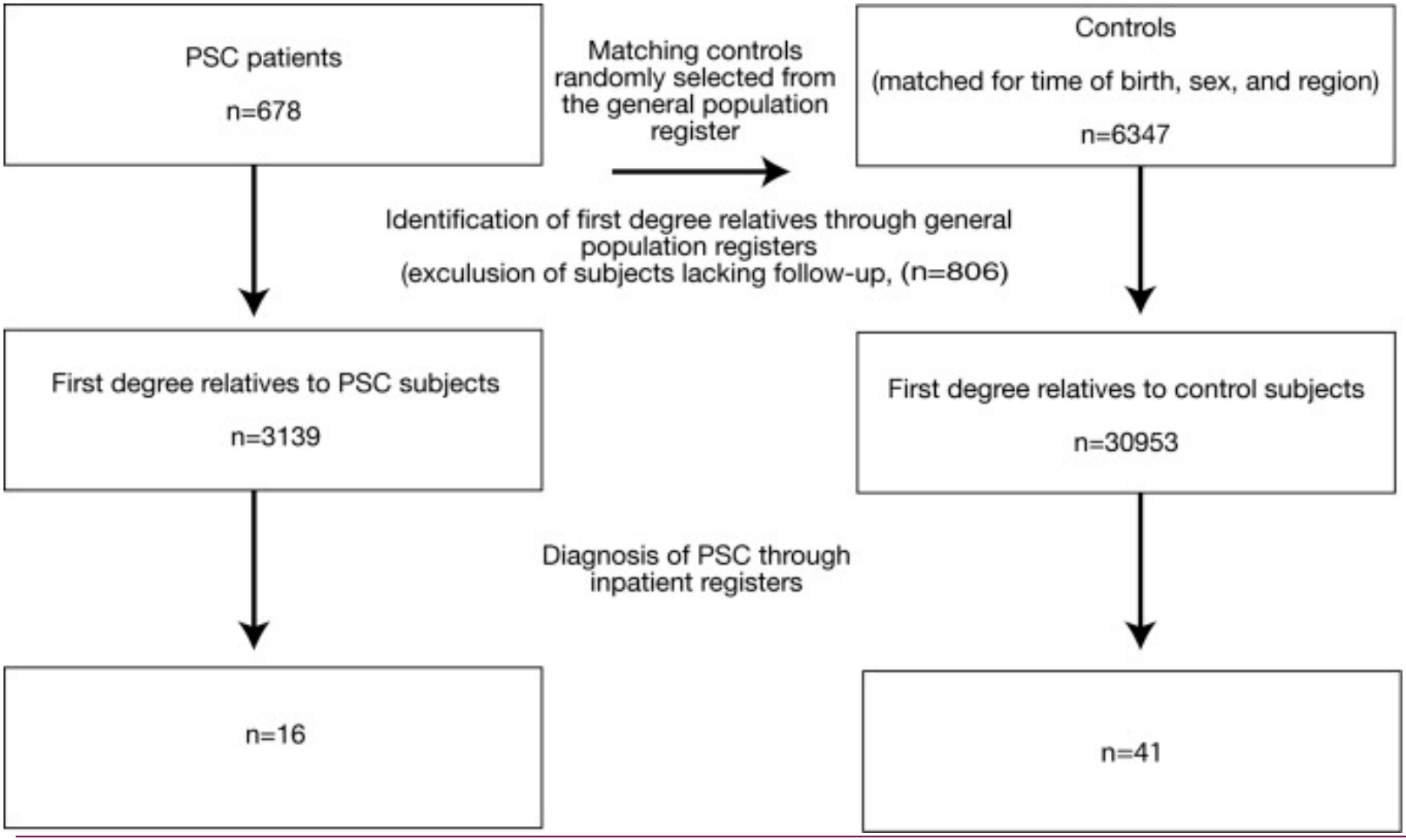
→ Too many unknown factors (genes, environmental)

→ NO

Inheritance in PSC?



Risk of PSC and UC in First-Degree Relatives of Patients With PSC



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PSC Among First-Degree Relatives of Patients With PSC: Risks Compared With First-Degree Relatives of a Comparison Cohort

	Cholangitis (RR CI95%)	Cholangitis and UC (RR CI95%)
Off Spring	11.5 (1.6–84.4)	21.0 (1.9–238.8)
Sibings	9.1 (2.9–29.3)	38.6 (4.3–345.4)
Parents	2.8 (1.2–6.6)	5.3 (0.3–89.9)
All	3.8 (2.1–6.8)	17.3 (5.1–59.2)

A Bergquist, Clin Gastroenterol 2008

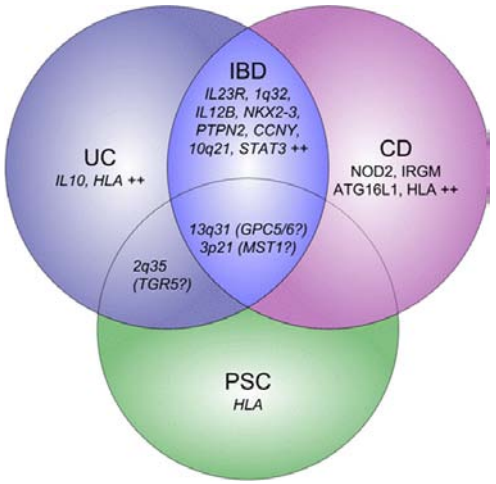
IBD Among First-Degree Relatives of Patients With PSC: Risks Compared With First-Degree Relatives of a Comparison Cohort

	UC (RR CI95%)	Crohns (RR CI95%)
Off Spring	4.2 (1.6–11.1)	5.4 (1.2–24.0)
Sibings	8.4 (4.1–17.3)	2.0 (0.9–4.7)
Parents	2.5 (1.2–5.3)	0.5 (0.1–2.4)
All	3.3 (2.3–4.9)	1.4 (0.8–2.5)

PSC and IBD Among First-Degree Relatives of Patients With PSC Without IBD: Events and Risks Compared With First-Degree Relatives of a Comparison Cohort

	PSC	UC (RR CI95%)	Crohns (RR CI95%)
All first degree relatives	4.9 (1.2–19.8)	7.4 (2.9–8.9)	4.2 (1.3–13.5)

- Increased risk for IBD in first degree relatives to PSC patients without IBD indicate shared genetic susceptibility factors for PSC and IBD



A Bergquist, Clin Gastroenterol 2008

What is the risk for my children to get PSC?

- 8/100 000 = 0.008%
- PSC increased risk by 4 = 32/100 000 = 0.032%
- IBD increased risk by 3= 24/100 000 = 0.024%
- LOW

Problems

- Many genes – complex disease
- Overlap to other diseases - few PSC specific SNPs
- Environmental factors poorly understood
- Rare disease
- Many phenotypes
- Secondary causes influence disease progression
- ……
- nevertheless

- Genetic studies have contributed considerably to the knowledge of PSC

- More to be discovered

Summary

- Genetics is the branch of biology that deals with the science of genes and heredity
- PSC is a complex disease with genetic overlap to other autoimmune diseases including IBD
- Genetics is not alone going to explain PSC (<<<25%?)
- Increased risk for first degree relatives (3-4 times) , however, still very rare
- Genetic studies have contributed considerably to the knowledge of PSC- more to be discovered

THANK YOU FOR YOUR ATTENTION