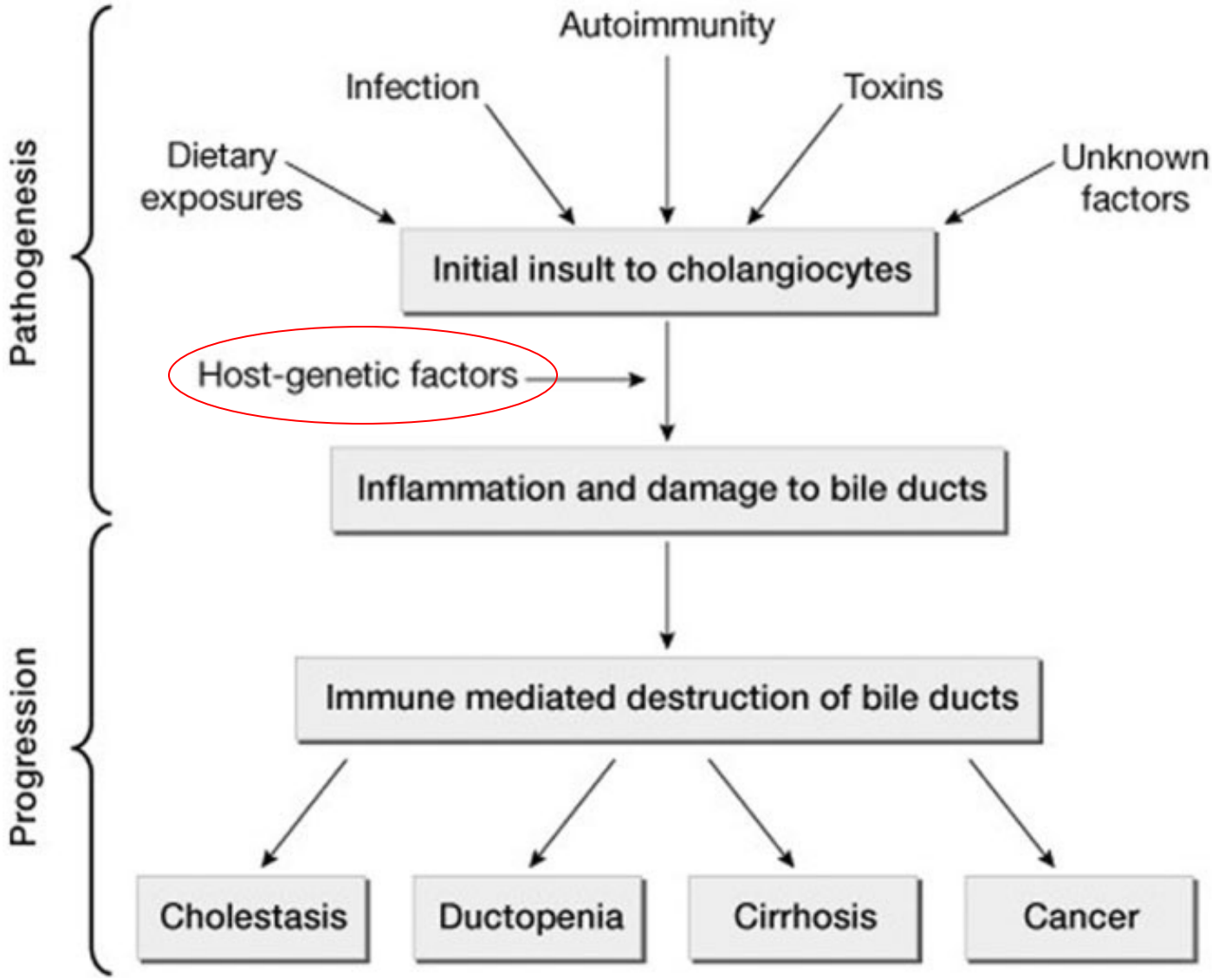
Genes Affecting IBD and PSC Susceptibility and Severity

David Rhodes

PSC Partners Seeking a Cure



Proposed pathogenesis and cause of progression in PSC

From: **LaRusso NF, Shneider BL, Black D, Gores GJ, James SP, Doo E, Hoofnagle JH (2006) Primary sclerosing cholangitis: summary of a workshop. Hepatology 44: 746-764.**

STOPSC Research Objectives Include:

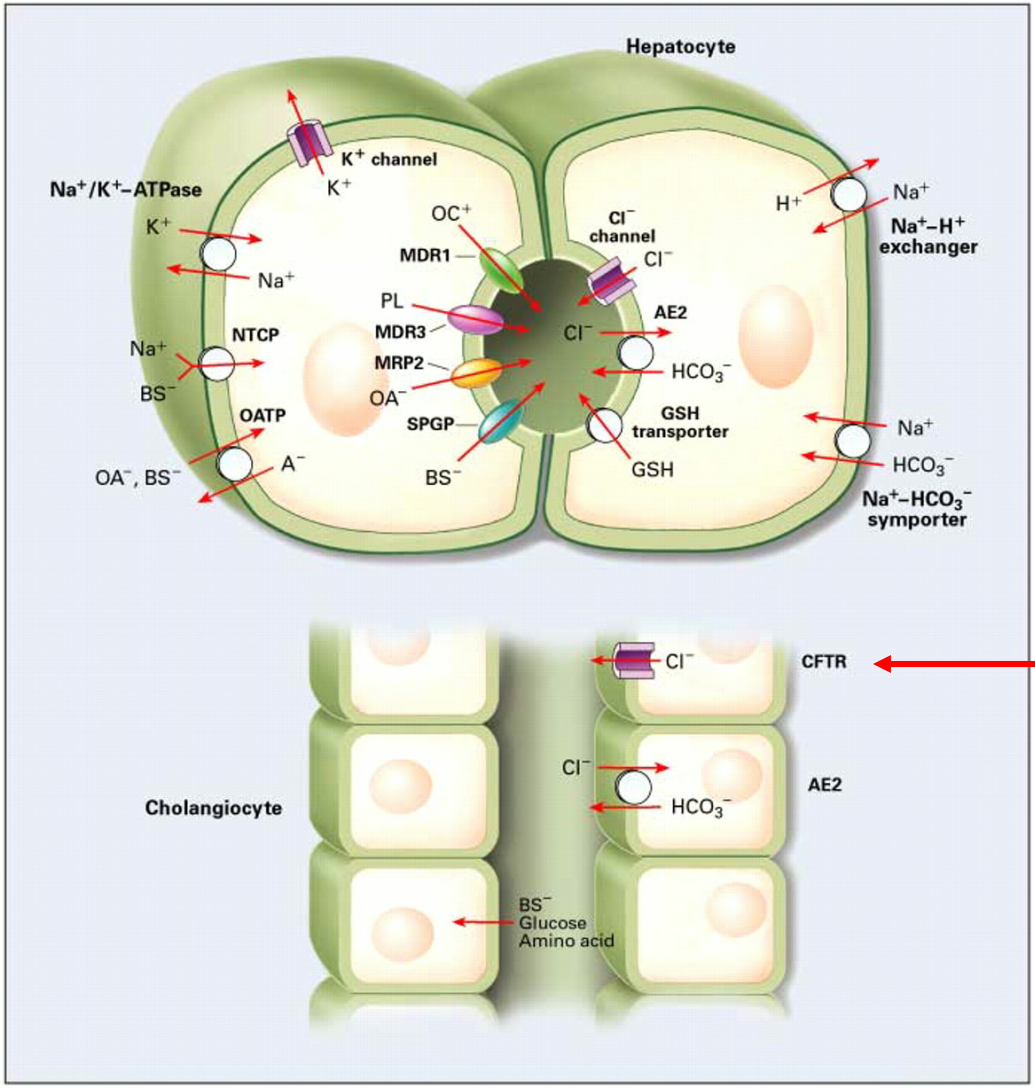
• To identify risk factors (**genetic** and environmental) for development of PSC and understand the mechanisms involved in pathogenesis of PSC.

• To identify the role of **genetic** factors in the **predilection for disease, disease severity and response to treatment** (**HLA haplotypes, cftr, mdr3, nod2, as well as inflammatory mediator gene polymorphisms, and liver disease modifier genes**).

Transport Proteins of Hepatocytes and Bile-Duct Epithelial Cells (Cholangiocytes)

Cystic
Fibrosis
Transmembrane
conductance
Regulator

a chloride
channel



CFTR

Trauner, M. et al. N Engl J Med 1998;339:1217-1227

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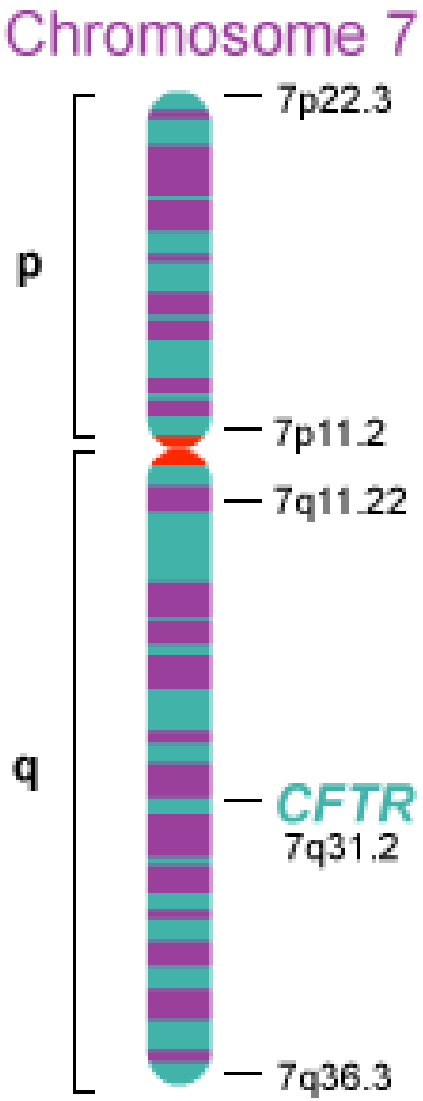


Most common mutation

CFTR Sequence:

Nucleotide	A	T	C	A	T	C	T	T	T	G	G	T	G	T	T
Amino Acid	Ile			Ile			Phe			Gly			Val		
	506						508						510		

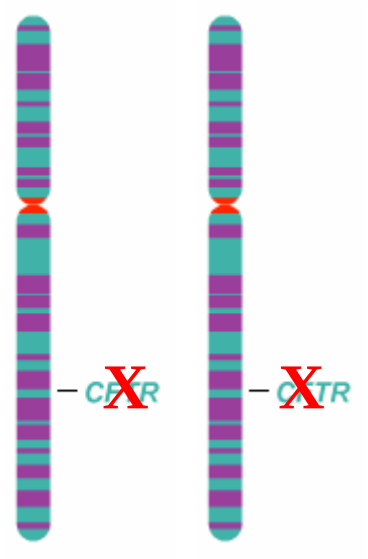
Deleted in ΔF508

ΔF508 CFTR Sequence:

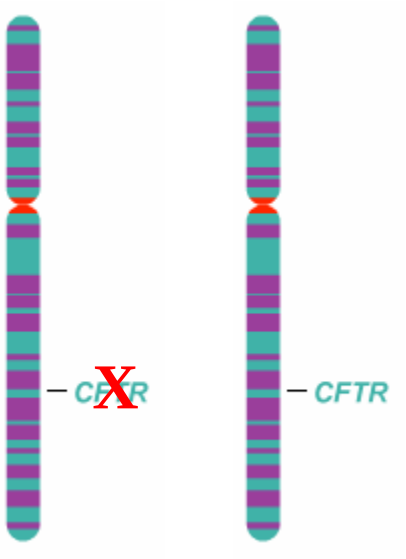
Nucleotide	A	T	C	A	T	T	G	G	T	G	T	T
Amino Acid	Ile			Ile			Gly			Val		
	506											

CFTR: The Gene Associated with Cystic Fibrosis Is Localized on Chromosome 7

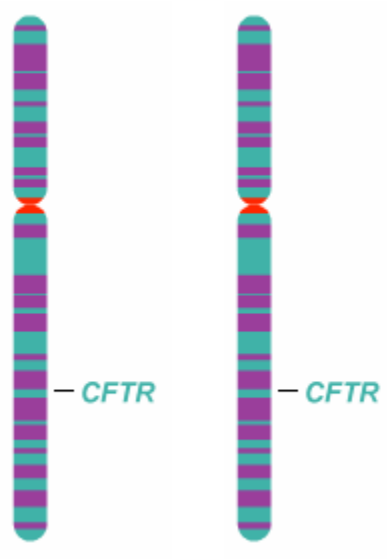
http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/cftr.shtml



Cystic fibrosis

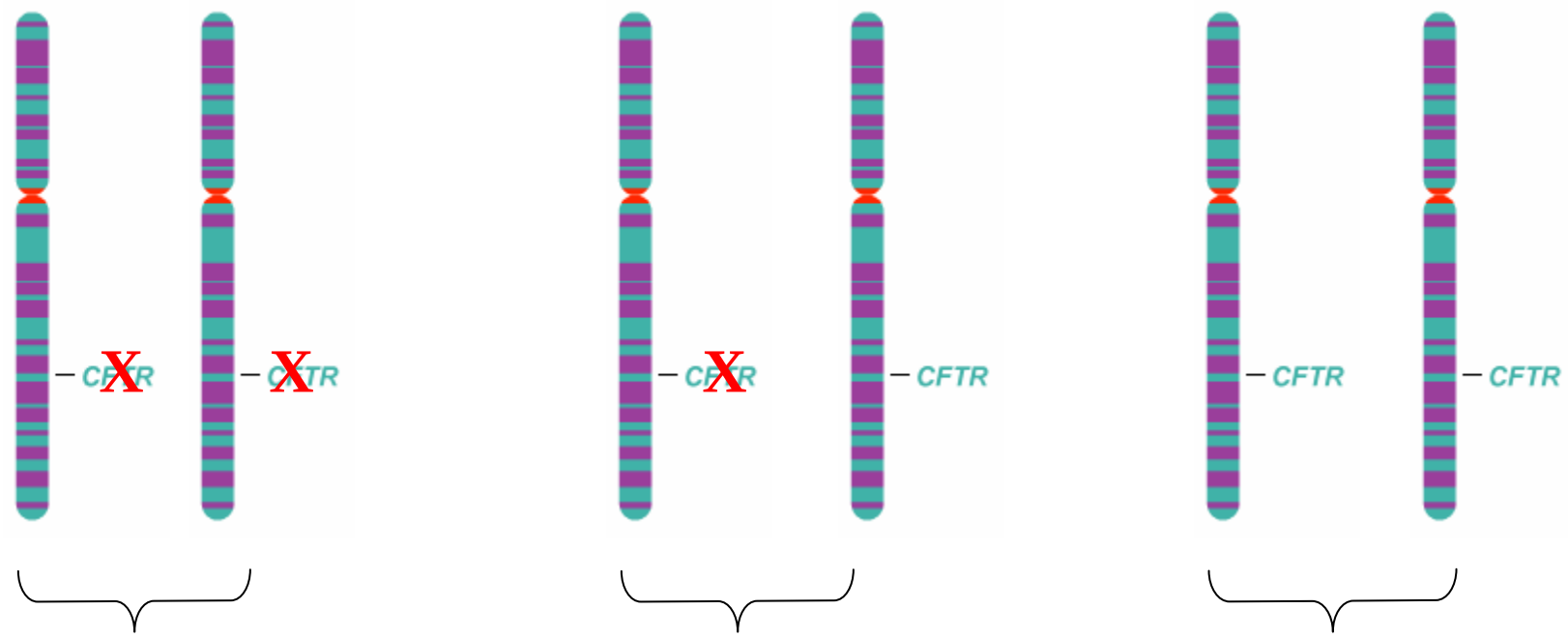


Carrier
(**heterozygous**)



Normal

- **Lung disease**
- **Sinusitis**
- **Congenital bilateral absence of the vas deferens**
- **Pancreatic insufficiency**
- **Liver disease**

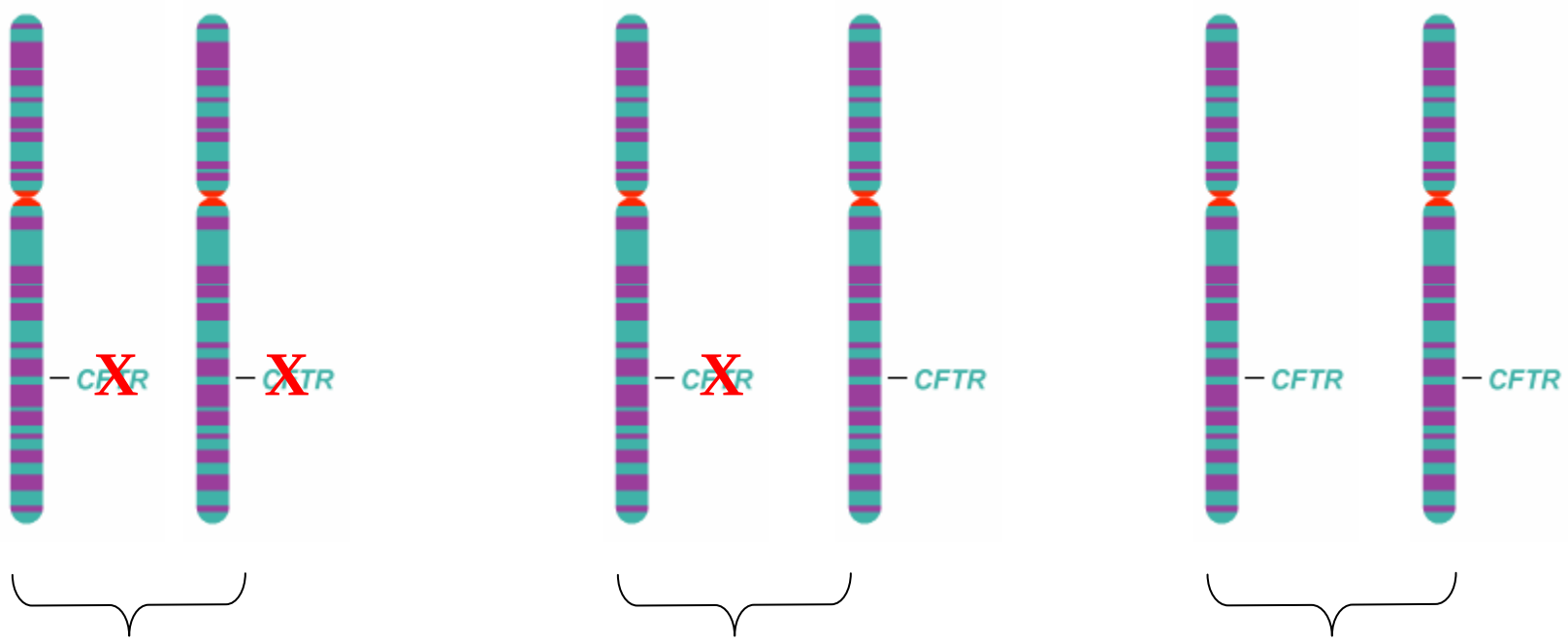


Cystic fibrosis **lung disease** requires 2 copies of the mutant CFTR allele (**X**). Lung disease severity is dependent upon the type of mutation (some mutations are more severe than others) and additional "**modifier**" genes that are inherited independently.

Cystic fibrosis (CF) liver disease

- **Bile duct injury in CF resembles PSC**
- **Male predominance (~ 2:1), as in PSC**
- **Severity of liver disease in CF affected by "modifier" genes, including:**
  - **HLA-DQ6**
  - **Mannose-binding lectin (MBL2)**
  - **Angiotensin converting enzyme**
  - **Glutathione *S*-transferase P1**

Cutting GR (2005) Modifier genetics: cystic fibrosis. Annu. Rev. Genomics Hum. Genet. 6: 237-260.



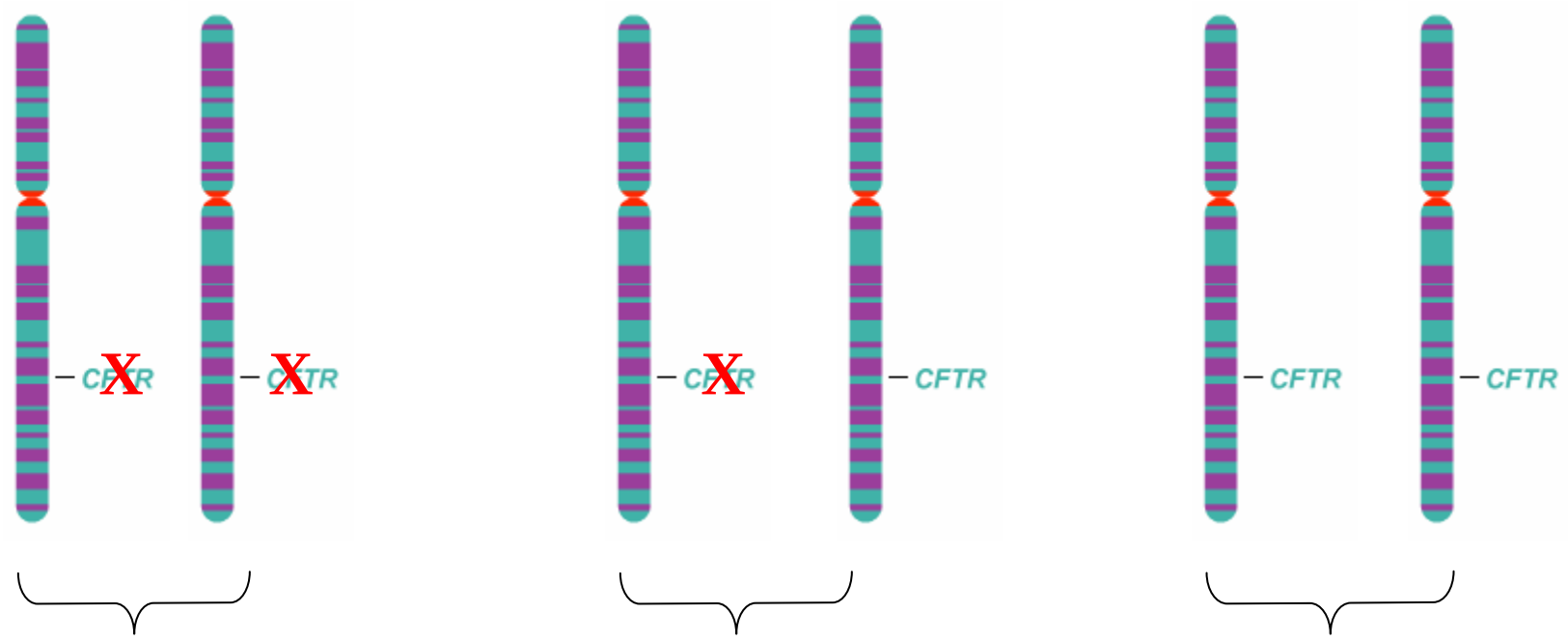
Cystic fibrosis

Carrier
(**heterozygous**)

Normal

Heterozygous “carriers” seem to be at higher risk for **pancreatitis**:

Weiss FU, Simon P, Bogdanova N, Mayerle J, Dworniczak B, Horst J, Lerch MM (2005) Complete cystic fibrosis transmembrane conductance regulator gene sequencing in patients with idiopathic chronic pancreatitis and controls. Gut 54: 1456-1460.



Cystic fibrosis

Carrier
(**heterozygous**)

Normal

Sheth et al (2003) have proposed that CFTR **heterozygous** “carriers” [**with a background of IBD**] may be at increased risk of **PSC**:

Sheth S, Shea JC, Bishop MD, Chopra S, Regan MM, Malmberg E, Walker C, Ricci R, Tsui LC, Durie PR, Zielenski J, Freedman SD (2003) Increased prevalence of CFTR mutations and variants and decreased chloride secretion in primary sclerosing cholangitis. Hum. Genet. 113: 286-292.

Consistent with this, cftr (-/-) mice develop sclerosing cholangitis only when given colitis

- **Docosahexaenoic acid (DHA) protects against bile duct injury in this animal model**

- **This is the rationale for DHA trial in PSC**

Pall H, Zaman MM, Andersson C, Freedman SD (2006) Decreased peroxisome proliferator activated receptor alpha is associated with bile duct injury in cystic fibrosis transmembrane conductance regulator (-/-) mice. J. Pediatr Gastroenterol. Nutr. 42: 275-281.

Other similarities between PSC/IBD and cystic fibrosis:

• Both result in inflammation - activation of **nuclear factor-kappa B** (NFKB or NF-kB)

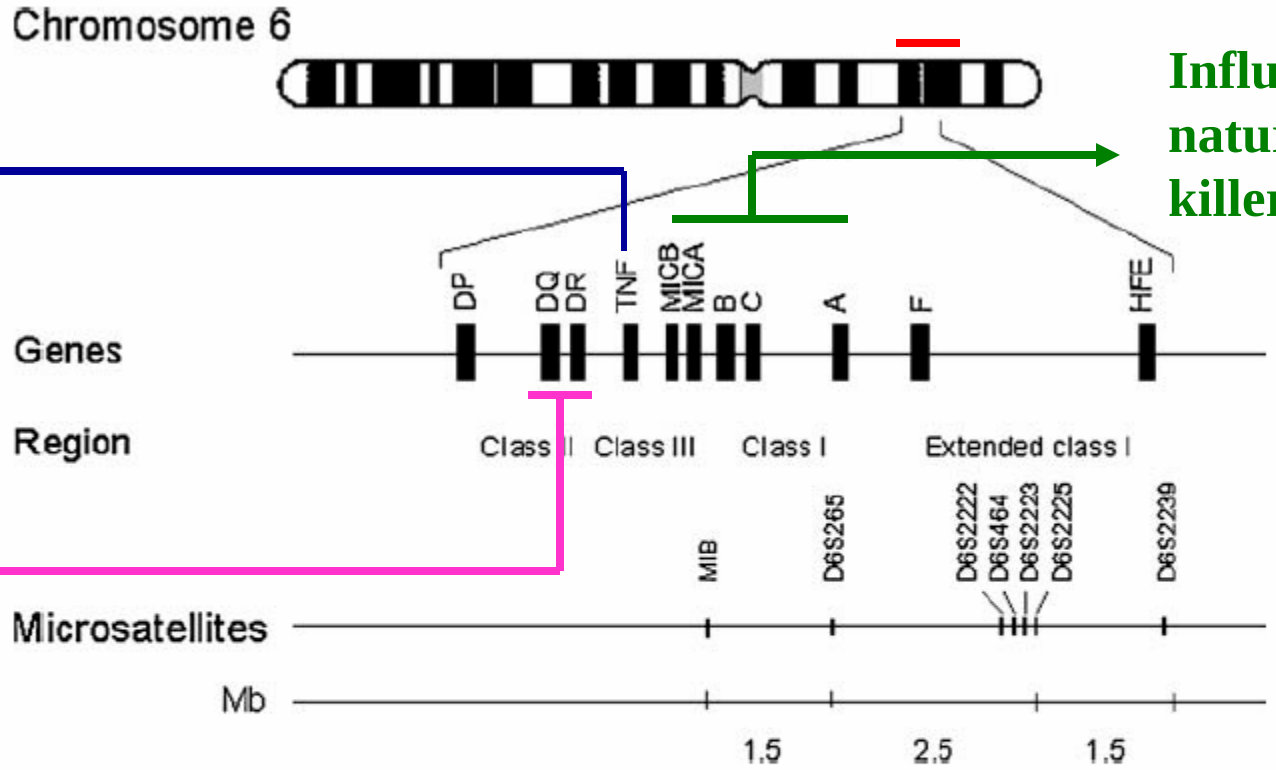
• Both are associated with antibodies to bactericidal/permeability-increasing protein (BPI); a neutrophil-granule protein with significant antimicrobial activity against gram-negative bacteria that strongly neutralizes the endotoxic activity of bacterial lipopolysaccharide (LPS) [**BPI-ANCA**].

Diseases associated with ANCA	Prevalence of BPI-ANCA
ANCA-associated vasculitides	5-45%
Necrotizing and crescentic glomerulonephritis	17-32%
Chronic inflammatory bowel disease (ulcerative colitis/Crohn's disease)	**14-39%**
Primary sclerosing cholangitis	**36-46%**
Cystic fibrosis	**83-91%**

From: Schultz H, Weiss J, Carroll SF, Gross WL 2001 The endotoxin-binding bactericidal/permeability-increasing protein (BPI): a target antigen of autoantibodies. J. Leukoc. Biol. 69: 505-512.

TNF is involved in inflammation

HLA-DR/DQ encode proteins involved in antigen presentation to T helper (Th) cells.



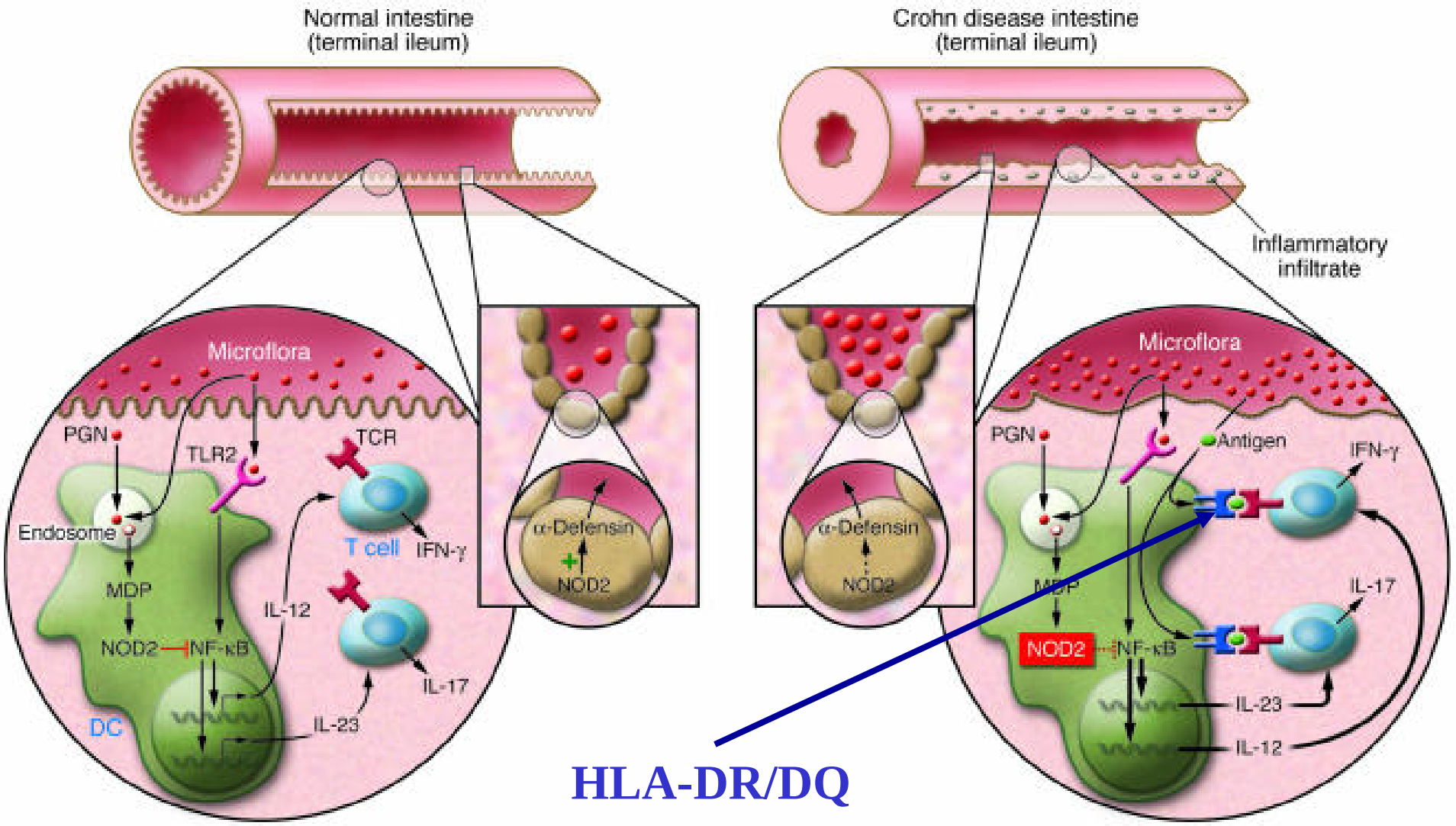
Influence natural killer cells

PSC Susceptibility Genes are Localized in the HLA Region of the Major Histocompatibility Complex on Chromosome 6

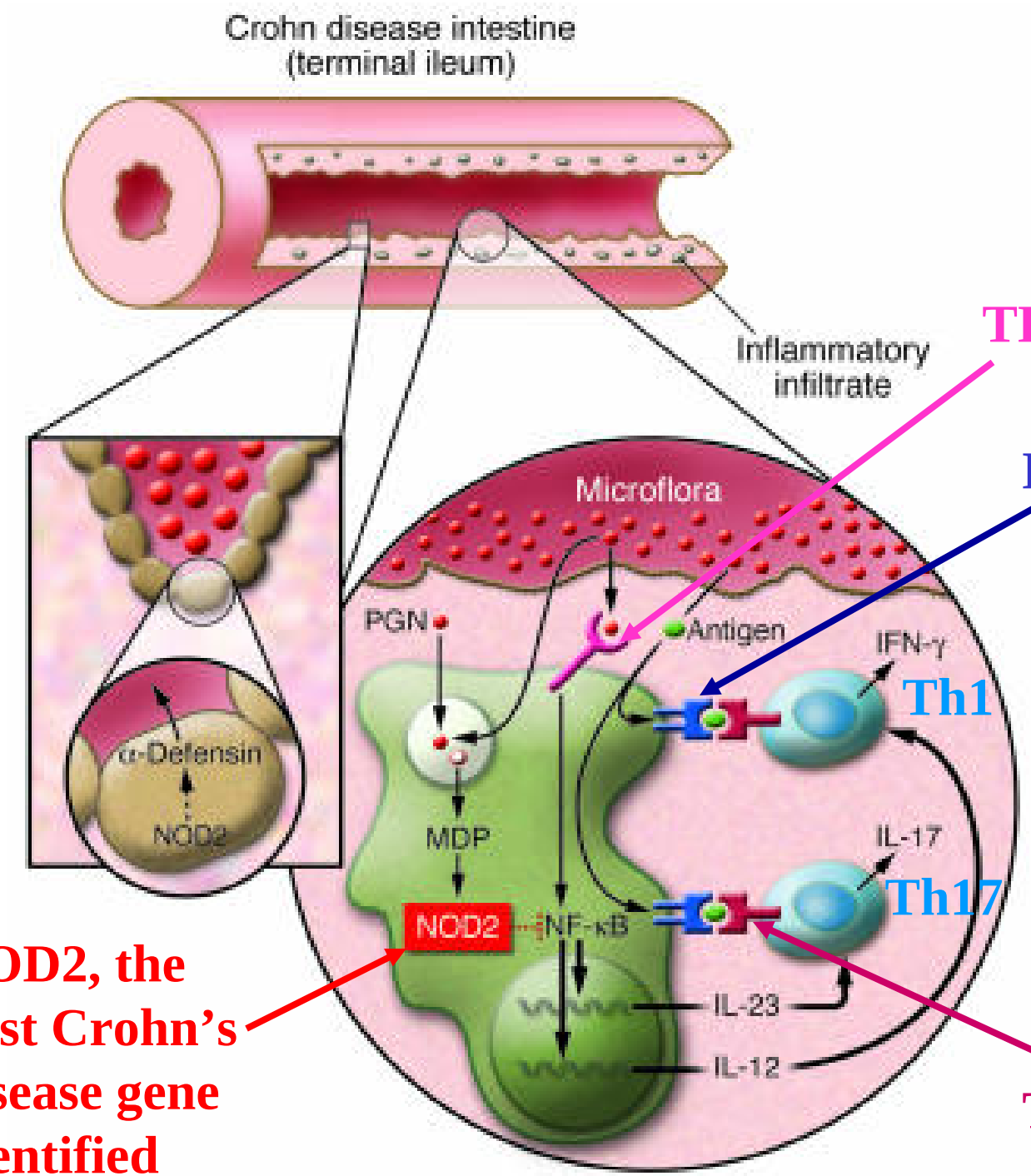
Wiencke K, Karlsen TH, Boberg KM, Thorsby E, Schrumpf E, Lie BA, Spurkland A (2007) Primary sclerosing cholangitis is associated with extended HLA-DR3 and HLA-DR6 haplotypes. Tissue Antigens 69: 161-169.

Karlsen TH, Boberg KM, Olsson M, Sun JY, Senitzer D, Bergquist A, Schrumpf E, Thorsby E, Lie BA (2007) Particular genetic variants of ligands for natural killer cell receptors may contribute to the HLA associated risk of primary sclerosing cholangitis. J Hepatol. 2007 Feb 27 [Epub ahead of print].

BACKGROUND/AIMS: **Combinations of killer immunoglobulin-like receptors (KIRs) and HLA class I ligands that reduce natural killer (NK) cell inhibition have been shown to increase risk for autoimmune diseases.** We aimed to clarify to what extent such combinations influence susceptibility to primary sclerosing cholangitis (PSC). METHODS: Three hundred and sixty-five Scandinavian PSC patients and 368 healthy controls were genotyped for the presence or absence of genes encoding all KIRs using a PCR-SSP approach. KIR binding site variation of HLA-A, -B and -C was also determined. RESULTS: The KIR gene frequencies were similar among patients and controls. However, the frequency of HLA-Bw4 and -C2, which are ligands for the inhibitory KIRs 3DL1 and 2DL1, respectively, was significantly reduced in PSC patients as compared with controls (38.2% vs. 54.7%, P(corrected)[P(c)]=0.0006 and 42.7% vs. 56.9%, P(c)=0.009, respectively). Two HLA risk haplotypes in PSC (carrying DRB1*0301 or DRB1*1501, respectively) were devoid of both of these alleles, and carried the 5.1 variant of the major histocompatibility complex class I chain-related A (MICA) gene previously reported to influence PSC susceptibility. CONCLUSIONS: **Particular variants of ligands for NK cell receptors encoded at three neighbouring genes in the HLA complex may contribute to PSC associations observed in this genetic region.**



Strober W, Fuss I, Mannon P (2007) The fundamental basis of inflammatory bowel disease. J. Clin. Invest. 117: 514-521.



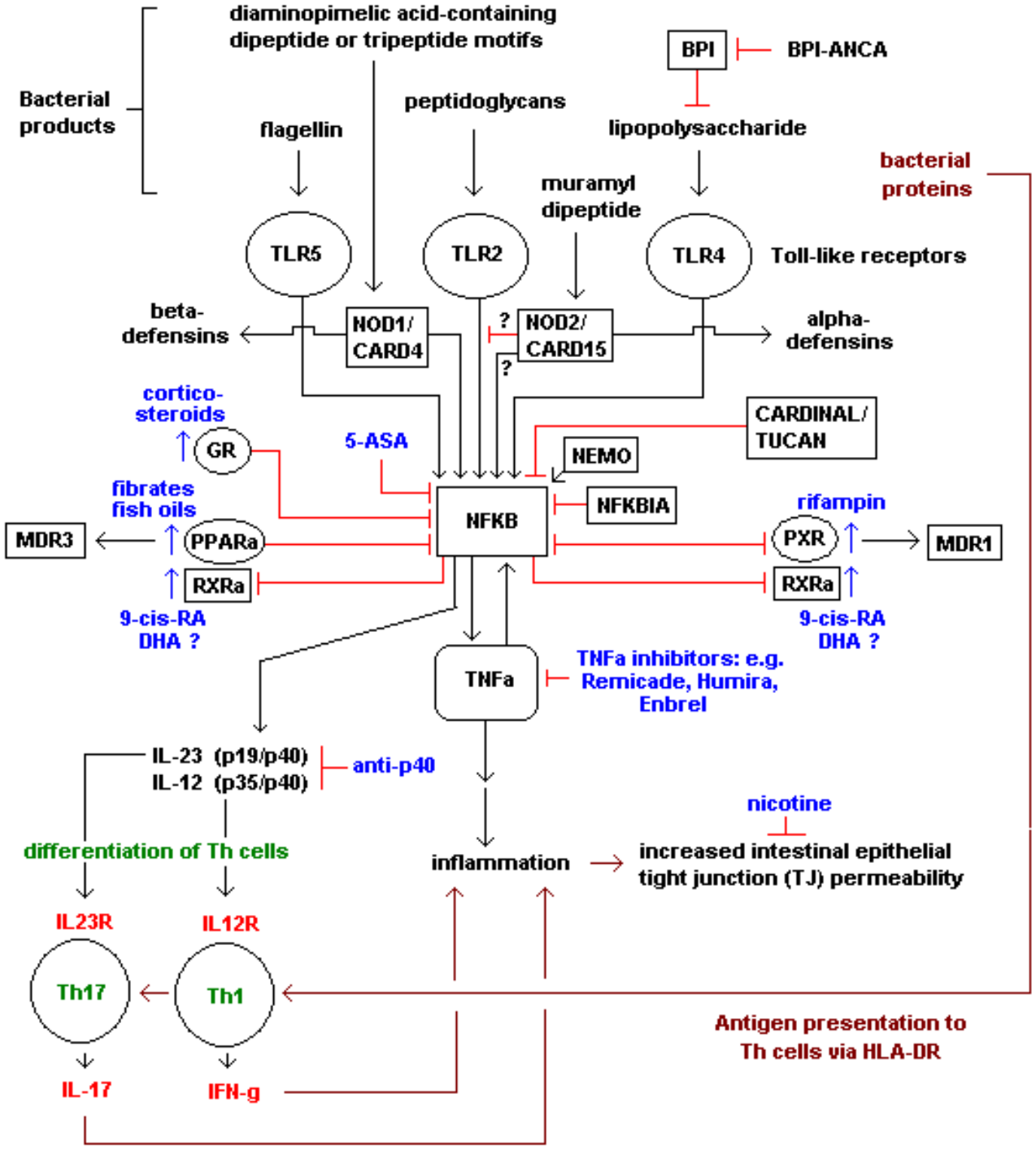
TLR2

HLA-DR/DQ

NOD2, the first Crohn's disease gene identified

T cell receptor

NFKB is at the center of inflammation in IBD



A newly discovered IBD susceptibility gene is IL23R; a receptor on Th17 cells

Concluding Comments

• Much progress is being made in identifying genes involved in IBD and PSC

• Genes provide clues to pathogenesis and possible therapies

• Further progress will be critically dependent upon $ for research and patient participation in genetic studies