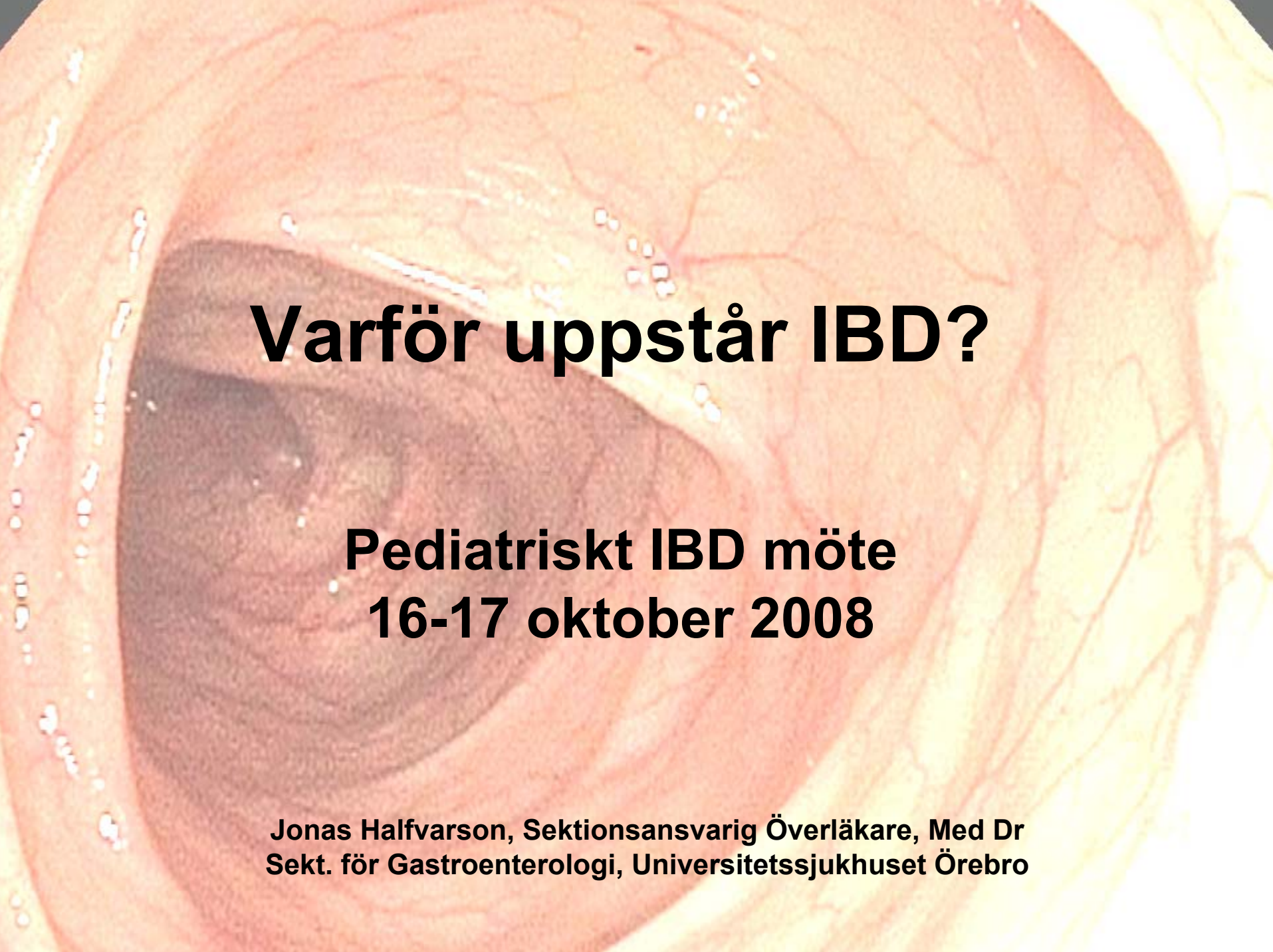
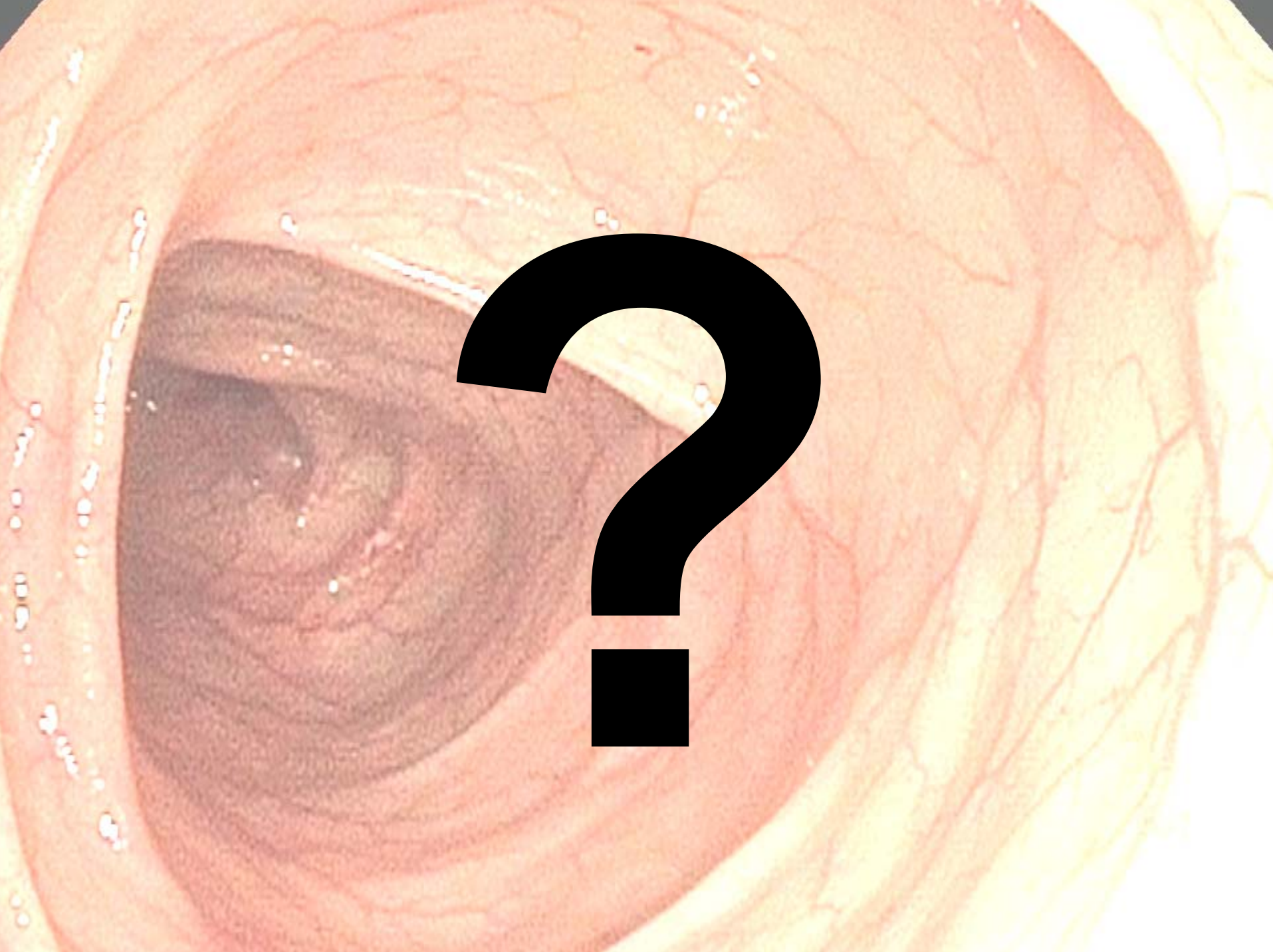


Varför uppstår IBD?

Pediatriskt IBD möte
16-17 oktober 2008

Jonas Halfvarson, Sektionsansvarig Överläkare, Med Dr
Sekt. för Gastroenterologi, Universitetssjukhuset Örebro



Pathogenesis of IBD

Overly aggressive immune response to commensal enteric bacteria in genetically susceptible individuals, where environmental factors precipitate the onset/reactivation of the disease

Sartor R B. Nat Clin Pract Gastroenterol Hepatol. 2006; 3: 390-407

Genetics – pathogenesis

Concordance rates in twins

Crohn's disease

	British cohort at follow up*	Danish cohort at follow up**	Swedish cohort at follow up***
MZ	33%	56%	50%
DZ	10%	4%	4%

Ulcerative colitis

	British cohort at follow up*	Danish cohort at follow up**	Swedish cohort at follow up***
MZ	13%	14%	19%
DZ	4%	4%	4%

* Subhani J et al. Gut 1998; 42 (suppl 1)

** Jess T et al. Am J Gastroenterol 2005; 100:1-7

*** Halfvarson J, Bodin L, Lindberg E, Tysk C, Järnerot G. Gastroenterology 2003;124:1767-73

Genetics - phenotype of CD

Year of birth	Year of diagnosis	Location at diagnosis	Behaviour
1920	**1977** **1977**	**Term, ileum** **Term, ileum**	**Penetr.** **Penetr.**
1929	1964 1974	**Term, ileum** **Term, ileum**	**Strict.** **Strict.**
1940	1966 1992	Term, ileum iteocolon	Strict. Penetr.
1946	**1967** **1969**	**Term, ileum** **Term, ileum**	Penetr. Strict.
1947	**1973** **1974**	**Term, ileum** **Term, ileum**	**Strict.** **Strict.**
1948	**1974** **1975**	Ileocolon colon	**Inflam** **Inflam**
1949	**1966** **1966**	**Ileocolon** **Ileocolon**	**Penetr.** **Penetr.**
1953	**1976** **1976**	**Term, ileum** **Term, ileum**	**Inflam** **Inflam**
1954	1968 1982	**Ileocolon** **Ileocolon**	Inflam Penetr.

Halfvarson J, et al. Gastroenterology 2003;124:1767-73

Phenotypic concordance in 9 MZ twin pairs

	Observed no of twin pairs with concordance (n=9)	p-value
Age at diagnosis	6 pairs	0.01
Location	7 pairs	0.006
Behaviour	6 pairs	0.07

Halfvarson J, Bodin L, Lindberg E, Tysk C, Järnerot G. Gastroenterology 2003;124:1767-73

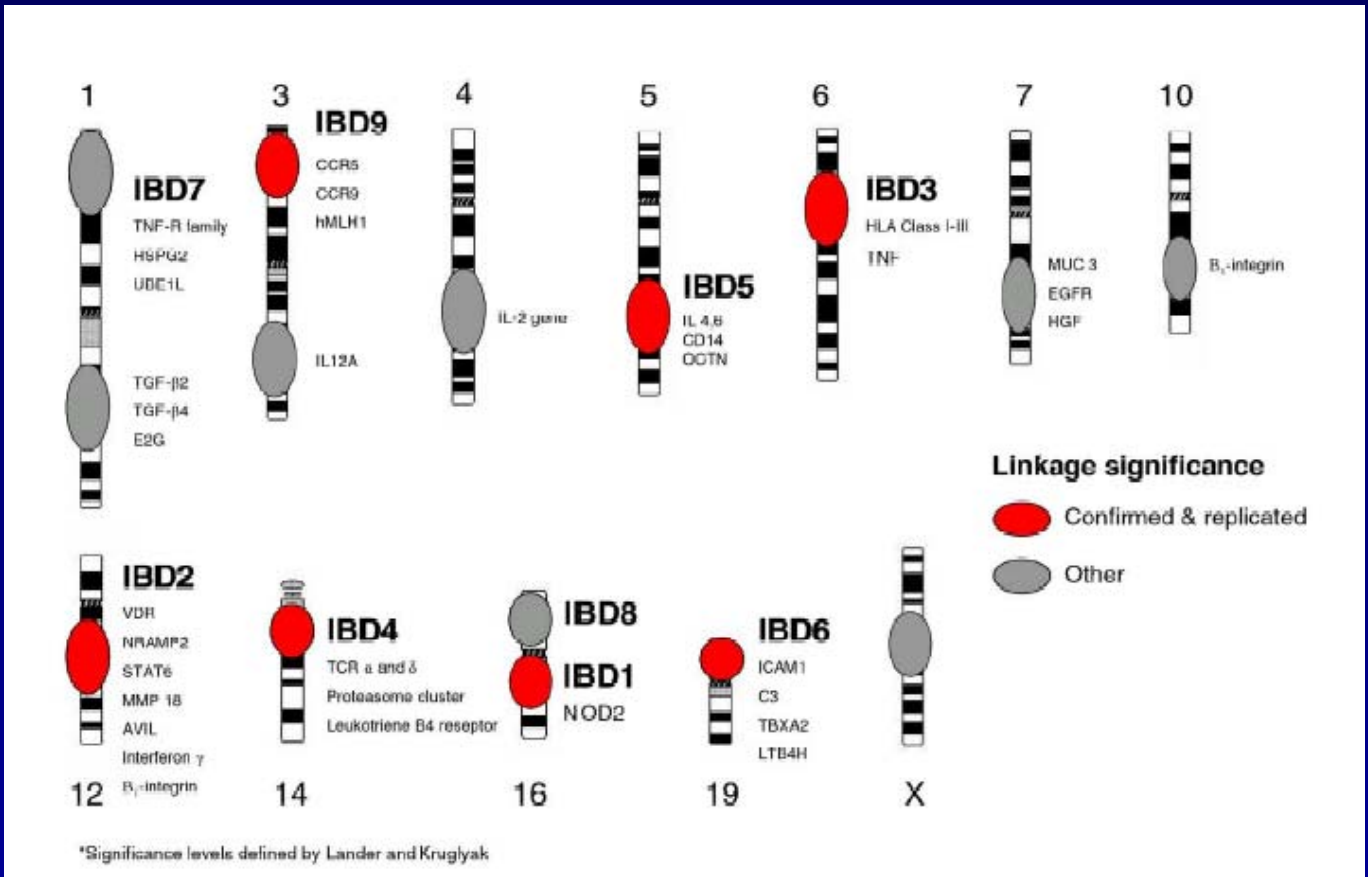
Longitudinal phenotypic concordance in CD

Pair no	Location at diagnosis	Location after 10 years	Behaviour at diagnosis	Behaviour after 10 years	Perianal disease
1	L3 L3	L3 L3	B1 B1	B1 B1	No No
2	L3 L3	L3 L3	B1 B1	B3 B1	Yes Yes
3	L2 L2	L2 L2	B1 B1	B3 B3	Yes No
4	L1 L1	L1+L4 L1+L4	B1 B1	B3 B2	No No
5	L1 L1	L1 L1	B2 B2	B2 B2	No No
6	L3 L1	L3 L1	B2 B2	B2 B2	No No
7	L1 L1	L1 L1	B2 B2	B2 B2	No No
8	L4 L3	L4 L3	B2 B1	B2 B1	No No
9	L1 L1	L1 L1	B1 B1	B1 B1	No No
10	L3+L4 L2	L3+L4 L2	B1 B1	B1 B1	No No
11	L3 L3	L3 L3	B1 B2	B3 B2	No No
12	L3 L1	L3 L1	B1 B2	B1 B2	No No
13	L3 L3	L3 L3	B1 B1	B1 B1	No No
14	L3 L2	L3 L2	B1 B1	B1 B1	No No
15	L1 L3	Followed <10 years	B1 B1	Followed <10 years	No No
16	L1 L1	L3 L3	B2 B2	B2 B2	Yes No
17	L1 L1	L1+L4 L1+L4	B2 B3	B3 B3	No No

Halfvarson et al. IBD. 2007 Sep 7;[Epub ahead of print]

Genetics – pathogenesis

IBD linkage areas



Ahmad T et al. Gastroenterology 2004; 126: 1533-49

Genetics – pathogenesis

CARD15/NOD2

Acknowledgements

We thank D. Tani and M. Monteilh-Zoller for technical assistance. This work was funded in part by a Beth Israel Pathology Foundation grant, a BIDMC Fireman Fellowship award to A.M.S. and NIH grants to A.M.S. and M.J.B. A.L.F. is supported by the German Academic Exchange Service (DAAD). In memory of Q. Zhu.

Correspondence and requests for materials should be addressed to A.M.S. (e-mail: andrewm@u.washington.edu). The GenBank accession number for NUD T9 cDNA and protein sequences is AF026252.

Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease

Jean-Pierre Hugot*†‡, Mathias Chamaillard*†, Habib Zouali*, Suzanne Lesage*, Jean-Pierre Cézard‖, Jacques Belaiche§, Sven Almer‖, Curt Tysk¶, Colm A. O'Morain#, Miquel Gassull, Vibeke Binder**, Yigael Finkel††, Antoine Cortot‡‡, Robert Modigliani§§, Pierre Laurent-Puig†, Corine Gower-Rousseau‡‡, Jeanne Macry‖, Jean-Frédéric Colombel‡‡, Mourad Sahbatou* & Gilles Thomas*†¶¶**

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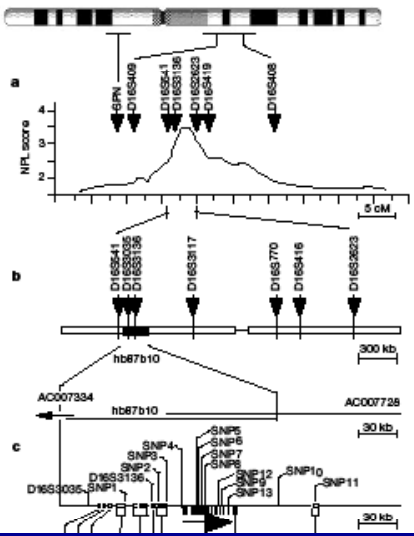
¶ Department of Gastroenterology, Örebro Medical Center Hospital, SE-701 85 Örebro, Sweden
 # Department of Gastroenterology, Adelaide & Meath Hospital, Dublin 24, Ireland
** Department of Gastroenterology, Hospital Universitari Germans Trias i Pujol, Badalona, 08916 Spain*
*** Department of Gastroenterology Herlev Hospital, 2730 Herlev, Denmark*
†† Astrid Lindgren Children's Hospital, SE-161 76 Stockholm, Sweden
‡‡ Registre EPIMAD, Hôpital Calmette, 59037 Lille, France
§§ Department of Gastroenterology, Hopital Saint Louis, 75475 Paris, France
‖‖ INSERM U458, Hôpital Robert Debré, 75019 Paris, France
¶¶ Department of Surgery, Hôpital Saint Antoine, 75012 Paris, France

Crohn's disease[1,2] and ulcerative colitis, the two main types of

adults, with an estimated prevalence of 1 in 1,000 in western countries[1]. Its incidence has increased markedly over the past half century, arguing for the involvement of recent, unidentified, environmental factors[2]. Familial aggregation of the disease suggests that genetic factors may also be involved—an hypothesis that was substantiated in 1996 by the discovery of a susceptibility locus for CD, *IBD1*, on chromosome 16 (ref. 3). Identification of the exact nature of the genetic changes that are implicated in CD susceptibility would provide a specific approach to understanding this common disorder.

Because candidate genes previously localized on chromosome 16 failed to show an association with CD[4,5], we refined the localization of the *IBD1* susceptibility locus by typing 26 microsatellite markers spaced at an average distance of 1 cM in the pericentromeric region



29. Rioux, J.D. *et al.* Genome-wide search in Canadian families with inflammatory bowel disease reveals two novel susceptibility loci. *Am. J. Hum. Genet.* 66, 1863–1870 (2000).
30. Leonard-Jones, J. E. Classification of inflammatory bowel disease. *Scand. J. Gastroenterol.* 170 (suppl.), 2–6 (1989).

Acknowledgements

We acknowledge patients and their families, and thank family recruitment doctors: J. Balanzo, B. Bonaz, Y. Bouhnik, G. Cadiot, S. Cacchiara, B. Causius, J. J. Delchier, B. Duclos, J. L. Dupas, J. P. Galmiche, J. P. Gendre, D. Golfain, C. Géanno, D. Hentsch, A. Lachaux, H. Lautraite, C. Lenaerts, E. Lenbours, V. Levy, R. Lötberg, H. Matthow, P. Marteau, A. Morali, F. Pallone, S. Pena, A. Rotenberg, I. Rousseau, J. Schmitz, F. Shanahan, I. Sobhani, H. Svenson, A. Van Gossum, M. Van Winckel and M. Veyrac. For assistance we are grateful to J. C. Beaudoin, F. Chaveyre, C. Giudicelli, T. Hung Bui, M. Legrand, A. Marcadet, A. Martins. C. de Toma, E. Tubacher. We thank H. Cann for critically reading the manuscript. This project received support from European Community, MENRT, INSERM, Direction Générale de la Santé, Association François Aupetit, IBM AD and the Swedish Society of Medicine.

Correspondence and requests for materials should be addressed to G.T. (e-mail: thomas@cephb.fr).

A frameshift mutation in *NOD2* associated with susceptibility to Crohn's disease

Yasunori Ogura*†, Denise K. Bonen††, Naohiro Inohara*, Dan L. Nicolae§, Felicia F. Chen*, Richard Ramos‡, Heidi Britton‡, Thomas Moran‡, Reda Karaliuskas‡, Richard H. Duerr‖, Jean-Paul Achkar¶, Steven R. Brant#, Theodore M. Bayless#, Barbara S. Kirschner, Stephen B. Hanauer‡, Gabriel Nuñez*†† & Judy H. Cho‡††**

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¶ Department of Gastroenterology, The Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA
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† These authors contributed equally to this work
†† These authors share senior authorship

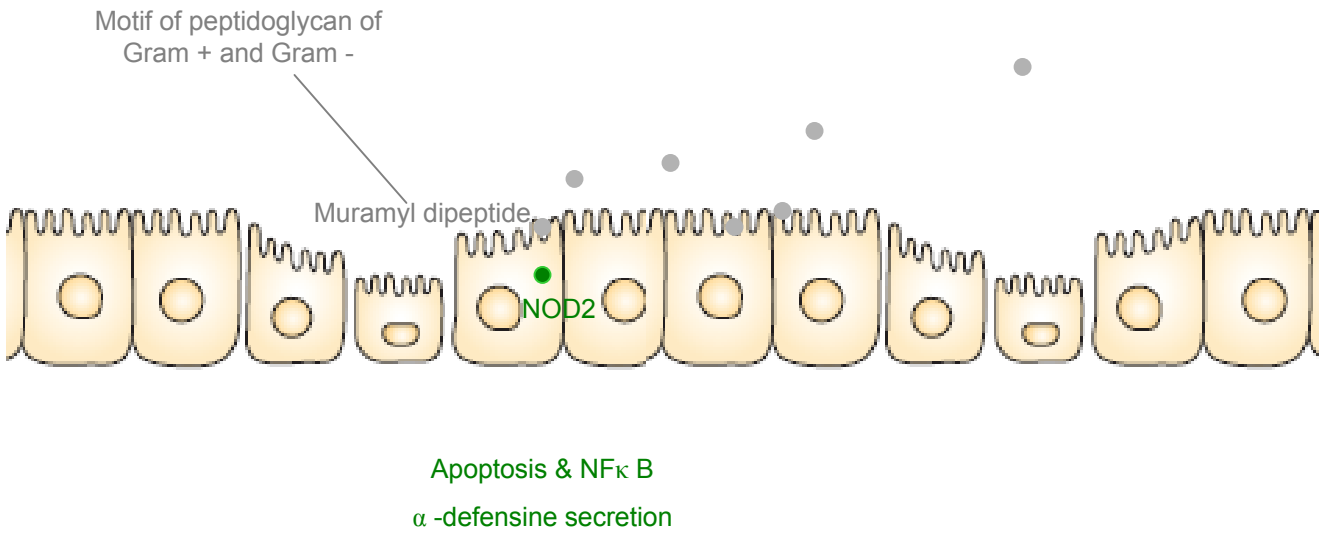
Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract, which is thought to result from the effect of

Figure 4: Allelic frequency of *CARD15* frameshift mutation in Crohn's disease populations in Europe
Variant allelic frequencies of the *CARD15* frameshift Leu1007fsinC in people with Crohn's disease are substantially lower in northern European[36–41] than in populations with Crohn's disease in central or southern Europe.[29,44–49]

Gaya DR et al. Lancet 2006: 1271-1284

Genetics – pathogenesis

CARD15/NOD2 – intracellular bacterial recognition



Genetics – pathogenesis
Consequences of CARD15/NOD2

- Altered tolerance to chronic bacterial stimulation

  Chronic activation of NOD2 ➡ hyporesponsiveness to MDP

  Impaired tolerizing effects of commensal bacteria (TLRs) in NOD2 mutated

Hedl M et al. PNAS 2007; 19440-5
Watanabe T et al. J Clin Invest 2008

Genetics – pathogenesis
Consequences of CARD15/NOD2

- Altered tolerance to chronic bacterial stimulation
- Impaired clearance of oral pathogenes

  Oral inoculation *Listeria monocytogenes* in Nod2 mice -/- ➡ increased spleen & liver

  Capacity to control *Salmonella typhimurium* ↘

Kobayashi K S et al. Science 2005; 731-34
Hisamatsu T el al. Gastroenterology 2003; 993-1000

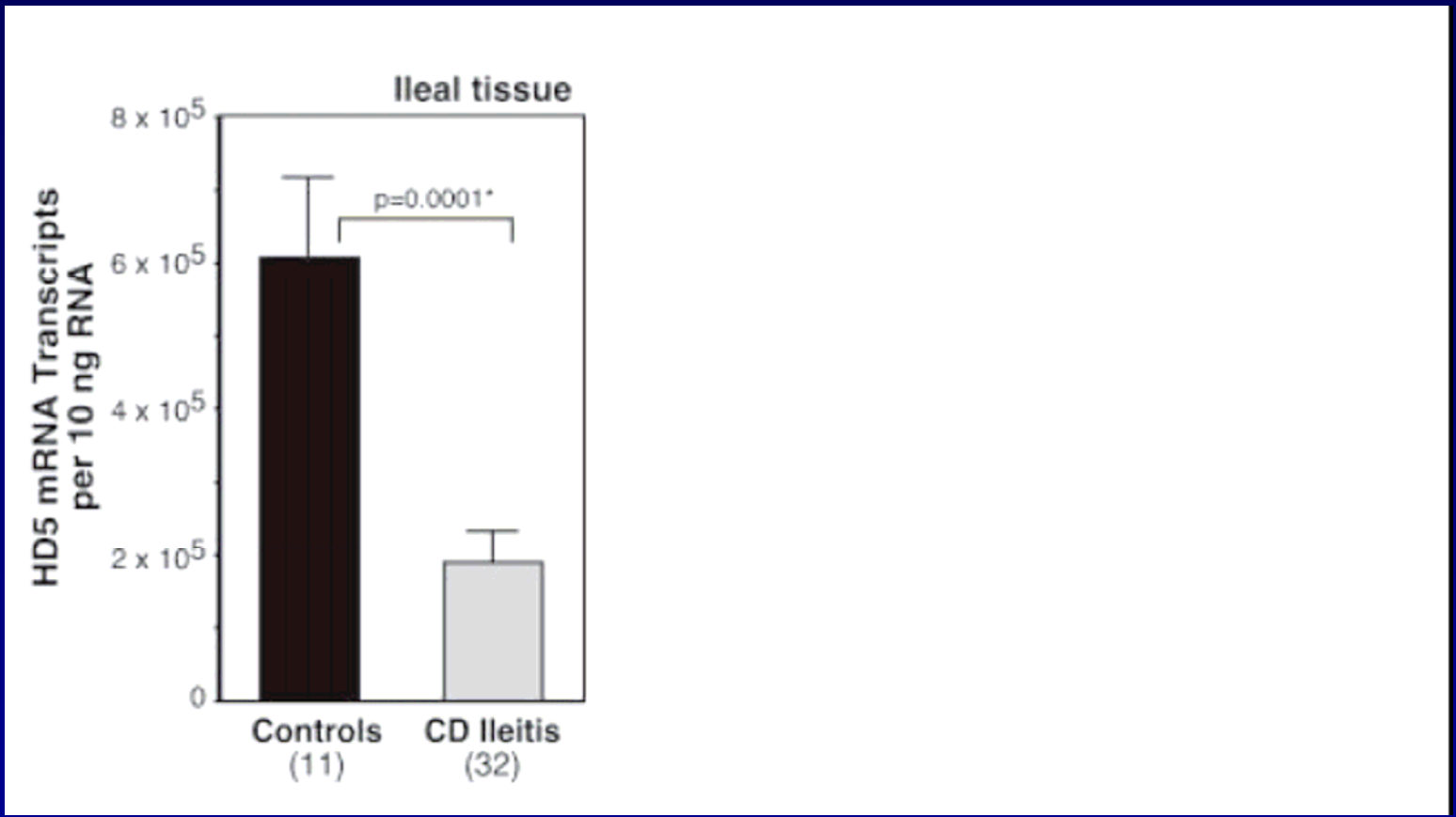
Genetics – pathogenesis
Consequences of CARD15/NOD2

- Altered tolerance to chronic bacterial stimulation
- Impaired clearance of oral pathogenes
- Dysbiosis (E. Coli ↗) due to defensin deficiency

Cho J. Nature Review Immunol 2008

Genetics – pathogenesis

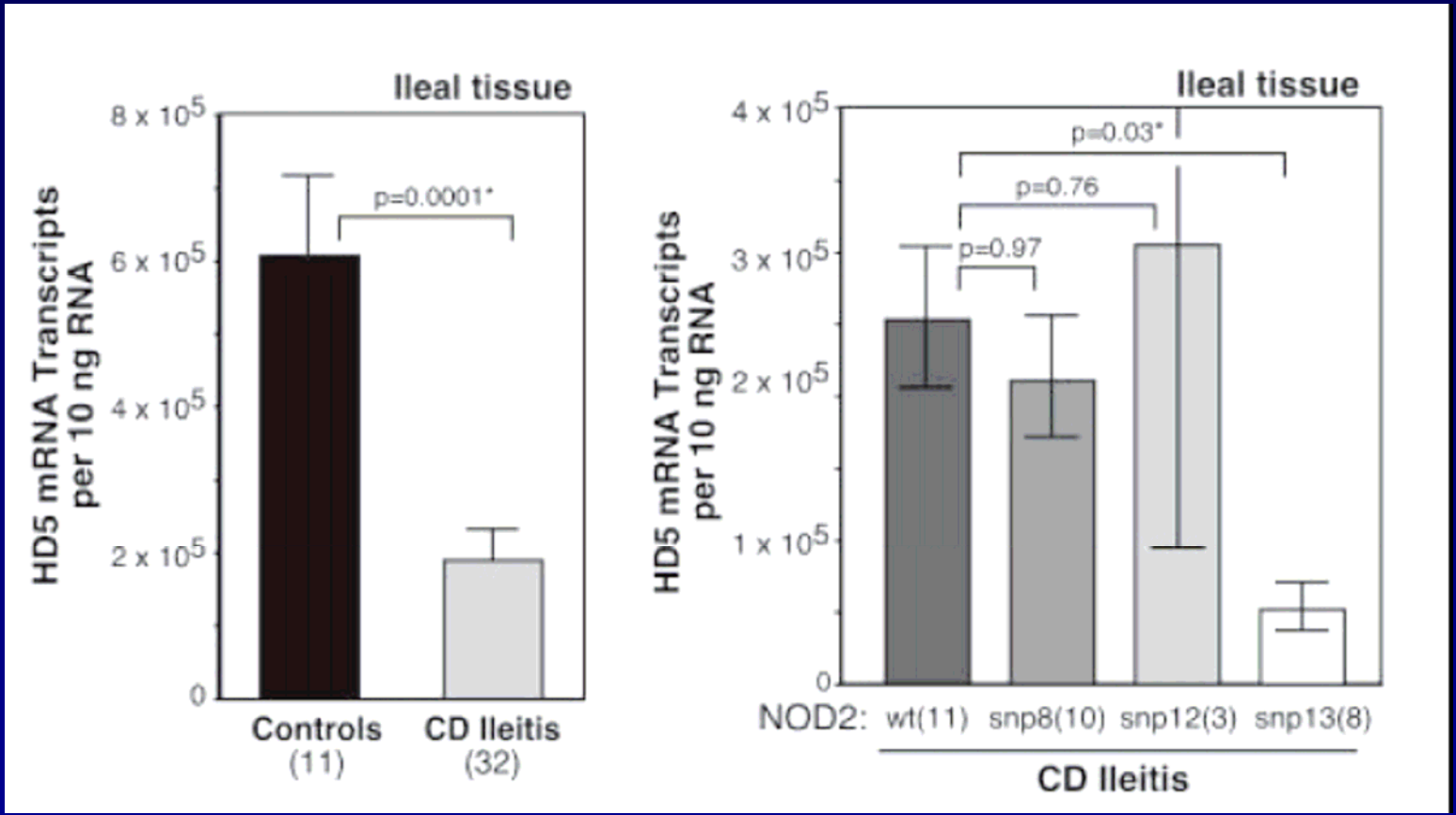
Consequences of CARD15/NOD2



Wehkamp J et al. Proc Natl Acad Sci U S A. 2005

Genetics – pathogenesis

Consequences of CARD15/NOD2



Wehkamp J et al. Proc Natl Acad Sci U S A. 2005

Genetics – pathogenesis

Consequences of CARD15/NOD2

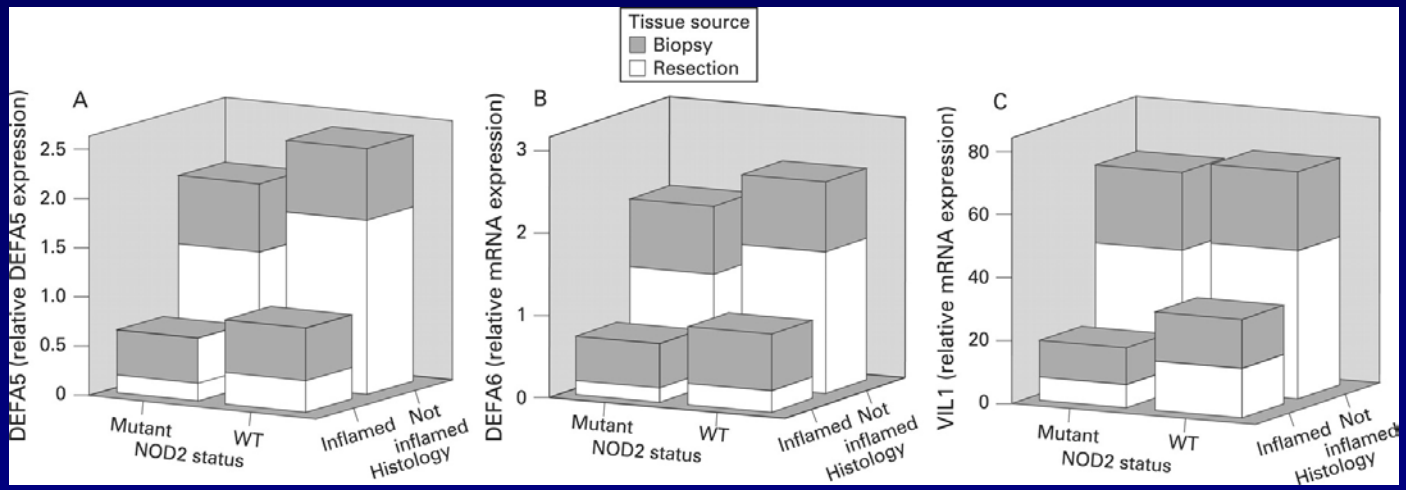


Figure 2 Three-dimensional plots showing the effects of inflammation (defined according to histology) and NOD2 mutation status on mRNA expressions for the genes (A) {alpha}-defensin 5 (DEFA5), (B) {alpha}-defensin 6 (DEFA6), and (C) vilin (VIL1).

Simms, L A et al. Gut 2008;57:903-910

Pathogenesis of IBD

Overly aggressive immune response to
commensal enteric bacteria
in genetically susceptible individuals,
where environmental factors precipitate
the onset/reactivation of the disease

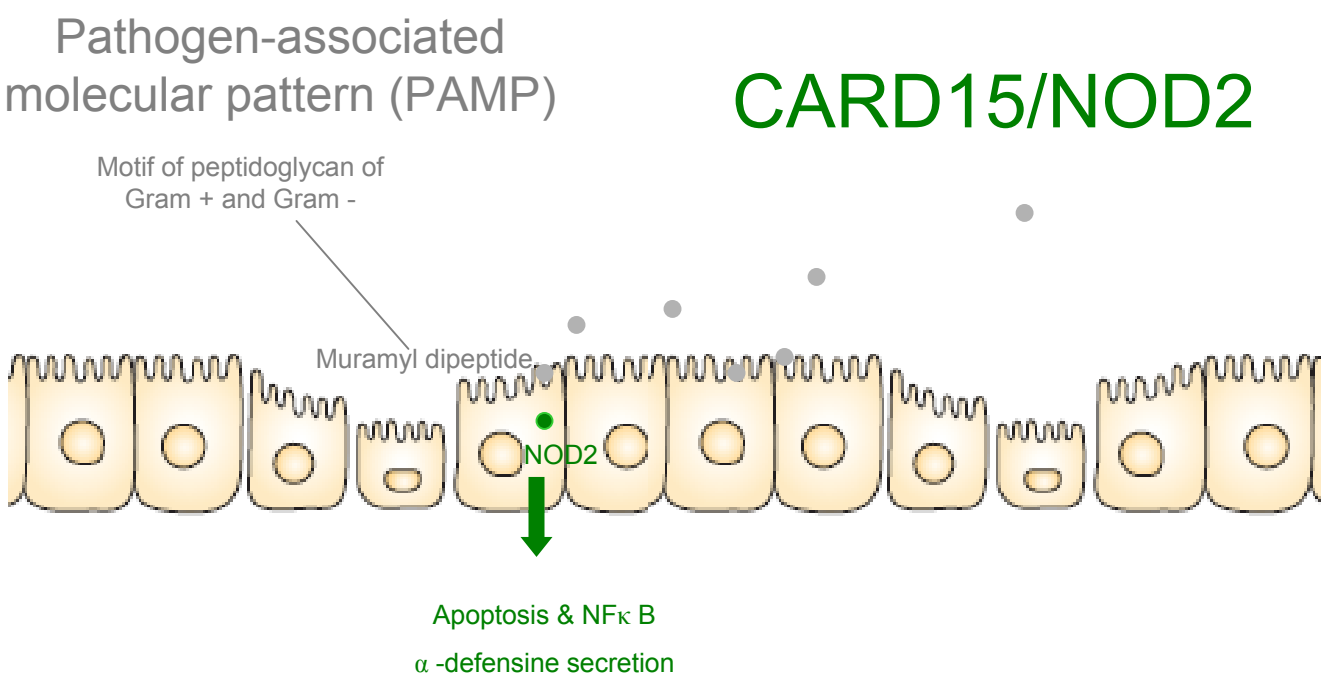
Sartor R B. Nat Clin Pract Gastroenterol Hepatol. 2006; 3: 390-407

Pathogenesis of IBD

Genetics → Microbiota

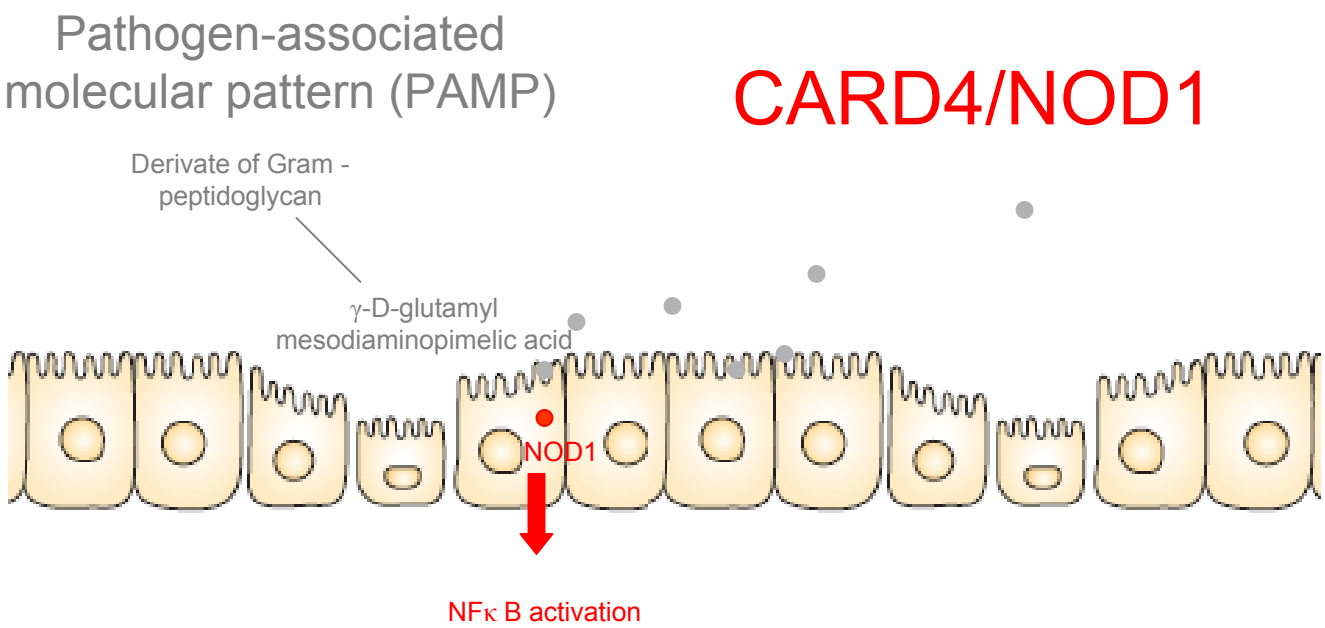
Intracellular bacterial recognition

Pattern Recognition Receptor (PRR)



Intracellular bacterial recognition

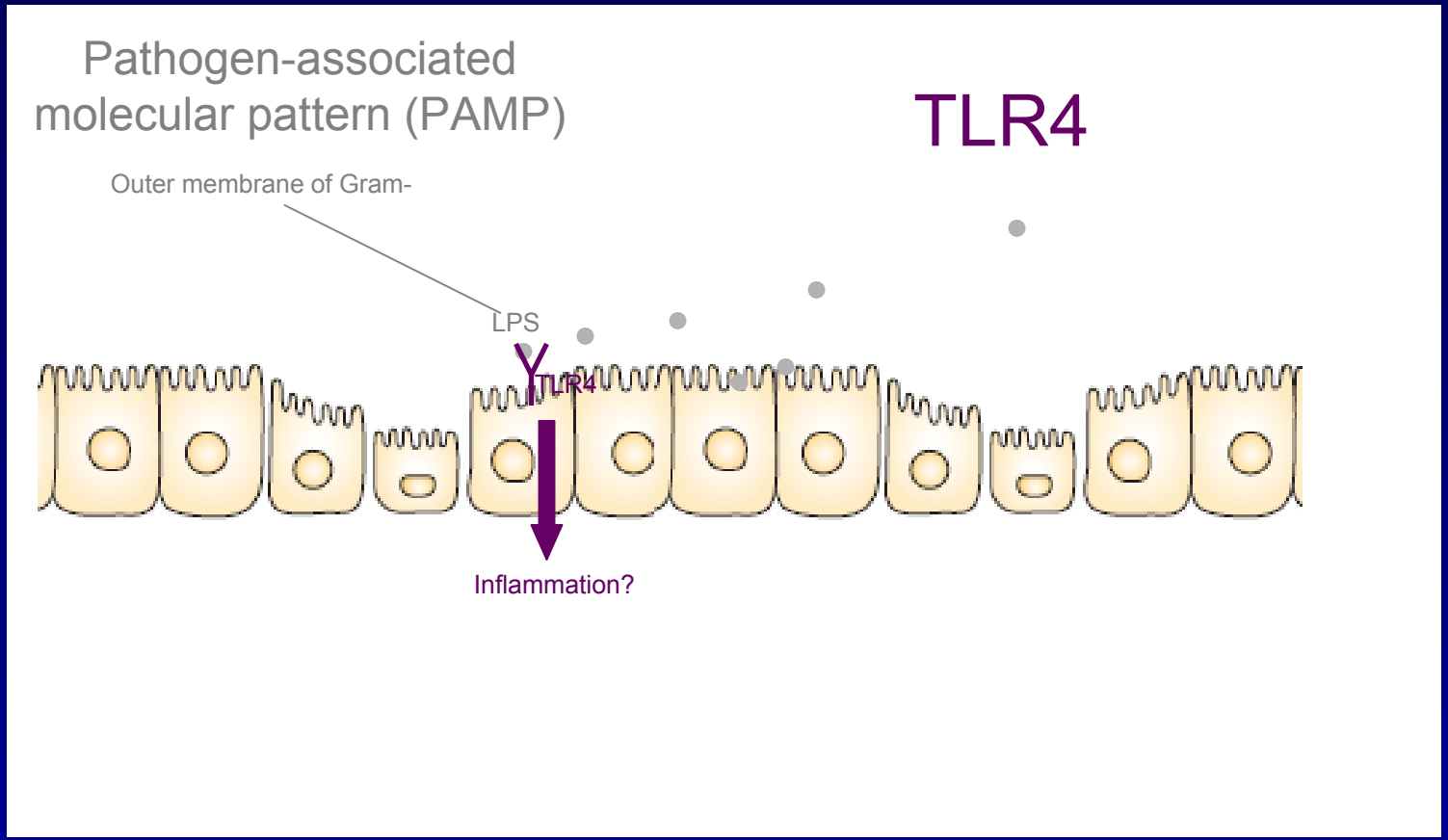
Pattern Recognition Receptor (PRR)



McGovern D et al. Hum Mol Genet 2005;14: 1245-50

Cell surface bacterial recognition

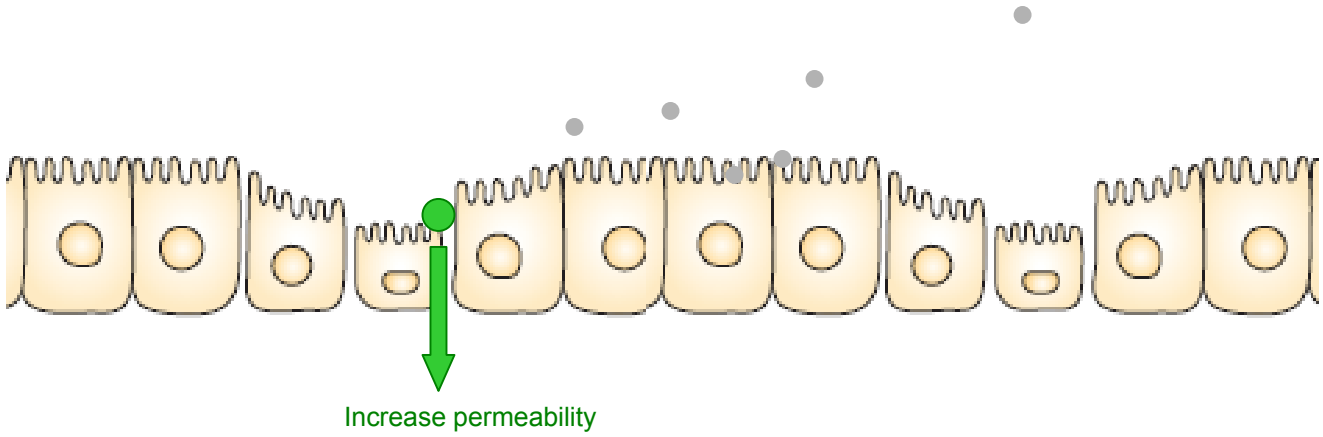
Pattern Recognition Receptor (PRR)



Franchimont D et al. Gut 2004; 53: 987-92

Epithelial integrity

Drosophila discs large homologue 5 gene (DLG5)



Stoll M et al, Nat Gen 2004; 36: 476-80

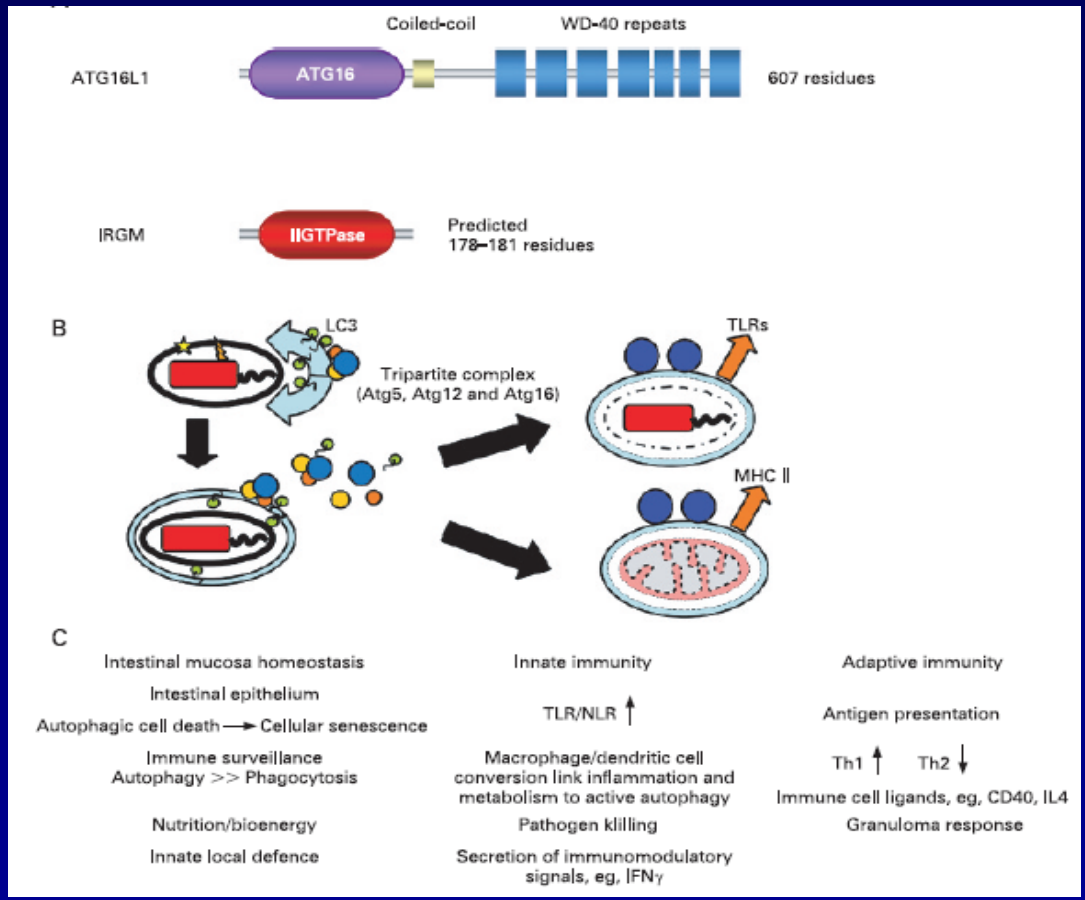
Gaya DR et al. Lancet 2006; 367: 1271-84

Genetics ➞ Microbiota

GWA > 30 Crohn's disease susceptibility genes and loci

Genetics ➞ Microbiota

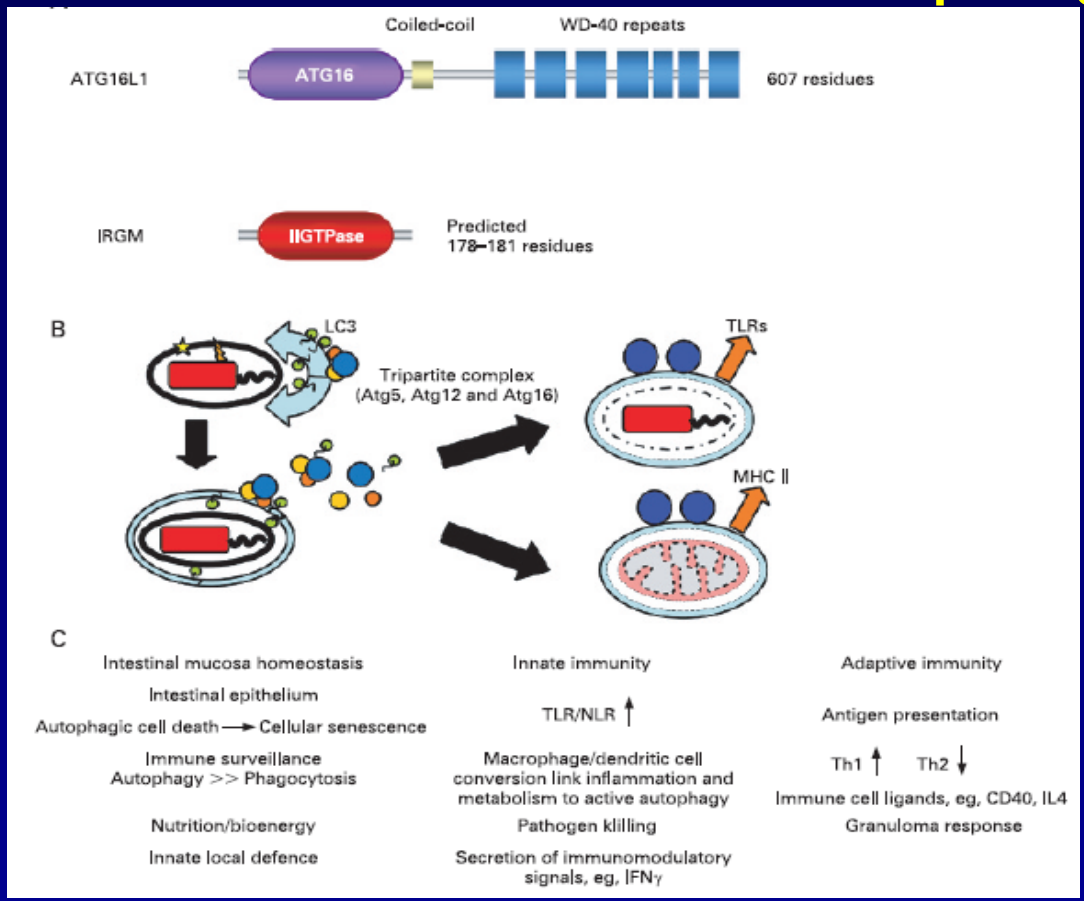
ATG16L1 Autophagy gene



Xavier RJ et al. Gut 2008;717-20

Genetics ➞ Microbiota

ATG16L1 Autophagy gene



IRGM

Immunity-Related

GTPase family, M

Xavier RJ et al. Gut 2008;717-20

Wellcome trust case control consortium. Nature 2007

Pathogenesis of IBD

Enteric bacterial flora

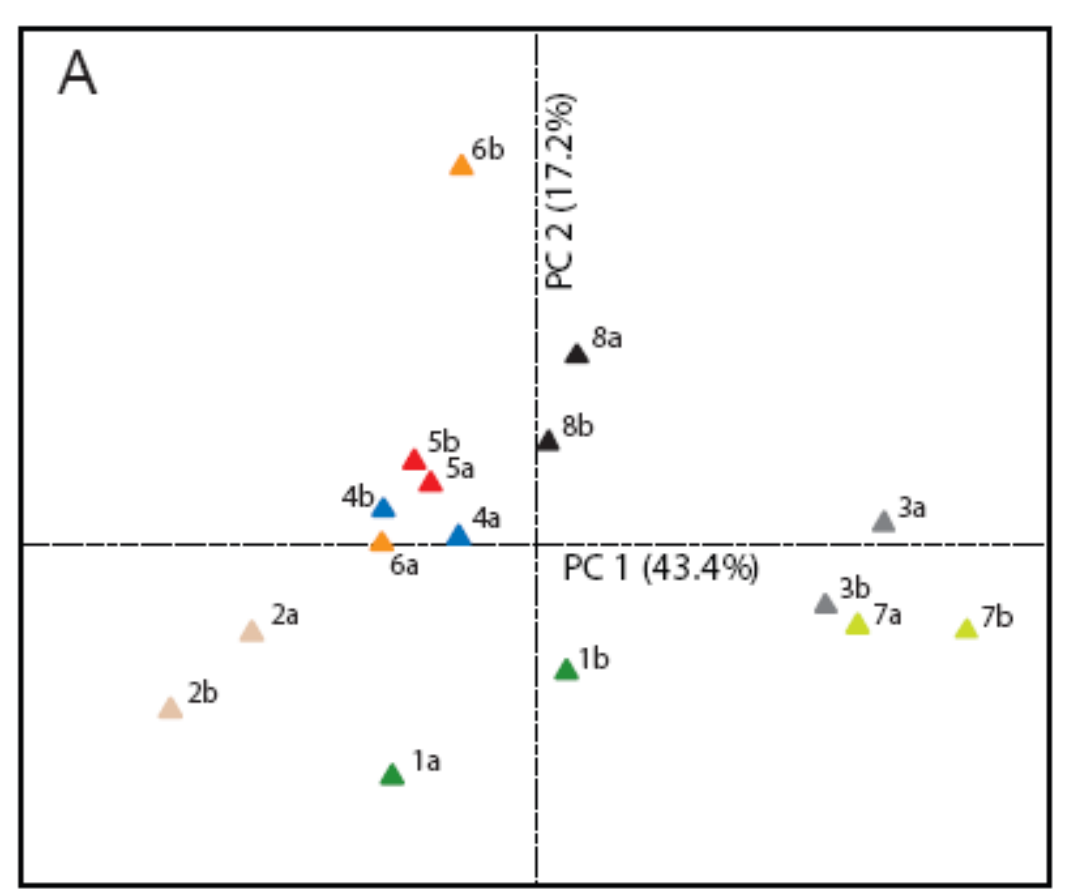
Faecal flora in CD

- Bacteroides vulgatus ↗
- Lactobacilli ↘
- Bifidobacteria ↘
- Enterobacteria ↗ (E. Coli, Klebsiella…)
- Unusual phylogenetic groups ↗

Seksik P et al. APT 2006; 24 (Suppl. 3): 11-18

Pathogenesis of IBD

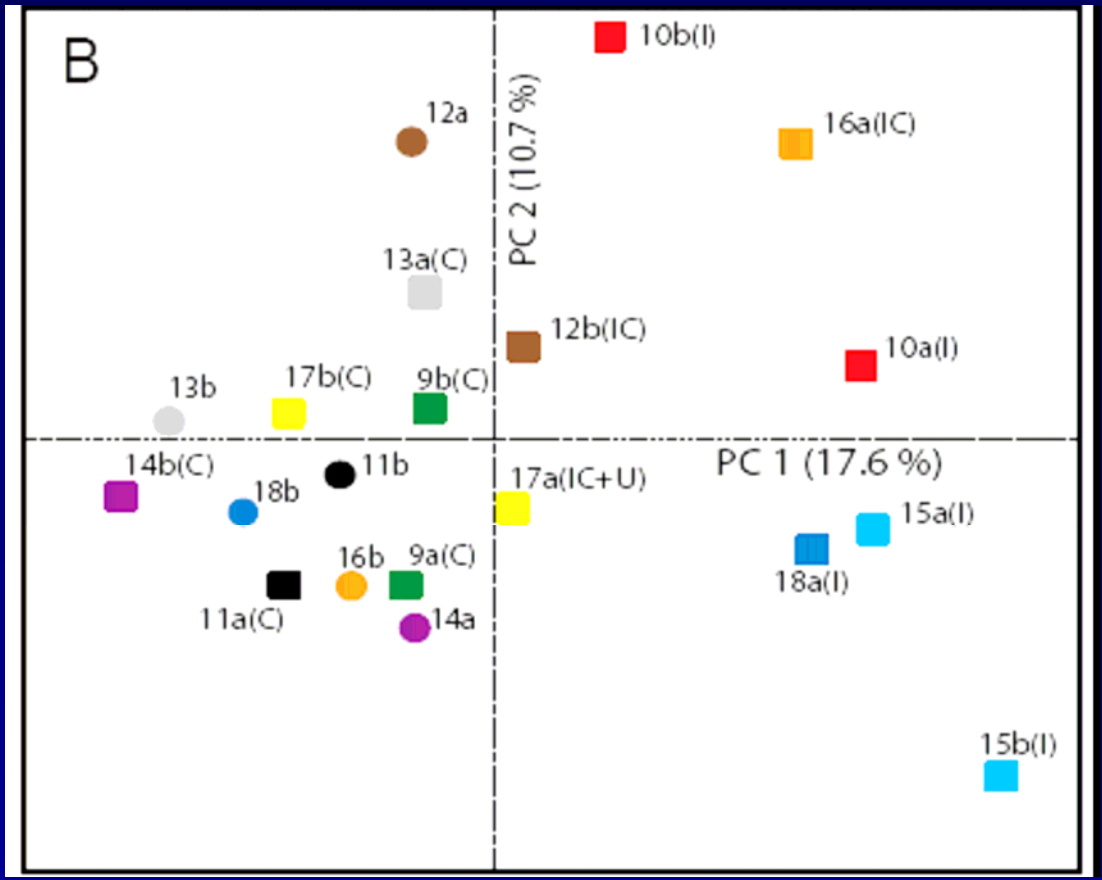
Enteric bacterial flora



Dicksved J et al. ISME 2008

Pathogenesis of IBD

Enteric bacterial flora

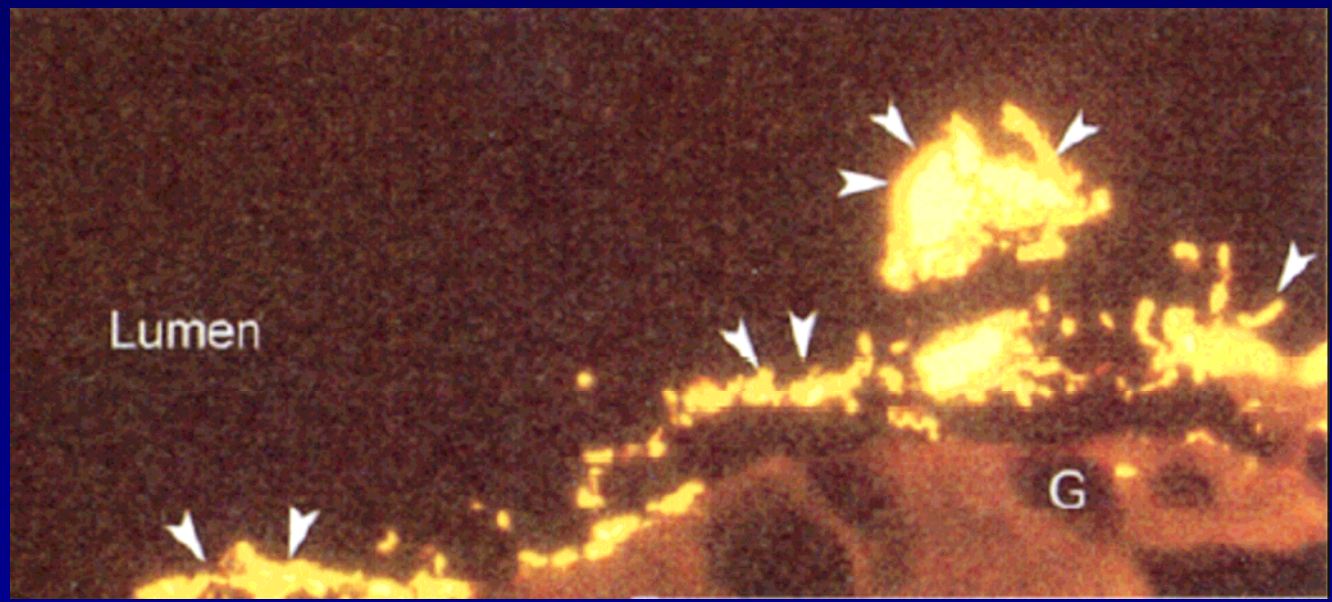


Dicksved J et al. ISME 2008

Pathogenesis of IBD

Enteric bacterial flora

Increased mucosal adherent enteric bacteria in IBD, CD>UC



Swidsinski A et al. Gastroenterology 2002; 122: 44-54

Pathogenesis of IBD

Enteric bacterial flora

Possible mechanisms

- Activate innate immune system (MDP, LPS…)
- Activate adaptive immune system
  - Antigens stimulating clonal expansion of T-cells
  - Specific antibodies – diagnostic subsets CD

Braat H et al. Ann. N.Y. Acad. Sci. 2006; 1072: 135-54
Sartor B. Nature clinical practice 2006
Targan SR et al Gastroenterology 2005; 128: 2020-28

Pathogenesis of IBD

Overly aggressive immune response to commensal enteric bacteria in genetically susceptible individuals, where environmental factors precipitate the onset/reactivation of the disease

Sartor R B. Nat Clin Pract Gastroenterol Hepatol. 2006; 3: 390-407

Pathogenesis of IBD
Immune response

Activated innate immune response

(Mucos, Pattern Recognition Receptors (PRR), FAE
-transportation, defensin deficiency, increased number activated macrophages, neutrophils and dendritic cells)

Braat H et al. Ann. N.Y. Acad. Sci. 2006; 1072: 135-54
Neuman M G. Translational Research 2007; 129: 173-86

Pathogenesis of IBD

Innate immune response

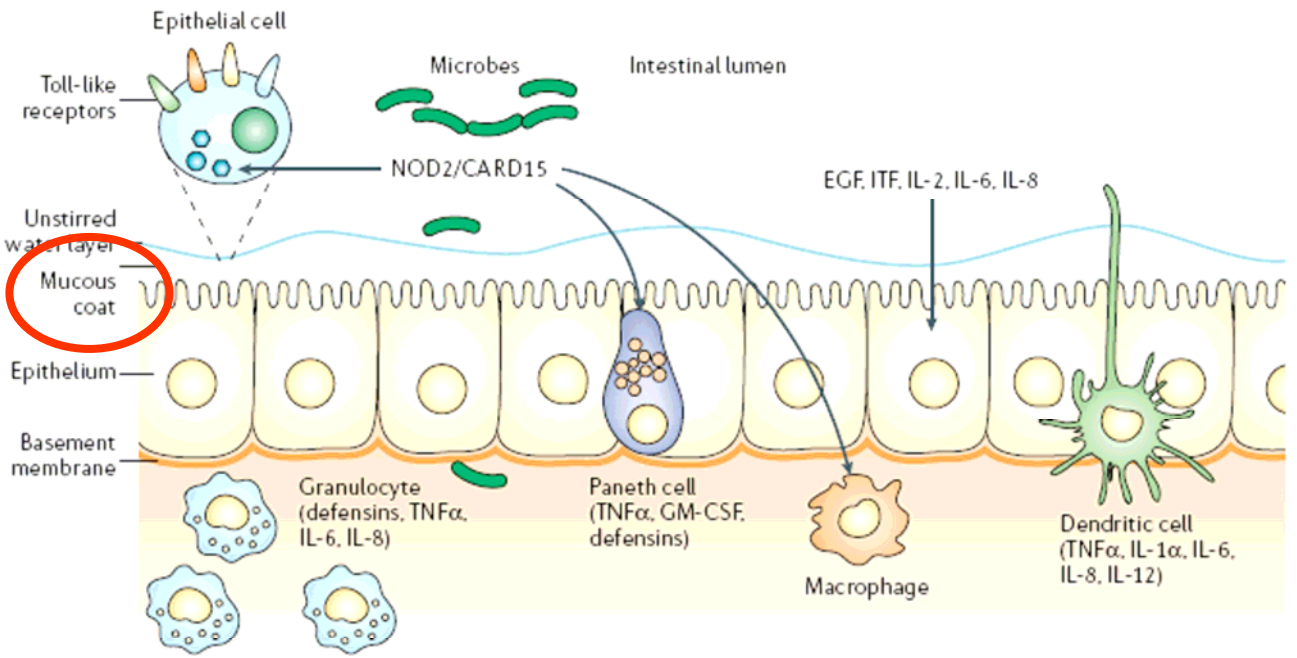
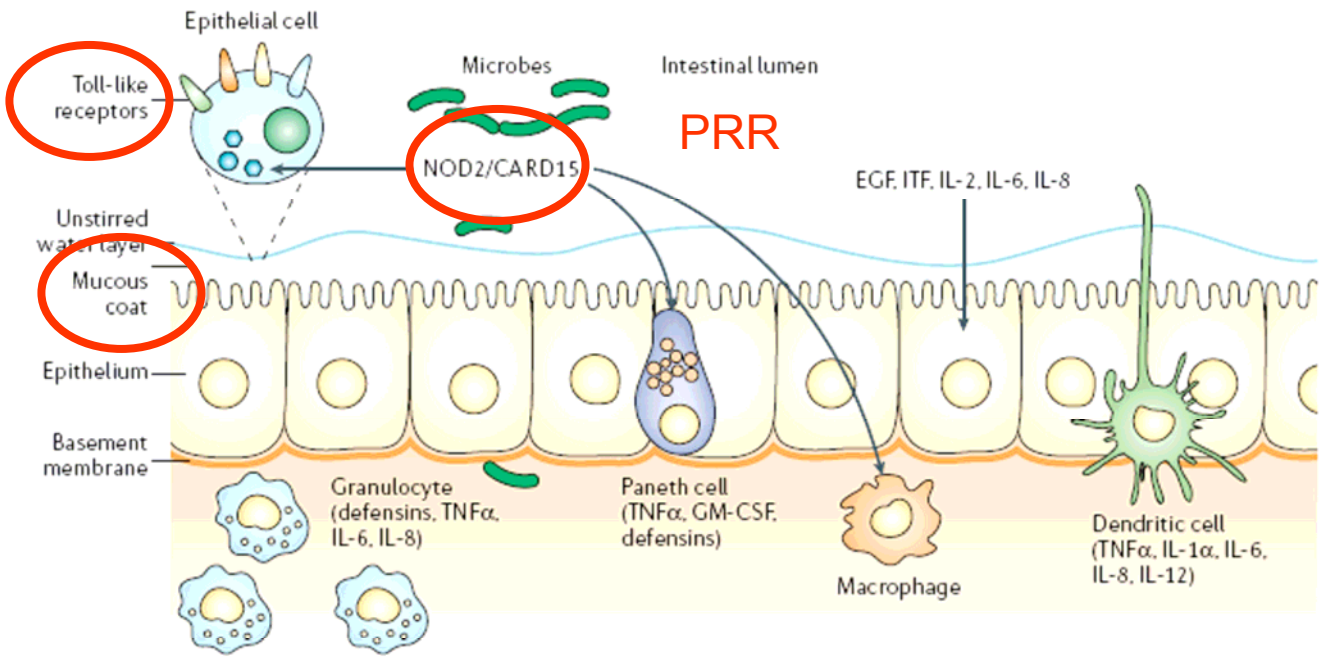


Figure 2 | **The intestinal innate immune barrier.** The innate immune system is currently seen as the likely initiator of the cascade of events which culminates in Crohn's disease (CD). This shift in focus is in part due to the identification of *NOD2* as a gene associated with CD. The precise understanding of the aberrant innate immune response is uncertain. The components of the intestinal innate immune barrier are multiple and include the intestinal bacteria themselves, the biofilms, circulating elements such as complement, and numerous cell types including the epithelial cell, neutrophils, macrophages and Paneth cells among others. The cellular products are listed by the cells of origin. These elements are potential therapeutic targets for inflammatory bowel disease. EGF, epidermal growth factor; IL, interleukin; ITF, intestinal trefoil factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; TNF, tumour-necrosis factor.

Korzenik JR and Podolsky D. Nature Reviews Drug Discovery 2006

Pathogenesis of IBD

Innate immune response



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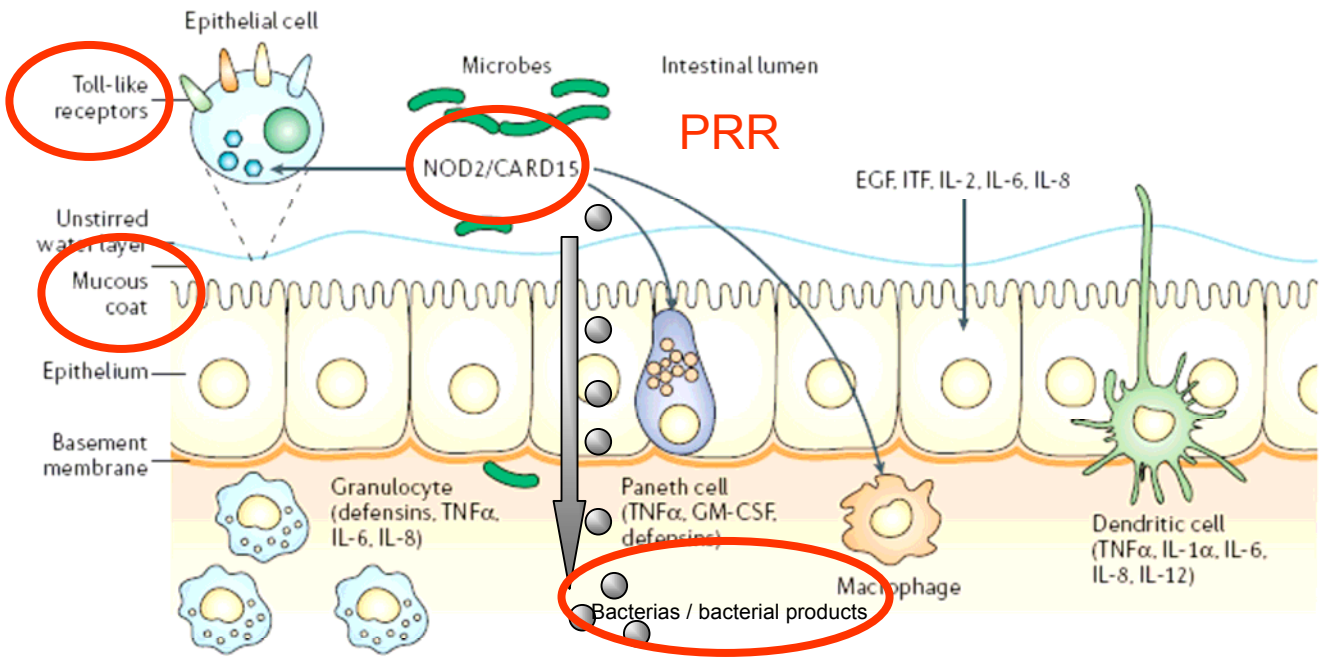
Innate immune response



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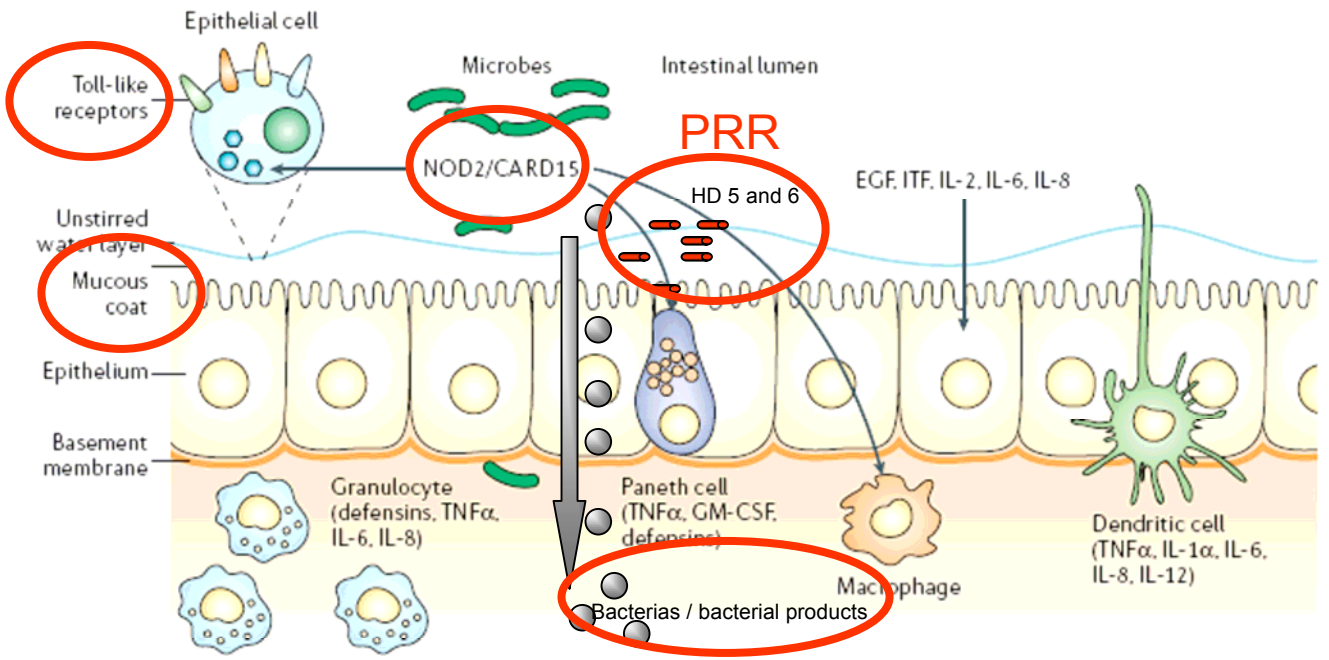

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Pathogenesis of IBD

Innate immune response

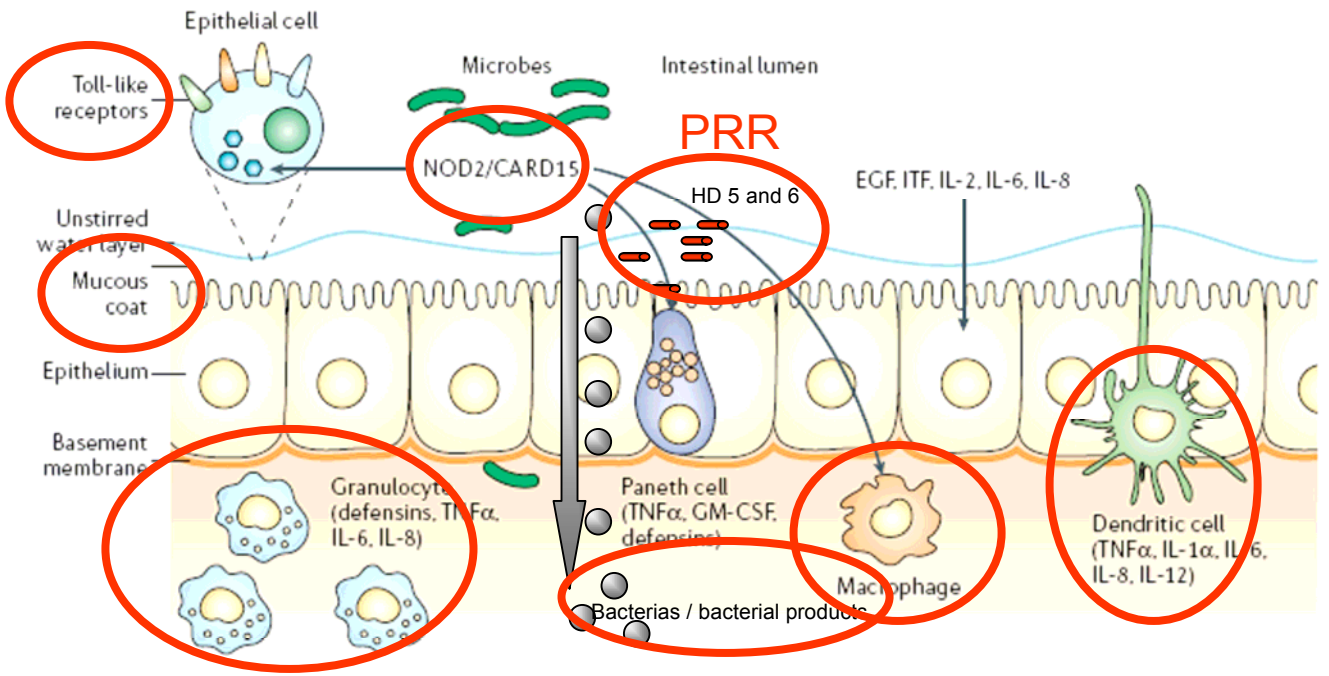


Figure 2 | **The intestinal innate immune barrier.** The innate immune system is currently seen as the likely initiator of the cascade of events which culminates in Crohn's disease (CD). This shift in focus is in part due to the identification of *NOD2* as a gene associated with CD. The precise understanding of the aberrant innate immune response is uncertain. The components of the intestinal innate immune barrier are multiple and include the intestinal bacteria themselves, the biofilms, circulating elements such as complement, and numerous cell types including the epithelial cell, neutrophils, macrophages and Paneth cells among others. The cellular products are listed by the cells of origin. These elements are potential therapeutic targets for inflammatory bowel disease. EGF, epidermal growth factor; IL, interleukin; ITF, intestinal trefoil factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; TNF, tumour-necrosis factor.

Korzenik JR and Podolsky D. Nature Reviews Drug Discovery 2006

Pathogenesis of IBD

Immune response

Activated innate immune response

(Mucos, Pattern Recognition Receptors (PRR), FAE
-transportation, defensine deficiency, increased number activated macrophages, neutrophils and dendritic cells)

Activated adaptive immune response

CD: T_H1 response (+ T_H17 response)
UC: Atypic T_H2 response (?)

GWA ➡ IL-23R

Braat H et al. Ann. N.Y. Acad. Sci. 2006; 1072: 135-54
Neuman M G. Translational Research 2007; 129: 173-86

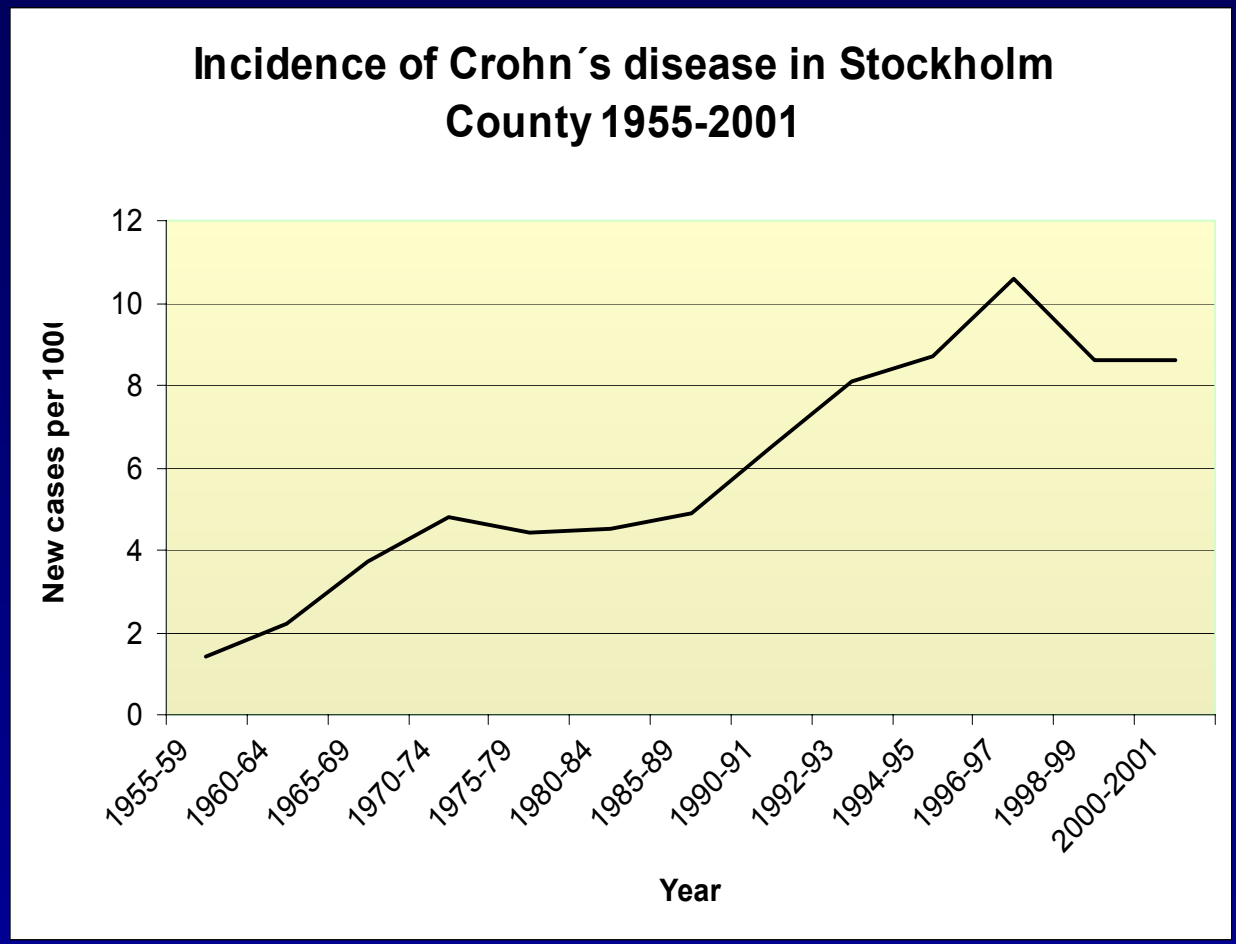
Pathogenesis of IBD

Overly aggressive immune response to commensal enteric bacteria in genetically susceptible individuals, where environmental factors precipitate the onset/reactivation of the disease

Sartor R B. Nat Clin Pract Gastroenterol Hepatol. 2006; 3: 390-407

Pathogenesis of IBD

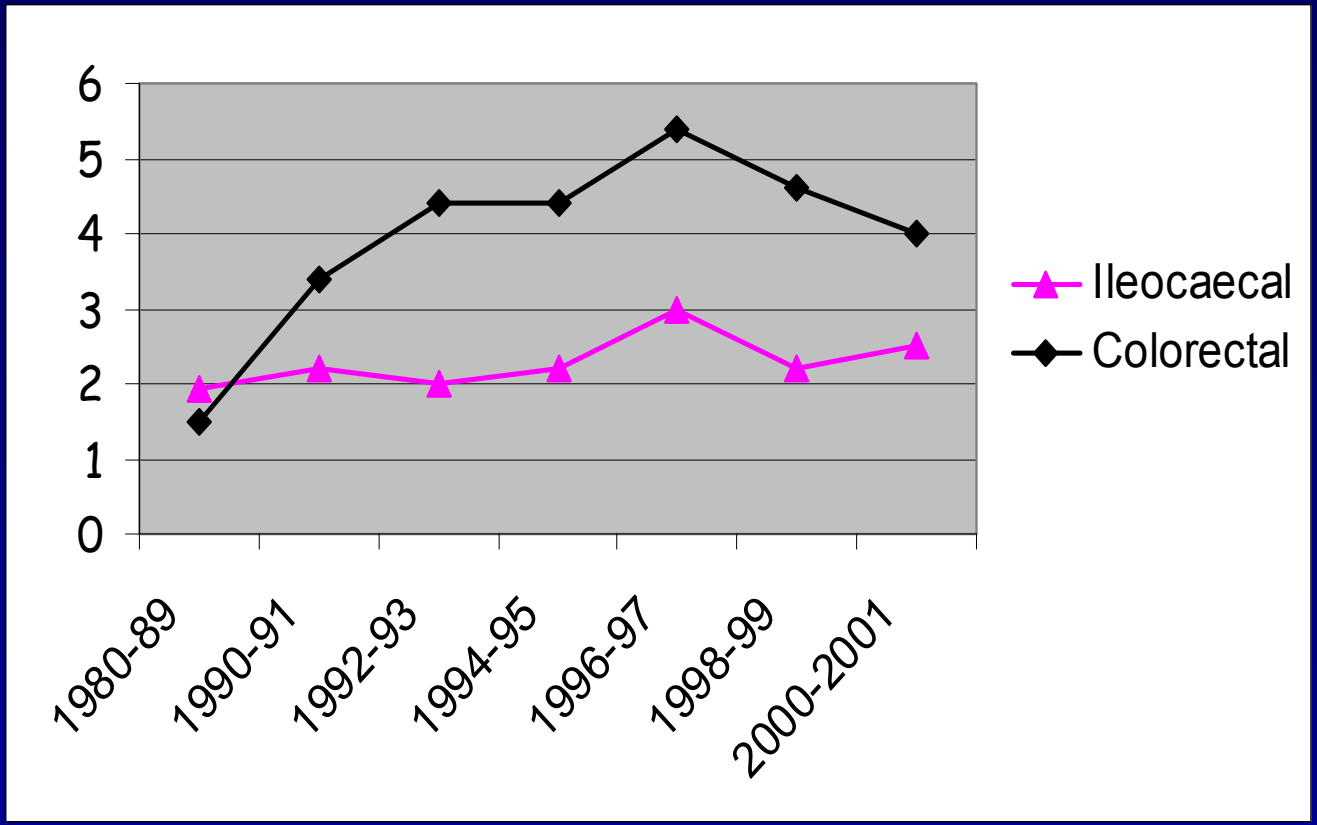
Environmental factors



Lapidus A. World Journal of Gastroenterology 2006; 1: 75-81

Pathogenesis of IBD

Environmental factors



Lapidus A. World Journal of Gastroenterology 2006; 1: 75-81

Pathogenesis of IBD

Environmental factors

Smoking

Pathogenesis of IBD

Environmental factors

Infections and NSAIDs

Break mucosal barrier & activate innate immune response

→ Uptake of commensal bacterial antigens + adjuvants ↗

→ Prolonged inflammation in genetic susceptible host (IL10 knockout mice)

Berg D J et al. Gastroenterology 2002; 123: 1527-42

Pathogenesis of IBD

Environmental factors

Table 1. Gastrointestinal Inflammation in NSAID-Treated Mice

Genetic background	*n*	Treatment	% Of mice with colitis	Colitis disease score per group (0–4)[a]
129/SvEv/wild type	5	Control	0	0
129/SvEv/wild type	18	Piroxicam	25	0.37 ± 0.74[b]
129/SvEv/IL-10−/−	14	Control	0	0
129/SvEv/IL-10−/−	21	Piroxicam	100	3.82 ± 0.41[b]

NOTE. Gastrointestinal inflammation in NSAID-treated wild-type and IL-10$^{-/-}$ mice. Four-week-old mice were fed either control diet or diet containing piroxicam, 200 ppm, for 2 weeks. The gastrointestinal tract was subsequently evaluated histologically. *n* indicates the number of mice per group.

[a]Colitis was graded on a scale of 0–4, with 0 = no colitis and 4 = severe colitis (see Materials and Methods section for further Details). Data are reported as mean ± SD per group.

[b]$P < 0.001$, piroxicam-treated IL-10$^{-/-}$ vs. control mice.

Berg D J et al. Gastroenterology 2002; 123: 1527-42

Pathogenesis of IBD
Environmental factors

Epidemiological data (General practice research database)

Antibiotic prescription OR 1.53 (95% CI 1.12-2.07)

In patients with no symptoms or prescribed gastrointestinal drugs, 2-5 years prior to CD diagnosis

Card T et al. Gut; 2004; 53: 246-50

Pathogenesis of IBD

Environmental factors

Stress

Increased permeability in rats

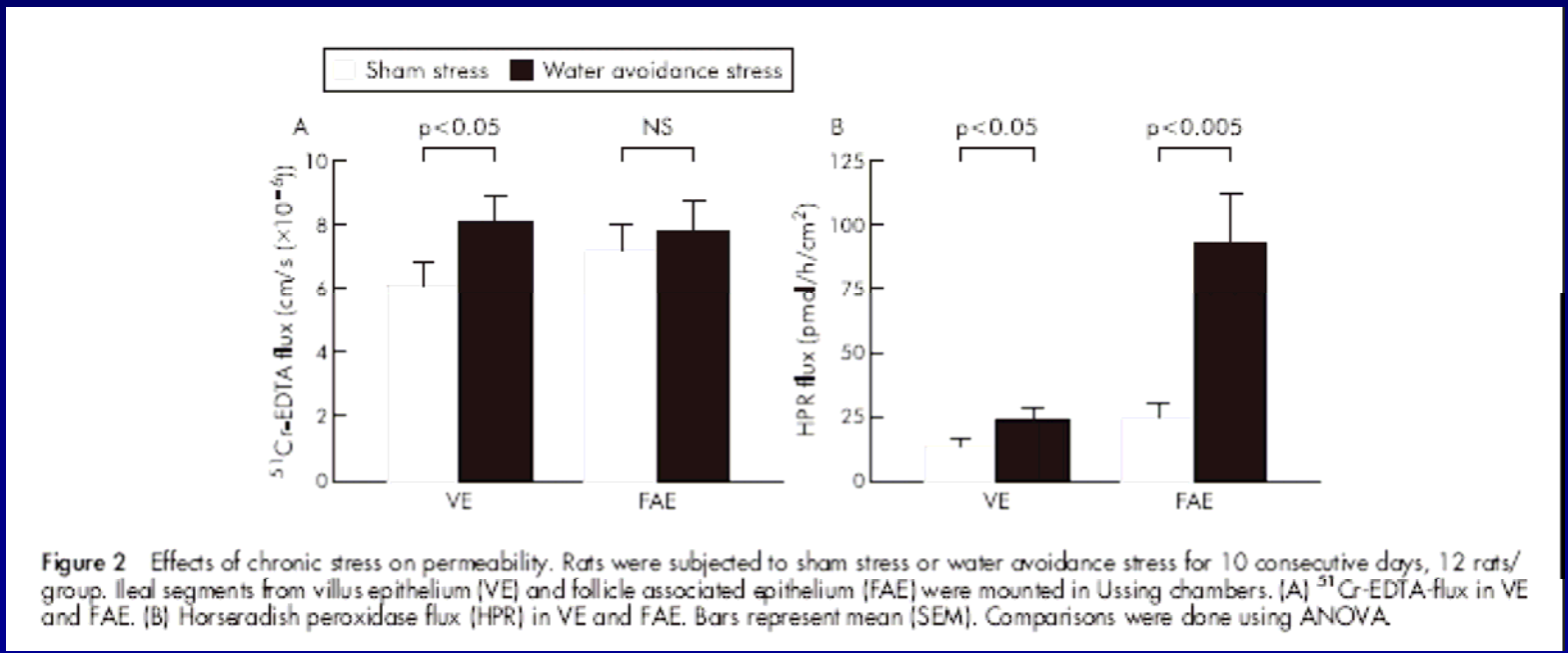


Figure 2 Effects of chronic stress on permeability. Rats were subjected to sham stress or water avoidance stress for 10 consecutive days, 12 rats/group. Ileal segments from villus epithelium (VE) and follicle associated epithelium (FAE) were mounted in Ussing chambers. (A) ^{51}Cr-EDTA-flux in VE and FAE. (B) Horseradish peroxidase flux (HPR) in VE and FAE. Bars represent mean (SEM). Comparisons were done using ANOVA.

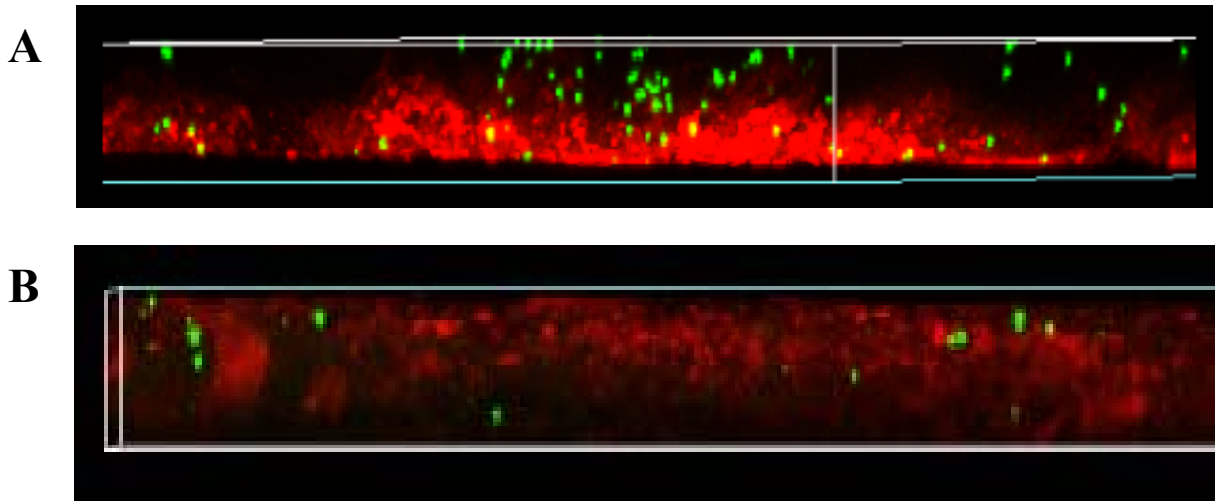
Keita Å et al. Gut 2004; 53: 494-500

Pathogenesis of IBD

Environmental factors

Stress

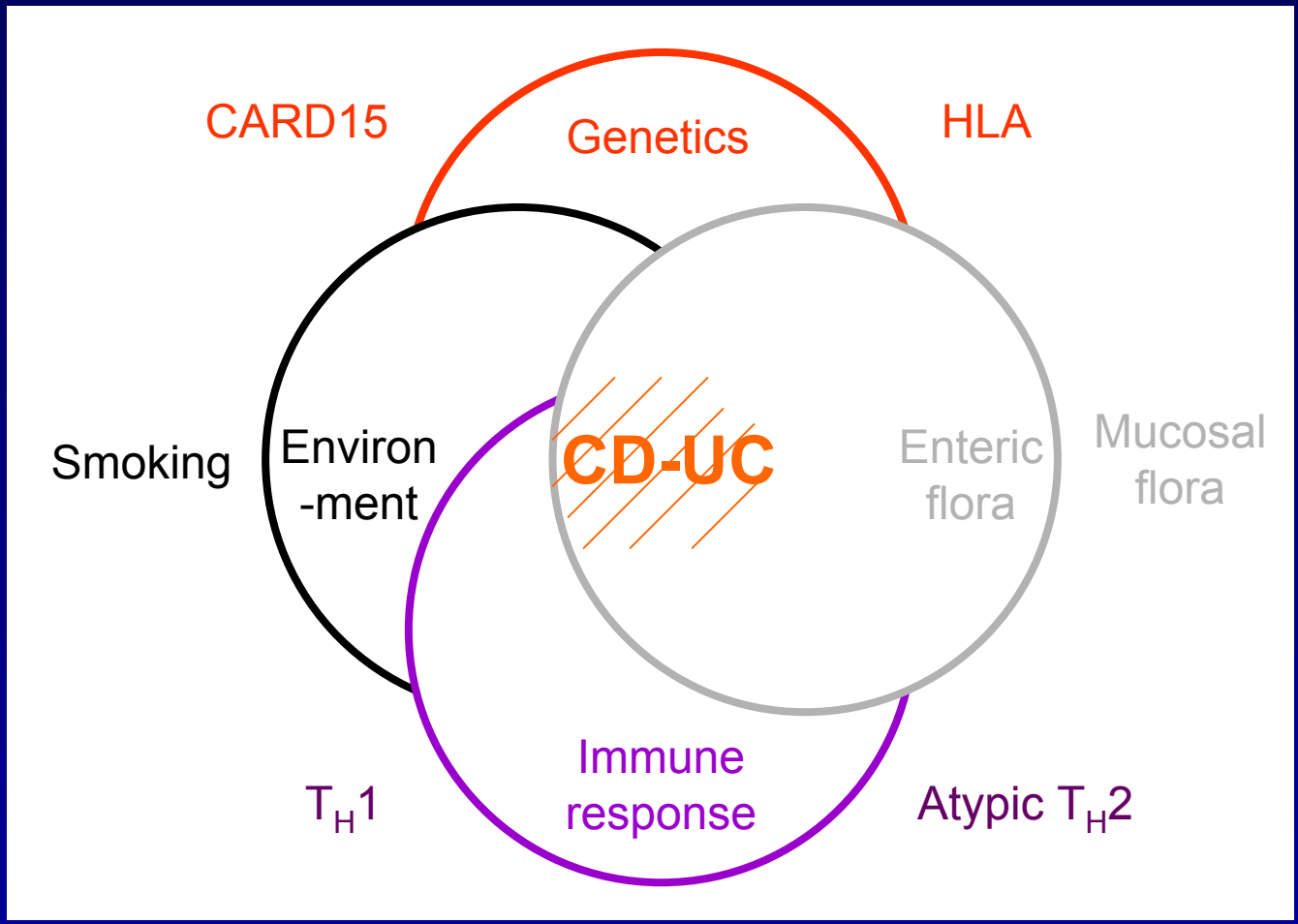
Increased permeability and bacterial uptake (FAE) in rats

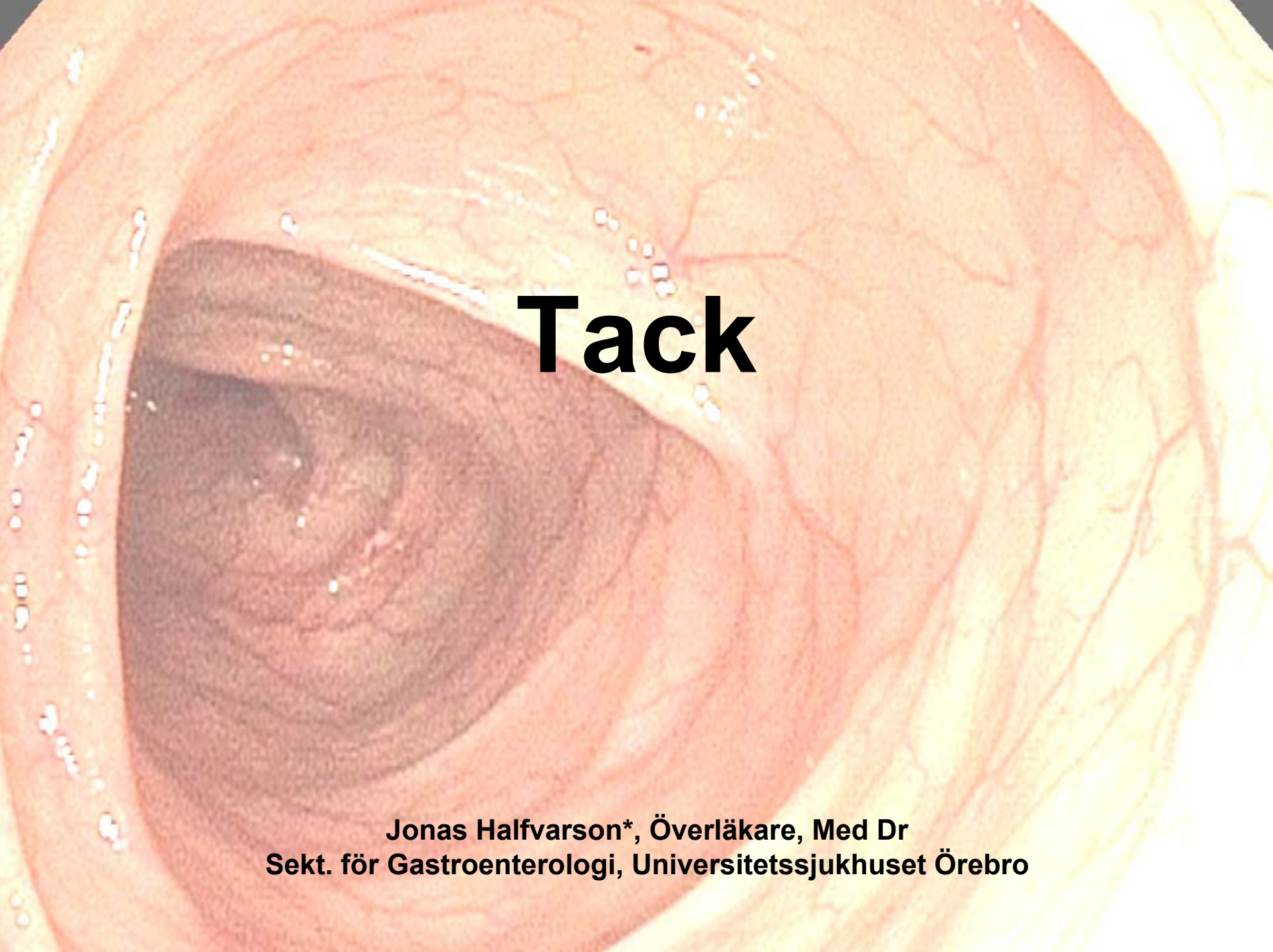


Bacterial passage in follicle-associated epithelium (FAE) studied in confocal microscopy. Rats were submitted to water avoidance stress for ten days, 1 h/day. Segments of FAE were mounted in Ussing chambers and passage of chemically-killed E. coli K-12 was studied over time. (A) After 45 min bacteria were seen close to the epithelial surface, (B) After 90 min bacteria were penetrating into the epithelium, Red=Alexa Flour ® 594-conjugated wheat germ agglutinin, green= fluorescein-conjugated E. coli K-12.

Keita Å et al. Gut 2004; 53: 494-500

Pathogenesis of IBD
conclusions





Tack

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