Progress Towards an Integrated Classification of IBD

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University of Alabama at Birmingham

An Integrated Classification of IBD

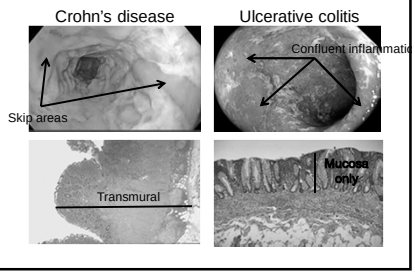
- The Current Paradigm of Crohn's versus UC
- Genetic and Epigenetic Signatures
- Cytokine Signatures
- Plans for the Future

An Integrated Classification of IBD:
The Current Paradigm of Crohn's versus UC

- An integrated classification implies:
  - more diagnostic certainty based on
  - interdependent characteristic mechanisms of disease that point to
  - application of more effective disease-specific treatments

An Integrated Classification of IBD:
The Current Paradigm of Crohn's versus UC

- Accepted criteria by endoscopic, imaging, histologic findings
  - Crohn's: "skip areas",non-caseating granulomata, fistulae and penetrating ulcers, perianal disease
  - UC: distal rectum with proximal confluent involvement, colon- and mucosa-limited inflammation, non-penetrating



An Integrated Classification of IBD:
The Current Paradigm of Crohn's versus UC

- Accepted criteria by endoscopic, imaging, histologic findings
  - No pathognomonic markers
- Histology and Anatomy: no new signatures (except UC-like Crohn's disease)
- Serology for anti-microbial antibodies

Bacterial flagellin is a dominant antigen in Crohn disease

Michael J. Lodes,[1] Yingzi Cong,[2] Charles O. Elson,[2] Raodoh Mohamath,[1] Carol J. Landers,[3] Stephan R. Targan,[3] Madeline Fort,[1] and Robert M. Hershberg[1,4]

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JCI 2004

Flagellin
- Ch3/HeJBir substrain bred for the phenotype of spontaneous colitis and perianal inflammation; B and T cell reactivity to enteric microbial antigens
- Th1 CD4 cell reactivity to flagellin, which transfers colitis to SCID mice
- Crohn's disease (not UC, HC) had serum IgG to these flagellins
- Unique among protein antigens in that it is recognized by T cells and by pattern recognition receptors as a TLR5 ligand; this drives anti-flagellin responses and establishes flagellin as an adjuvent
- A TLR5 dominant negative polymorphism (flagellin unable to activate NF-kB) blocks development of anti-flagellin Abs (and is associated with decreased Crohn's risk in susceptible populations)

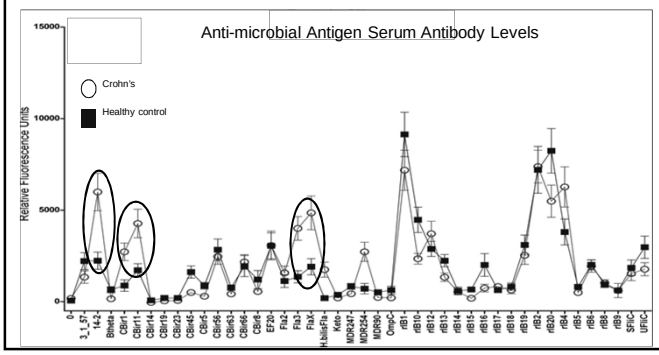
Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study

Subra Kugathasan*, Lee A Denson*, Thomas D Walters*, Mi-Ok Kim, Urko M Marigorta, Melanie Schirmer, Kajari Mondal, Chunyan Liu, Anne Griffiths, Joshua D Noe, Wallace V Crandall, Scott Snapper, Shervin Rabizadeh, Joel R Rosh, Jason M Shapiro, Stephen Guthery, David R Mack, Richard Kellermayer, Michael D Kappelman, Steven Steiner, Dedrick E Moulton, David Keljo, Stanley Cohen, Maria Oliva-Hemker, Melvin B Heyman, Anthony R Otley, Susan S Baker, Jonathan S Evans, Barbara S Kirschner, Ashish S Patel, David C Ziring, Bruce C Trapnell, Francisco A Sylvester, Michael C Stephens, Robert N Baldassano, James F Markowitz, Judy Cho, Ramnikj Xavier, Curtis Huttenhower, Bruce J Aronow, Greg Gibson†, Jeffrey S Hyams†, Mario C Dubinsky†

Table 2: Competing-risk model for disease complications and early anti-TNFα comparative effectiveness analysis

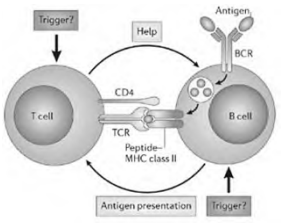
	Stricturing behaviour (B2)		Penetrating behaviour (B3)	
	HR (95% CI)	p value	HR (95% CI)	p value
Competing-risk model (n=913)				
Age at diagnosis	1·07 (0·97–1·17)	0·16	1·45 (1·17–1·80)	0·0008
African American race	1·08 (0·52–2·22)	0·84	3·19 (1·39–7·31)	0·0061
Isolated ileal location (L1)	1·60 (0·88–2·91)	0·12	1·23 (0·53–2·95)	0·64
ASCA IgA positive	1·69 (0·94–3·07)	0·0816	2·68 (1·19–6·04)	0·0171
CBir1 positive	2·30 (1·26–4·20)	0·0070	3·01 (1·31–6·93)	0·0097
Early anti-TNFα comparative effectiveness analysis of propensity-score matched cohort (n=382)				
Age at diagnosis	1·13 (0·97–1·31)	0·11	1·37 (1·03–1·81)	0·0278
African American race	1·25 (0·43–3·63)	0·68	3·02 (0·97–9·39)	0·0555
Isolated ileal location (L1)	1·66 (0·65–4·26)	0·29	1·26 (0·36–4·43)	0·72
ASCA IgA positive	2·87 (1·21–6·82)	0·0165	2·09 (0·71–6·12)	0·18
CBir1 positive	1·52 (0·63–3·70)	0·35	4·82 (1·53–15·2)	0·0072
Early anti-TNFα	1·13 (0·51–2·51)	0·76	0·30 (0·10–0·89)	0·0296

Lancet 2017; 389: 1710–18



B Cells Engage T Cells in an Antigen-Specific Manner

T cell dependent B cell Ig Class Switching: Mucosal antigen



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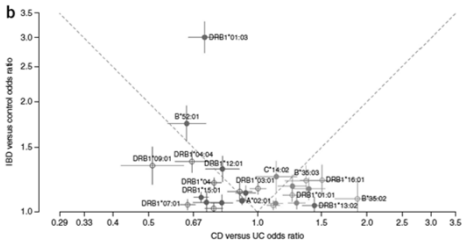
Odds Ratios for HLA Alleles Providing Risk for Crohn's versus UC



Goyette et al., Nature Genetics 2015

An Integrated Classification of IBD:
Serologic Determinants as a Clinical Biomarker

- So with the aberrant antibody response to certain flagellin molecules seen predominantly in CD
- And with shared but also restricted MHC II molecules between CD and UC

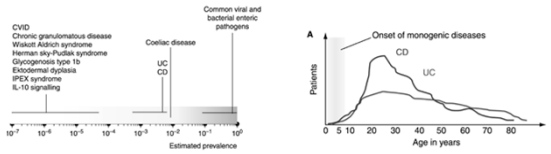
- It may be that TCR repertoire, patterns of antigen recognition may be another way to define the spectrum of IBD

An Integrated Classification of IBD:
Genetic Signatures

- GWAS studies have now identified >200 risk loci
  - Few coding region mutations (SNPs)
  - Over representation of risk SNPs in the healthy population
  - Overlap of many risk loci between CD and UC

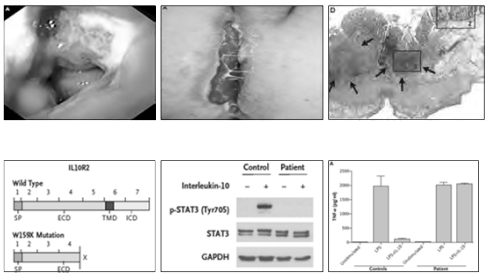
  - Complex contribution by multiple genetic risk loci (with as yet unexplained functional consequences) interacting with environmental factors

An Integrated Classification of IBD:
Monogenic Disease-associated IBD



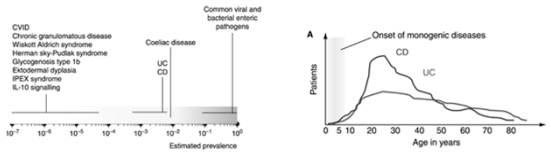
Uhlig HH. Gut 2013;62:1795–1805.

Immune Defects and IBD:
Very Early Onset Colitis in Babies with IL-10 Pathway Deficiency



Glocker et al., N Engl J Med. 2009 Nov 19;361(21):2033-45

An Integrated Classification of IBD:
Monogenic Disease-associated IBD

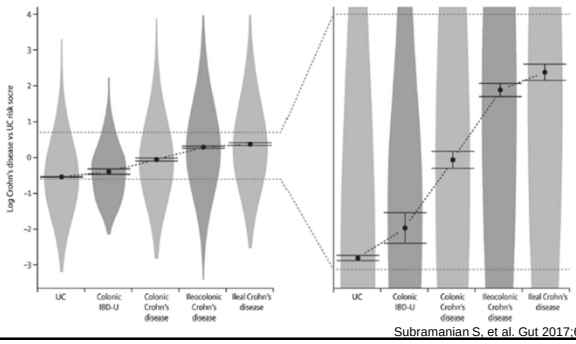


Uhlig HH. Gut 2013;62:1795–1805.

An Integrated Classification of IBD:
Ileal vs Colonic Crohn's

- Is there a third form of IBD, isolated colonic Crohn's
- The terminal ileum may be a separate organ, affected differentially by genetic risk and environment
- pANCA+/ASCA+ colonic CD (Ruemmele FM, et al. Gastroenterology 1998;115:822–829.)

An Integrated Classification of IBD:?A third type of IBD



Subramanian S, et al. Gut 2017;66:362–381

An Integrated Classification of IBD:?A third type of IBD

Table 11 A summary of the distinguishing features of the three IBDs: ileal/ileocolonic CD, isolated colonic CD, UC

	Ileal/ileocolonic CD	Isolated colonic CD	UC
Sex	Slightly commoner in females (55%)	Commoner in females (65%)	Equal or slight male predominance
Genetics	Crohn's-associated (genotype including NOD2/CARD15	Genotype midway between CD and UC Associated with HLA-DRB1*01:03 but not NOD2/CARD15	UC-associated genotype including HLA-DRB1*01:03
Smoking	Marked association Worsens prognosis	Weak association Possibly worsens prognosis	Marked negative association
Oral contraception	Positively associated	Positively associated	Positively associated (mainly in smokers)
Serology	ASCA commonly positive pANCA usually negative	ASCA less commonly positive than ileal/ileocolonic CD pANCA positive in minority	ASCA usually negative pANCA commonly positive
Mucosa-associated microbiota	Marked changes commonly including increased Proteobacteria (eg, *Escherichia coli*) and Fusobacteria, reduced Firmicutes (eg, *F. prausnitzii*)	Intermediate changes similar to ileal/ileocolonic CD but less consistent	Modest changes, including slight increase in *E. coli* but no reduction in *F. prausnitzii*
Response to mesalazine	No efficacy	No efficacy	Good efficacy
Response to anti-TNF	Good efficacy	Good efficacy—probably better than for ileal/ileocolonic	Good efficacy
Response to exclusive enteral nutrition	Good efficacy	Probably good efficacy but mixed reports	No efficacy
Surgery rate and type	Required in majority	Required in minority Segmental colectomy effective High failure for pouch-anal reconstruction	Required in minority Segmental colectomy not effective Low failure for pouch-anal reconstruction

CD, Crohn's disease; ASCA, anti-*Saccharomyces cerevisiae*; HLA, human leucocyte antigen; pANCA, perinuclear antineutrophil cytoplasmic antibodies; TNF, tumour necrosis factor.

An Integrated Classification of IBD:
Epigenetic Signatures

- Epigenetics measures types of DNA and histone modifications
  - Methodology:
    - Bisulphite sequencing
    - Methylation sensitive high-resolution melting
    - Chromatin immunoprecipitation (ChIP) on Chip assays
  - Inherited and Acquired (Transient vs. Permanent)
  - Drugs that can Affect the Epigenome

An Integrated Classification of IBD: Epigenetic Signatures

- Epigenetics measures types of DNA and histone modifications
  - Interest in UC (and long-standing IBD inflammation) for hyper-methylation of DNA (especially genes involved in carcinogenesis)
  - Discovery of hypermethylated gene "profiles" that may be disease-specific (potential biomarkers) Kang et al., Int. J. Mol. Sci. 2016, 17, 1291
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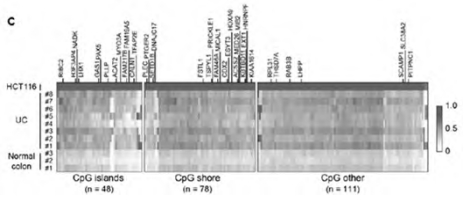
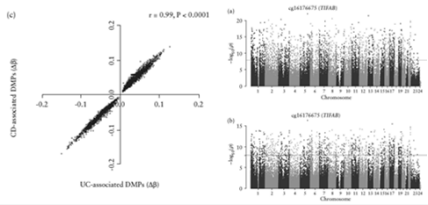


An Integrated Classification of IBD: Epigenetic Signatures

DNA Methylation Profiling in Inflammatory Bowel Disease Provides New Insights into Disease Pathogenesis

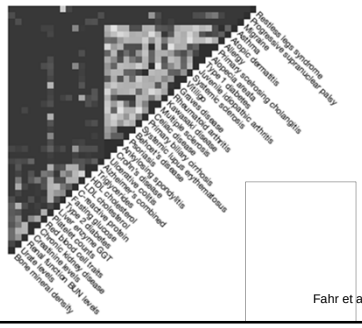
Edel McDermott[a,b], Elizabeth J. Ryan[a,b], Miriam Tosetto[a], David Gibson[a,b], Joe Burrage[a], Denise Keegan[a], Kathryn Byrne[a], Eimear Crowe[b,f], Gillian Sexton[a], Kevin Malone[b,d], R. Alan Harris[a], Richard Kellermayer[f], Jonathan Mill[c,g], Garret Cullen[a,b], Glen A. Doherty[a,b], Hugh Mulcahy[a,b,*], Therese M. Murphy[c,g]

Journal of Crohn's and Colitis, 2016, 77–86

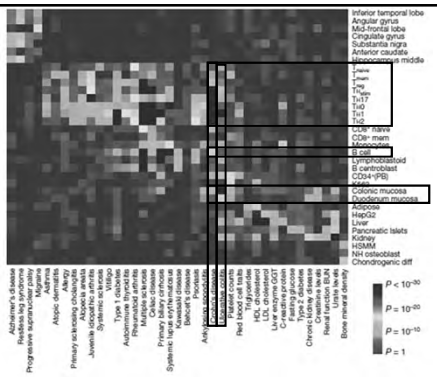


- PBMCs from CD and UC pts
- Na bisulphite sequencing
- No differences in epigenetics signatures (97% of the differentially methylated positions were also seen in CD, but only 55% of the CD sites matched the UC)
- Disease activity and concomitant biologic med use did not affect results

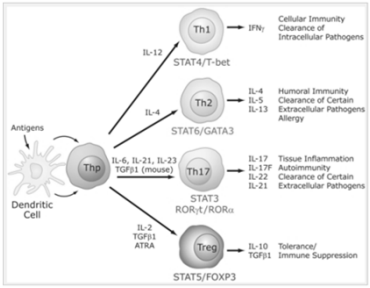
An Integrated Classification of IBD: Discrimination of Epigenetic and Genetic Signatures between CD and UC



Fahr et al. 2015 Nature



An Integrated Classification of IBD:
Cytokine



Jetten AM *Nucl Recept Signal* (2009)

An Integrated Classification of IBD

- Current genetic risk loci reflect our appreciation for the spectrum that IBD spans
- Fine mapping of MHC alleles implicates more prominent role for the adaptive immune response in UC
- Intriguing data about restriction of gut mucosal epigenetic signatures and UC
- Intriguing data about restriction of B cell epigenetic signatures and CD
- Future studies need to aim to integrate genetic, epigenetic and functional measures to form a more complete picture of the mechanism of disease that can reveal novel points for intervention