GI ReConnect

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Napa Valley, California

GI Health Foundation

GI ReConnect

Traditional vs. Regional Definitions of IBD

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Director Precision Health
Cedars-Sinai Medical Center

Cedars Sinai

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All additional planning committee members, the University of Cincinnati staff and the Gi Health Foundation staff have no relationships to disclose.

Faculty Disclosure

Dermot McGovern, MD:

Prometheus Biosciences (Consultant and Shareholder), Pfizer, Takeda, Gilead, Boehringer-Ingelheim, Palatin, Merck, Bridge Therapeutics (Consultant).

Seminal Observations

Landmark Article
Oct 15, 1932
(*JAMA* 1932;99:1323-1329)

Regional Ileitis

A Pathologic and Clinical Entity

Burrill B. Crohn, M.D.
Leon Ginzburg, M.D.
and
Gordon D. Oppenheimer, M.D.
New York

We propose to describe, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction of the remaining walls of the involved intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas.

Such, in essence, is the definition of a disease, the description of which is based on the study, to date, of fourteen cases. These cases have been carefully observed and studied in their clinical course; the pathologic details have resulted from a close inspection of resected specimens from thirteen of fourteen patients operated on by Dr. A. A. Berg.

RELATIONSHIP OF REGIONAL ILEITIS TO OTHER

We propose to describe, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration of the mucosa is accom-

THE CLINICAL FEATURES

Etiologically, young adults comprise the largest number of patients. Only two of the patients studied were over 40 years, the average incidence being at 32 years of age; the youngest patient was 17, the oldest 52. Males predominate over females in the proportion of nearly 2:1. There are no known predisposing factors.

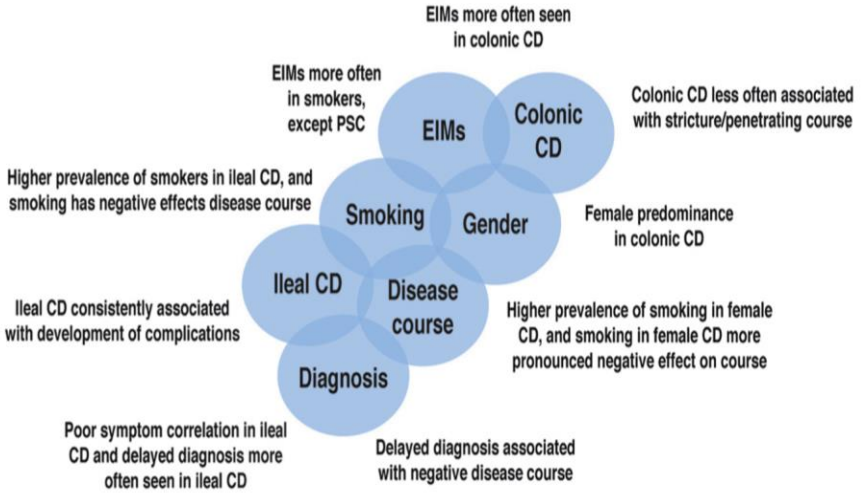
section). The terminal ileum is alone involved. The process begins abruptly at and involves the ileocecal valve in its maximal intensity, tapering off gradually as it ascends the ileum orally for from 8 to 12 inches (20 to 30 cm.). The familiar

"I am prepared to believe that this segmental colitis is a colonic form of Crohn's disease. Crohn himself does not sanction this extension of the entity to which we give his name…"

Charles Wells, FRCS, October 1952

Crohn, Ginzburg and Oppenheimer. *JAMA*. 1932.

Demographics & Clinical Presentation of Colonic and Ileal Crohn's Disease



	Colonic	Ileal
Smoking		✓
Women	✓	
OCP	✓	
Young onset	✓	
Elderly Onset	✓	
Delayed Present. & Complicated Dis.		✓
EIMs	**Eye, Joints EN, PG, PSC**	**SpA**
Perianal Dis.	✓	

Dulai et al. *Inflamm Bowel Dis*. 2019.

Seminal Observations

Regional Ileitis

A Pathologic and Clinical Entity

There are none of the perianal fistulas, condylomas or perirectal abscesses that characterize the complications of true colitis, for in this disease the rectum and colon are never involved. At times, particularly when the stenotic

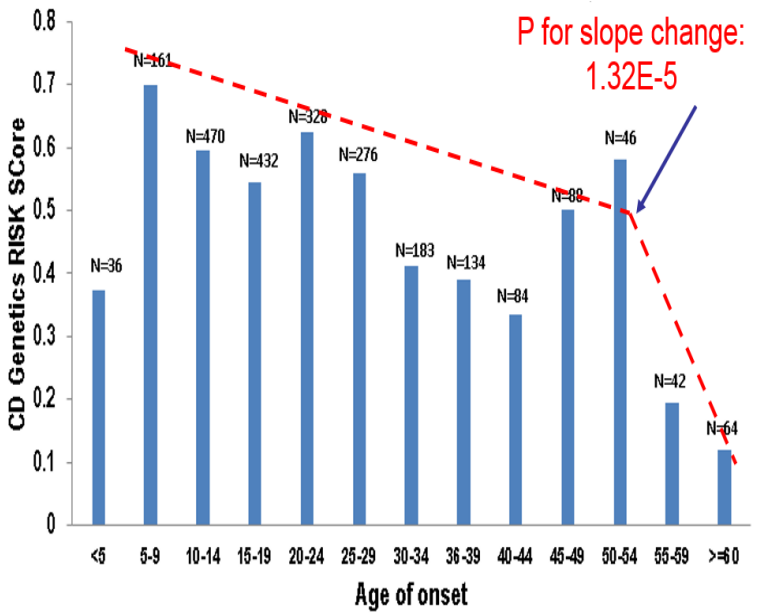
Perianal Crohn's Disease is Associated with Distal Colonic Disease, Stricturing Disease Behavior, IBD-Associated Serologies and Genetic Variation in the JAK-STAT Pathway

Not associated with perianal fistula

	Odds Ratio	
Clinical Variable	**(95% CI)**	***P***
L1, ileum	**0.38 (0.28–0.52)**	**<0.001**
L2, colon	**1.35 (1.04–1.75)**	**0.03**
L3, ileocolonic	**1.44 (1.16–1.8)**	**0.001**
L4, upper GI	**92 (0.70–1.20)**	**0.55**
Colonic disease:		
Ascending colon	**1.02 (0.81–1.29)**	**0.88**
Transverse colon	**1.4 (1.11–1.77)**	**0.01**
Descending colon	**1.58 (1.26–1.99)**	**<0.001**
Sigmoid colon	**1.99 (1.58–2.51)**	**<0.001**
Rectum	**4.32 (3.4–5.51)**	**<0.001**

Kaur et al. *Inflamm Bowel Dis*. 2016.

Late Onset Disease

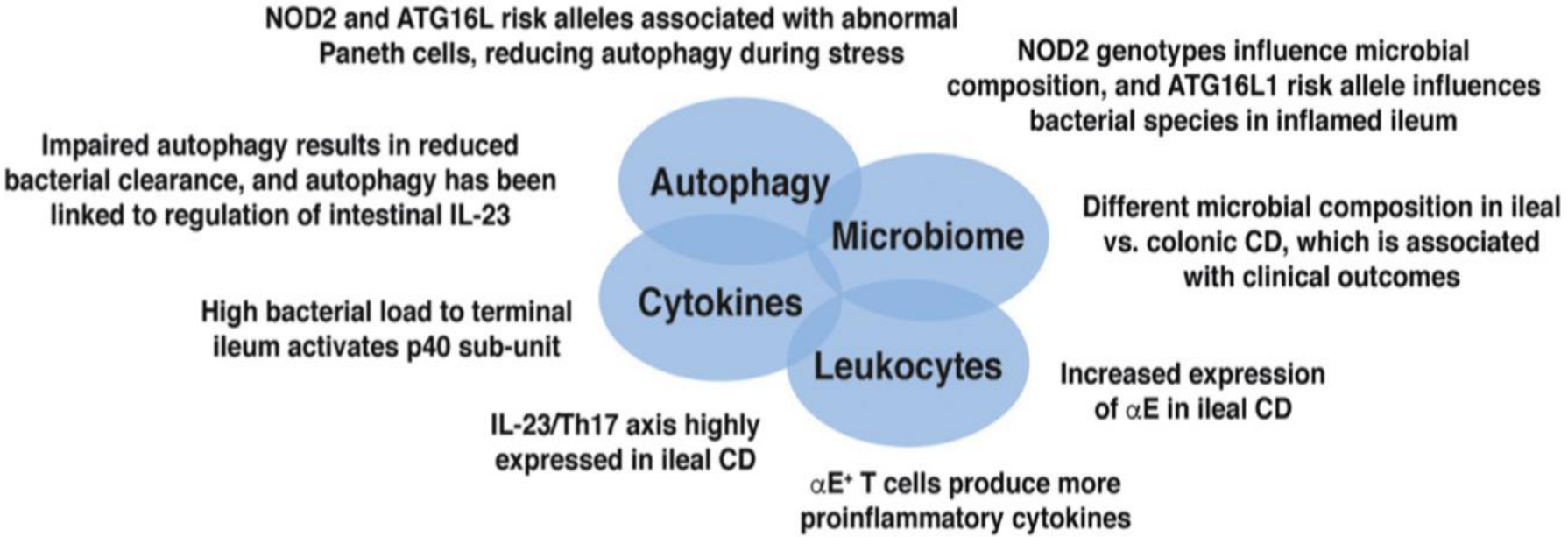


	LO vs 'Others'	
Phenotype	**OR**	**P**
L1	**1.21 (1.04,1.41)**	**0.013**
L2	**2.48 (2.13,2.88)**	**7.74E-31**
L3	**0.32 (0.27,0.39)**	**7.93E-36**
L4	**0.31 (0.21,0.47)**	**2.22E-08**
Perianal	**0.38 (0.31,0.48)**	**6.11E-18**
B2vsB1	**0.84 (0.70-0.99)**	**0.047**
B3vsB1	**0.40 (0.32-0.49)**	**1.30E-16**
B2B3vsB1	**0.59 (0.51-0.70)**	**4.90E-11**
Surgery	**0.47 (0.41-0.55)**	**7.65E-22**

Late Onset CD ↑ ANCA, ↓ CBir1, ↓↓ ASCA, ↓ Smoking

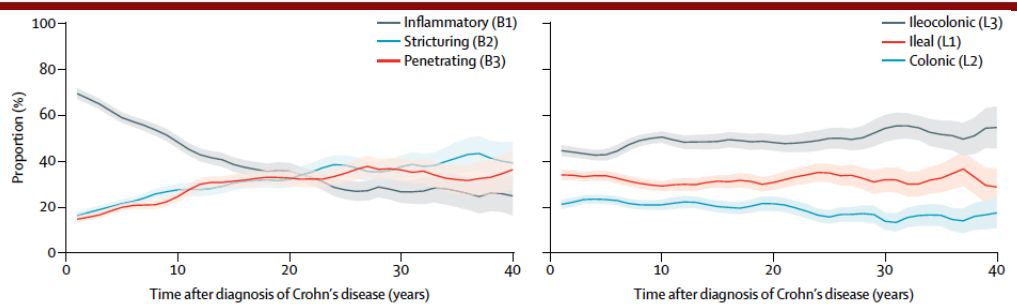
Li et al. *Inflamm Bowel Dis*. 2019.

Different Biology in Ileal and Colonic CD



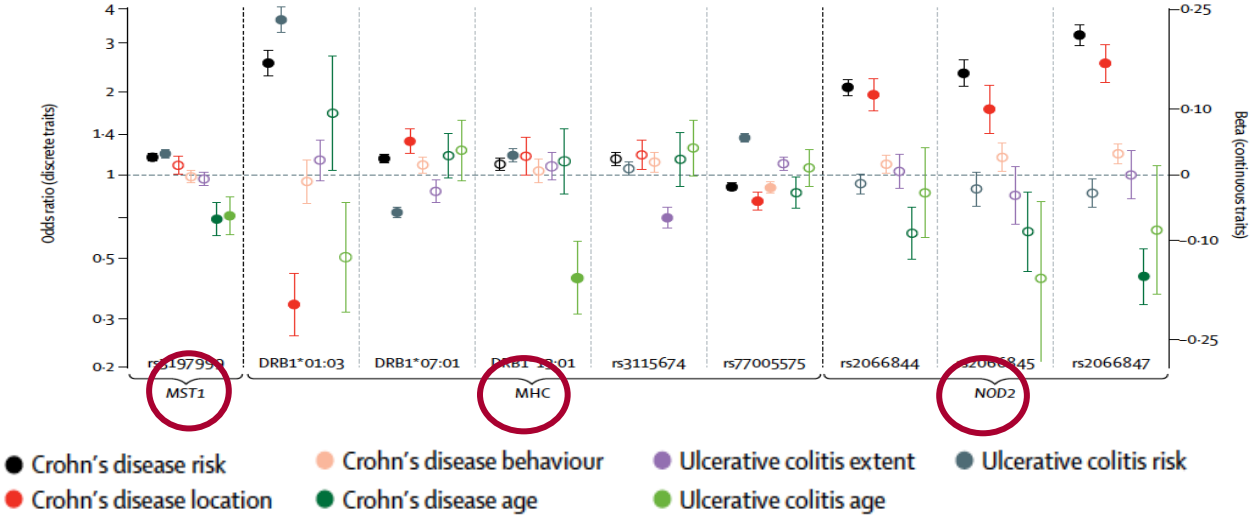
Dulai et al. *CGH Dis*. 2019.

Genetic Determinants of Crohn's Disease and Ulcerative Colitis Phenotypes in 34819 Patients: A Genetic Association Study



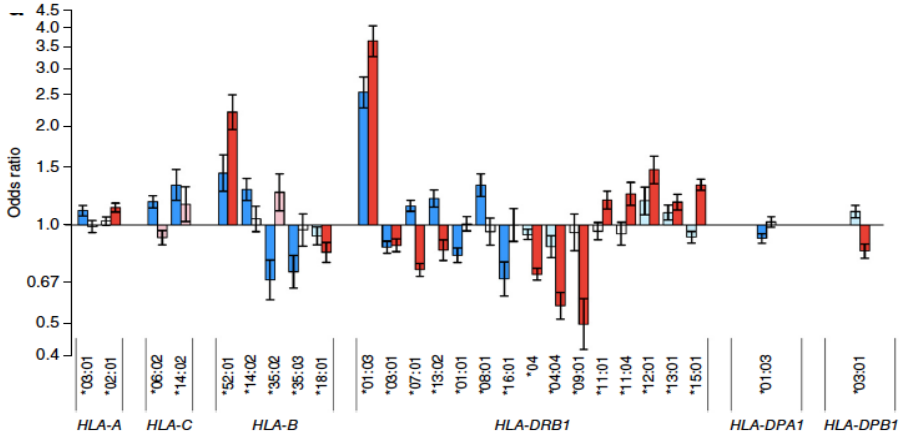
3 Phenotype associations

- **NOD2**
- **MHC**
- **MST1**

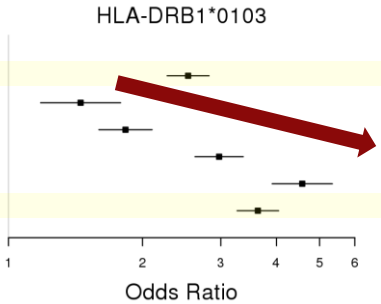


Cleyen et al. *Lancet*. 2015.

HLA Associations With Disease Location



Population Group	Cases
CD	18405
Ileal only CD	4193
Ileal only and ileocolonic CD	10413
Ileocolonic and colonic only CD	9330
Colonic only CD	3110
UC	14308



Cases
18405
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10413
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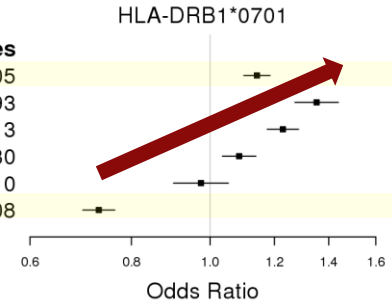
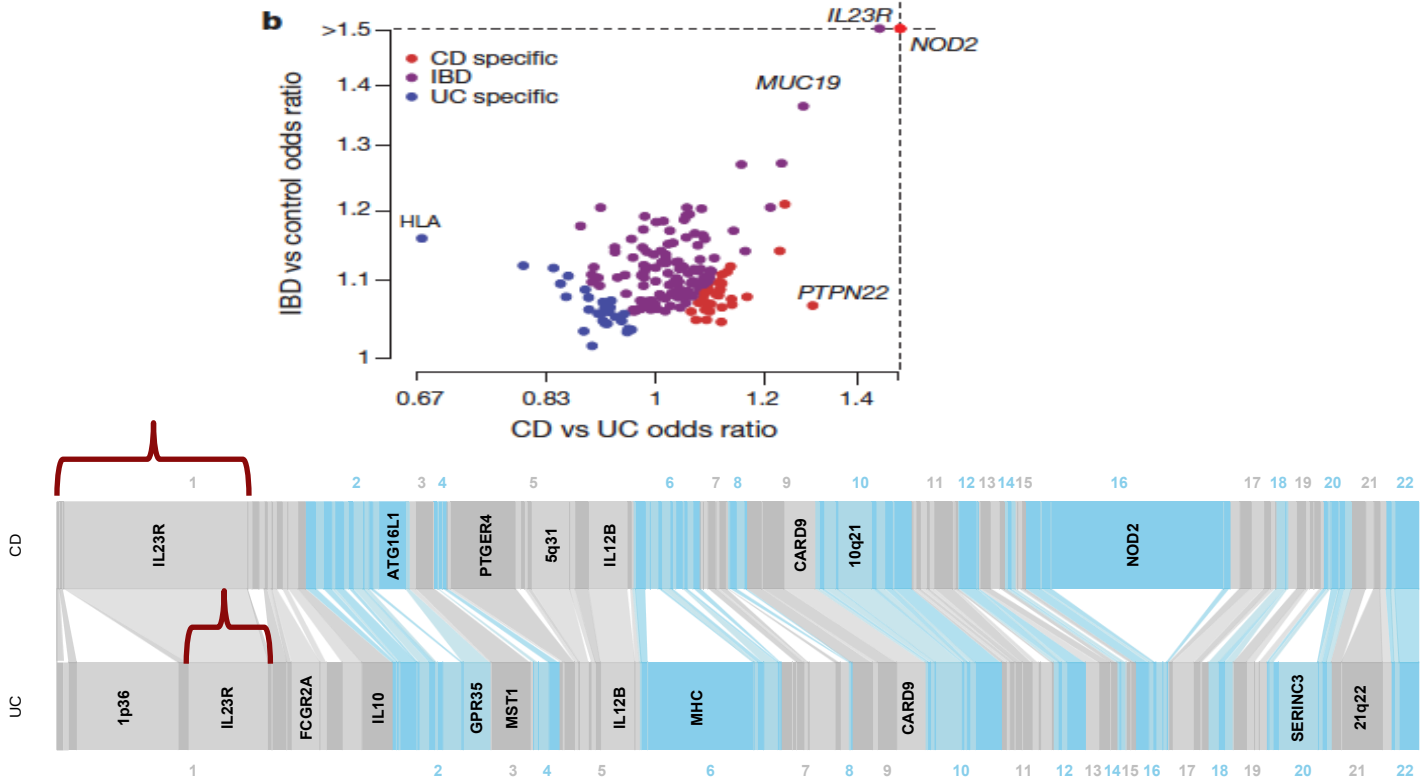
14308



Goyette et al, Nature Genetics 2015

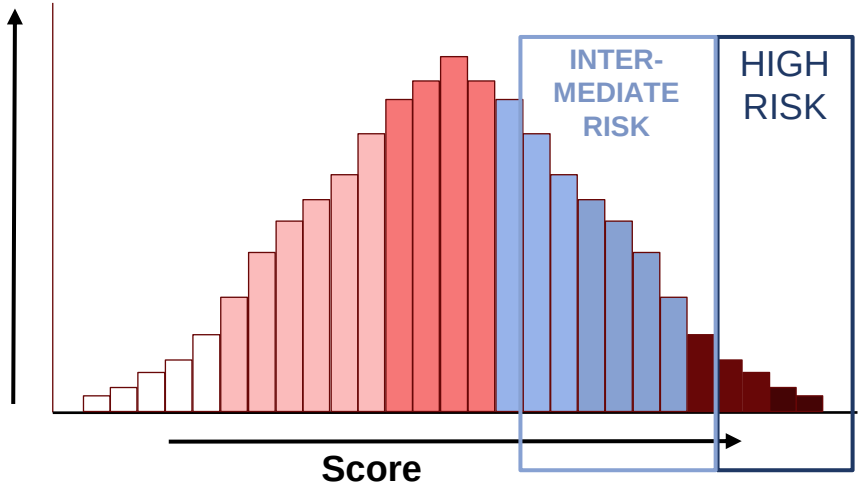
The ‘IBD Genome’

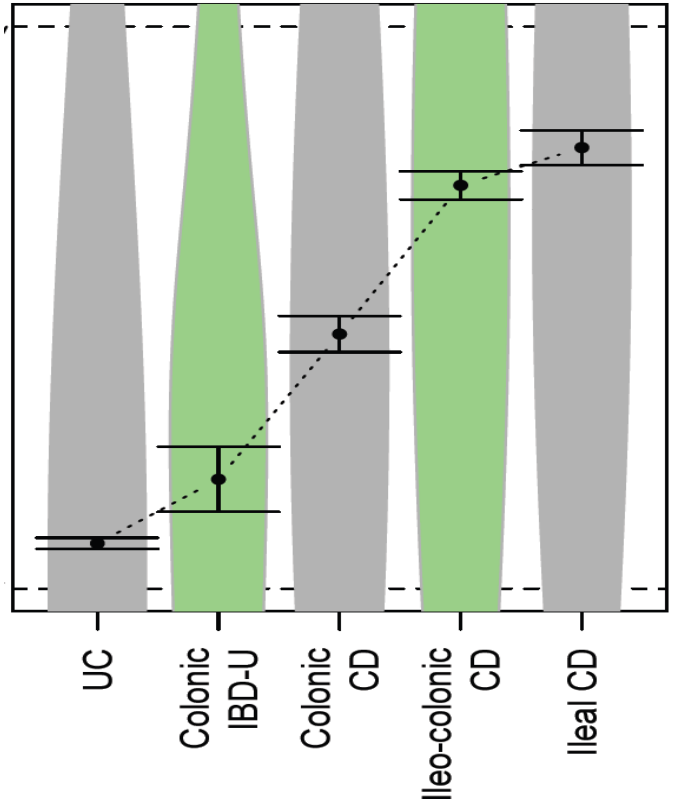


Jostins et al. *Nature*. 2012.

Polygenic Risk Scores (PRS) and Disease Location

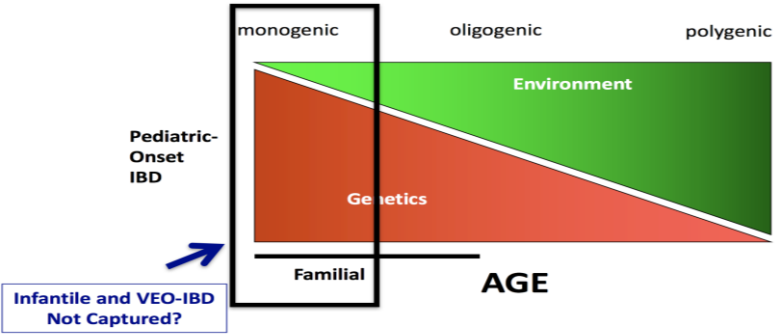
- Multiple risk alleles most with modest/weak effects
- Binomial distribution of risk score in populations
- Additive model for multiple risk variants weighted for effect size



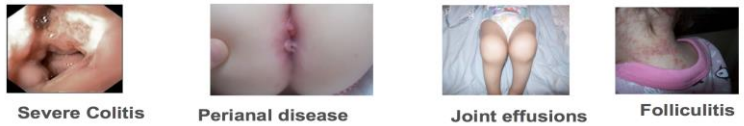


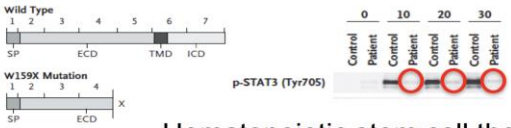
Cleyen et al. *Lancet*. 2015.

Lessons From the Most Extreme Phenotype



- Presented in 1st year of life with severe colitis
- Multiple enterocutaneous fistulae, recurrent folliculitis, recurrent infections, impaired wound healing





Hematopoietic stem cell therapy can be curative

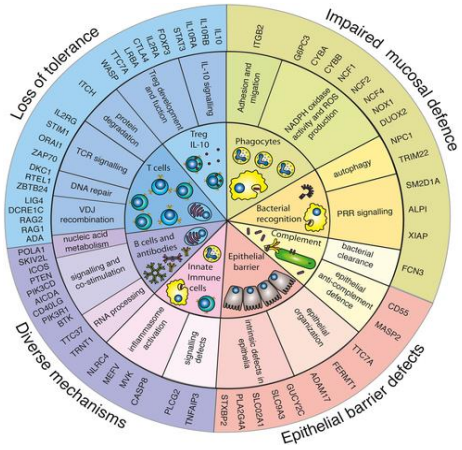


Table 3
Potential "actionable": gene defects recognized in VEO-IBD

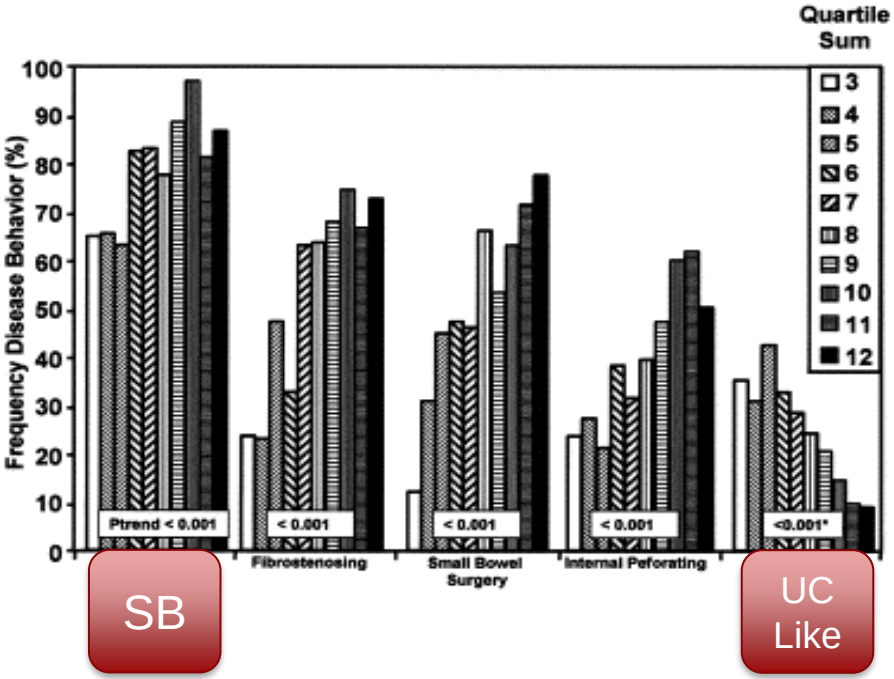
Gene Defect	Potential Therapeutic Approach	Contraindications to Therapy
IL10 and IL 10 receptor	HSCT likely curative[80,91]	
FOXP3, IL2RA, CTLA4, MALT1	HSCT likely curative[92]	
XIAP	HSCT likely curative[60]	
SH2D1A	HSCT likely curative[93]	
DCLRE1C	HSCT likely curative[94]	
ZAP70	HSCT likely curative[95]	
WAS	HSCT likely curative[96]	
CGD CYBB, CYBA, NCF1, NCF2, NCF4	HSCT likely curative[97] Leukine antibiotics, IL-1 receptor antagonist (Anakinra), possible use to bridge to HSCT or if HSCT not available[98,99]	Anti-TNF contraindicated: increase risk of severe infections, may be fatal[100]
EPCAM		HSCT not helpful[101]
TTC7A		HSCT not helpful[102]
Mevalonate kinase deficiency, *NLRC4* gene defects, IL-10 R deficiency	IL-1 targets[29]	
NLRC4	IL-18, ILR inhibition[103]	
LRBA deficiency	CTLA4 fusion protein: Abatacept (possible use to bridge to HSCT)[104]	
STAT1	HSCT *or* Janus kinase inhibitor Ruxolitinib[105]	

Abbreviations: HSCT, hematopoietic stem cell transplantation; IL, interleukin; TNF, tumor necrosis factor; VEO-IBD, very early onset inflammatory bowel disease.

Serology and Disease Heterogeneity

Serology markers: a window to heterogeneity in disease phenotype

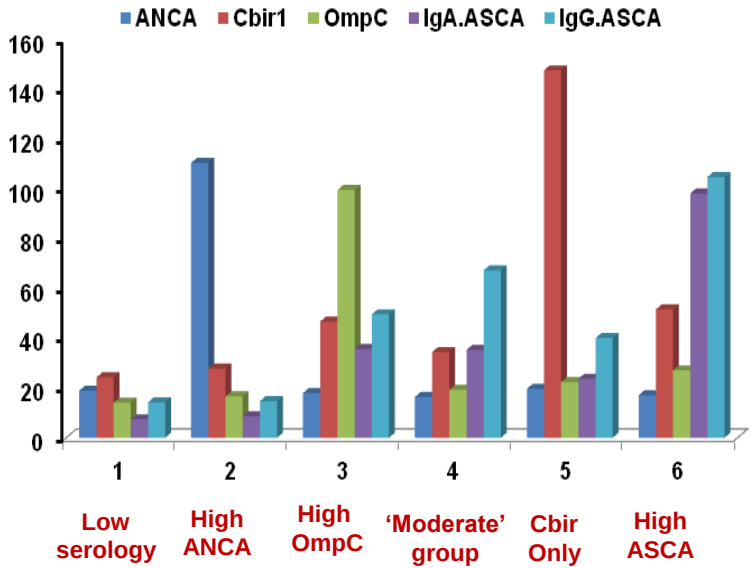
Marker	Epitopes	CD	UC
pANCA	perinuclear anti-neutrophil cytoplasmic protein	+	+++
ASCA	Saccharomyces cerevisiae cell wall	+++	+
OmpC	E. coli outer membrane porin	++	+/-
I2	Pseudomonas fluorescens associated sequence	++	+/-
CBir1	Bacterial flagellin	++	+/-



MOW et al. *Gastroenterology*. 2004.

Quantitative Traits as Phenotypes in IBD

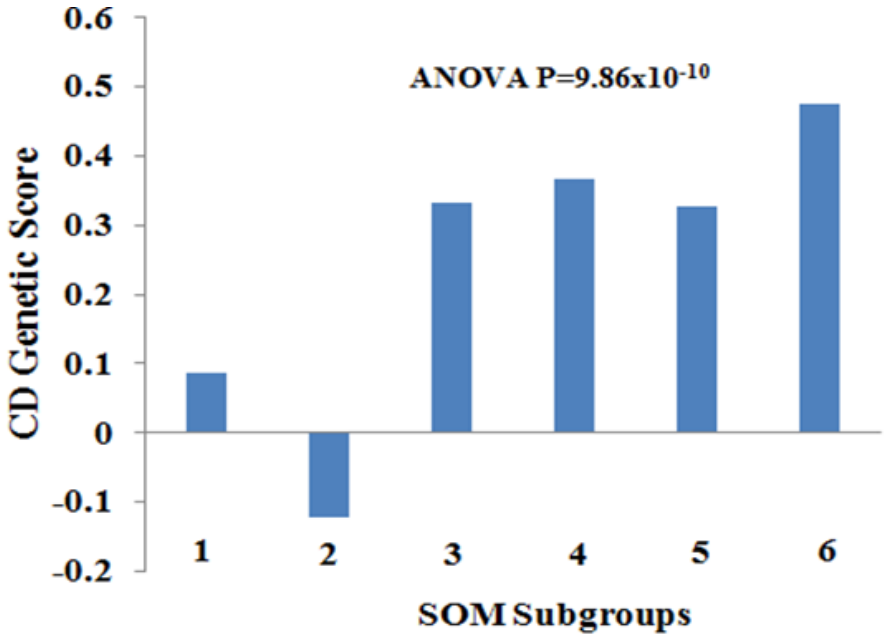
Six CD Self Organizing Map Groups



	jejunum		ileum		colon		perianal		Notes
	OR	P	OR	P	OR	P	OR	P	
Group1	.	.	.	.	.	.	.	.	Low serology
Group2	0.71	0.432	0.68	0.087	2.39	0.022	0.96	0.878	High ANCA
Group3	2.01	0.051	2.67	7.54×10^{-3}	0.70	0.233	1.56	0.094	High OmpC
Group4	1.70	0.015	5.63	7.47×10^{-12}	0.57	7.83×10^{-4}	1.07	0.661	Moderate
Group5	2.76	1.59×10^{-4}	2.83	4.78×10^{-4}	0.64	0.062	1.18	0.456	Anti-CBir1 Only
Group6	0.97	0.918	9.01	2.43×10^{-7}	0.69	0.095	2.22	2.35×10^{-4}	High ASCA

Dalin Li et al. (presented in abstract form).

Six Groups: Overall Genetic Load



Genetic Z score calculated using 140 known CD loci

Dalin Li et al. (presented in abstract form).

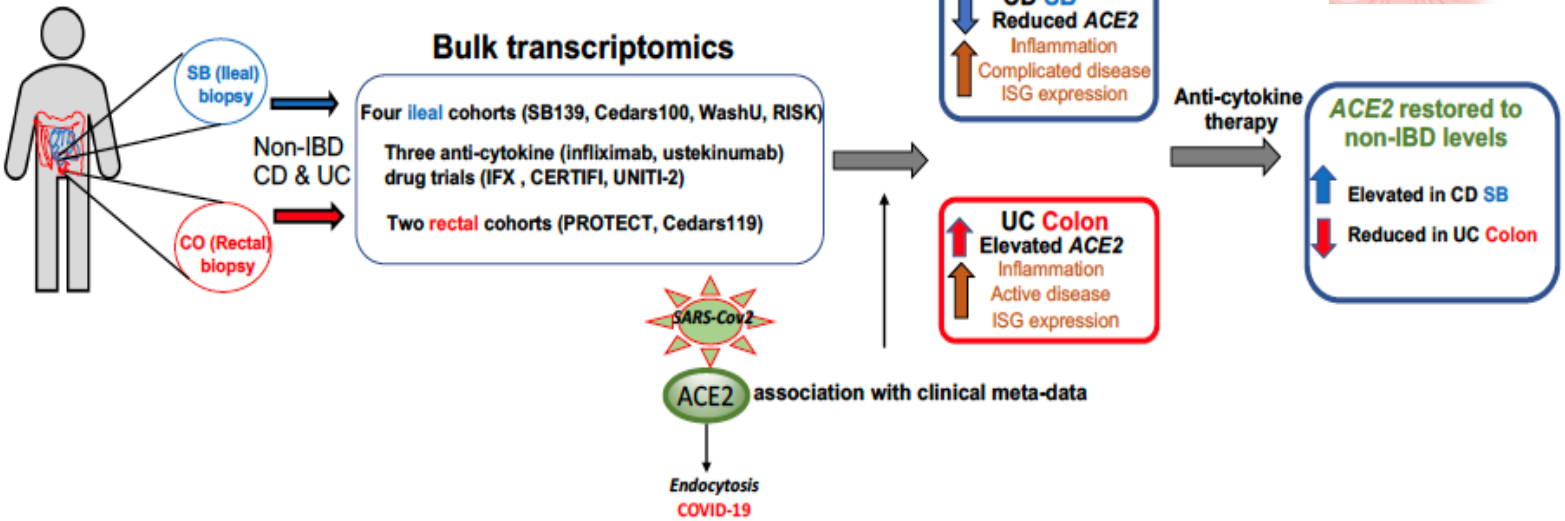
ACE2 and the GI Tract

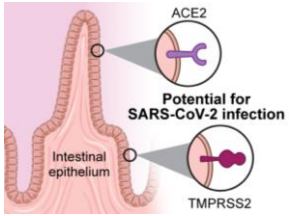
LETTER

doi:10.1038/nature11228

ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation

Tatsuo Hashimoto[1,2]*, Thomas Perlot[1]*, Ateequr Rehman[3]†, Jean Trichereau[1], Hiroaki Ishiguro[2], Magdalena Paolino[1], Verena Sigl[1], Toshikatsu Hanada[1], Reiko Hanada[1], Simone Lipinski[3], Birgit Wild[4], Simone M. R. Camargo[5], Dustin Singer[5], Andreas Richter[4], Keiji Kuba[6], Akiyoshi Fukamizu[7], Stefan Schreiber[3], Hans Clevers[8], Francois Verrey[5], Philip Rosenstiel[3] & Josef M. Penninger[1]





Hashimoto et al. *Nature*. 2012; Potdar, Dube et al. *Gastroenterology*. 2021.

Seminal Observations

Regional Ileitis

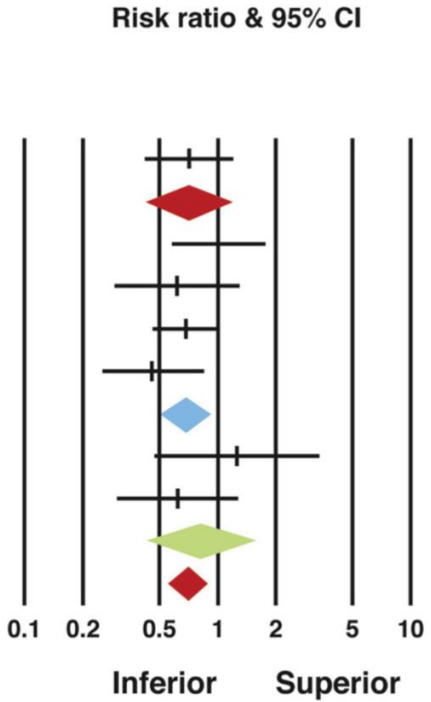
A Pathologic and Clinical Entity

Microscopically, no specific features can be demonstrated. The stained histologic sections showed various degrees of acute, subacute and chronic inflammation, with variations in the predominance of polymorphonuclear, round cell, plasma cell and fibroblastic elements. In

No Specific microscopic features

Disease Location and Response to Treatment

Group by study name / Drug	Risk ratio	Lower limit	Upper limit	Events/Total: Ileal CD	Events/Total: Colonic CD
Sandborn 2011	0.71	0.41	1.20	16 / 62	23 / 63
TNFi	0.71	0.41	1.20	16 / 62	23 / 63
CERTIFI	1.02	0.58	1.78	15 / 34	13 / 30
UNITI-1	0.62	0.29	1.30	8 / 37	14 / 40
UNITI-2	0.68	0.46	1.02	21 / 49	27 / 43
IM-UNITI	0.46	0.26	0.83	13 / 50	13 / 23
Ustekinumab	0.68	0.50	0.92	57 / 170	67 / 136
GEMINI-II	1.26	0.47	3.34	6 / 37	8 / 62
GEMINI-M	0.62	0.30	1.28	8 / 29	12 / 27
Vedolizumab	0.82	0.42	1.60	14 / 66	20 / 89
Overall	0.70	0.55	0.90	87 / 298	110 / 288



Dulai et al. *Inflamm Bowel Dis*. 2019.

Seminal Observations

Regional Ileitis

A Pathologic and Clinical Entity

There exists in the medical literature a heterogeneous group of benign intestinal lesions which have now and then been described under the caption of "benign granulomas." The latter loose term covers a multiplicity of conditions in which both large and small intestines may be involved; it includes all chronic inflammatory lesions of the intestine whose etiology is either unknown or attributable to an unusual physical agent. It represents a hodge-podge or melting-pot in which are thrown all those benign inflammatory intestinal tumors which are neither

Just as the generic term of typhus originally included various diseases, from which group eventually typhoid fever, Brill's disease, Rocky Mountain fever, tabardillo and others were split off, so, similarly, do we aim to disintegrate from the general group of varied diseases spoken of as a "benign granuloma" a specific clinical entity with constant and well defined characteristics, which we propose to name "regional ileitis."

'Hodge-podge' of diseases

(re)Defining IBD

All IBD patients

IBD1

Regional ileitis

IBD2

CD with Perianal Disease

IBD3

CD Non-Responsive to Anti-TNF

IBD4

Colonic CD

IBD5

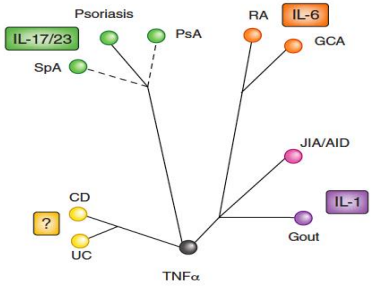
Medically Refractive UC

IBD6……

Etc….

Late Onset Disease (UC)

a



b

CID	TNF	IL-6R	IL-1	IL-12/23	IL-17A
Rheumatoid arthritis					
Giant cell arthritis					
JIA/AID					
Gout					
Crohn's disease					
Ulcerative colitis					
Psoriasis					
Psoriatic arthritis					
Ankylosing spondylitis					
Multiple sclerosis					
Drugs	Adalimumab Certolizumab Etanercept Golimumab Infliximab	Tocilizumab Sarilumab*	Anakinra Canakinumab Rilonacept	Ustekinumab Briakinumab*	Brodalumab* Ixekizumab* Secucinumab*

LEADING ARTICLE

The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications

J Satsangi, M S Silverberg, S Vermeire, J-F Colombel

Published online 2 December 2020

Nucleic Acids Research, 2021, Vol. 49, Database issue D1207–D1217
doi: 10.1093/nar/gkaa1043

The Human Phenotype Ontology in 2021

A1 below 16 y
A2 between 17 and 40 y
A3 above 40 y

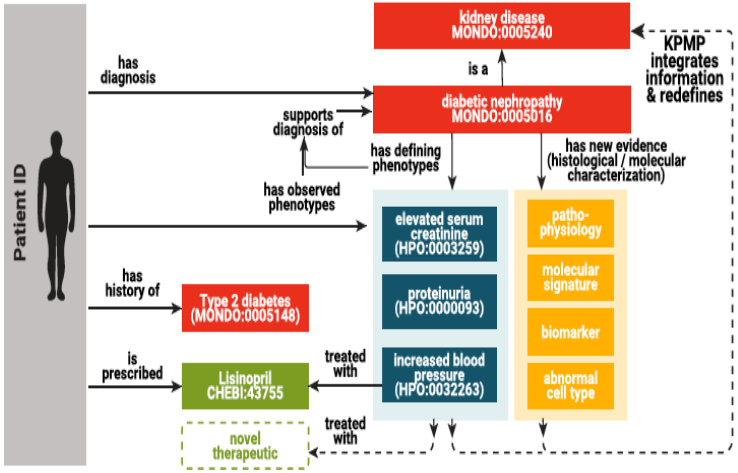
L1 ileal
L2 colonic
L3 ileocolonic
L4 isolated upper disease*

B1 non-stricturing, non-penetrating
B2 stricturing
B3 penetrating
p perianal disease modifier†

IOIBD

Extent		Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

"One goal of KPMP is to refine classification of kidney diseases in molecular, cellular, and phenotypic terms and thereby identify novel targeted therapies."



Most Important Conclusion!

"It is refreshing to address a medical organization of this kind where one can count on meeting [women and] men of large clinical experience"