Genetic Research in IBD: the keys to a ‘cure’

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Familial occurrences of ulcerative colitis, regional enteritis and ileocolitis
‘Genetics 101’

Human Genome Book
‘Genetics 101’

23 Chapters

23 Chromosomes
‘Genetics 101’

Each chapter contains ‘Genes’
several thousand stories

Each story is made up of paragraphs
‘Exons’

Interrupted by commercials
‘Introns’
‘Genetics 101’

Each paragraph is made up of words

Each word is written in letters

Codons

Bases
What is a polymorphism?

Also known as a SNP – Single Nucleotide Polymorphism
HapMap
Select SNPs to tag haplotypes

Genotyping
300,000–500,000 SNPs typed on high-density arrays

Case–control study
Compare SNP allele frequencies in disease cases and controls

Genome scan result
Significant differences in SNP allele frequencies indicate possible new disease genes and loci

Replication test
Confirm scan findings

Locus 1
A
B
C

Locus 2
A
B

Disease cases
Controls

Genotype-associated SNPs in an independent case–control sample

Nature Reviews | Genetics
CD Genetics 2010 – 71 Loci

- Linkage
- Initial GWAS
- 2008 meta-analysis
- Individual GWAS/candidate gene
- 2010 meta-analysis

Prior 2005 2006 2007 2008 2009 2010

- NOD2
- 5q31
- MHC
- TNFSF15
- ATG16L1
- IL23R
- PTGER4
- MST1
- ICOSLG
- MAP3K7IP1
- IL18RAP
- FUT2
- FADS1
- NOD2
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1q24 1q32 6q21 7p12 8q24 10p11 13q14 19p13 21q21 ITLN1

8q24 TAGAP BACH2 6p25 CPEB4 NDFIP1

2008 meta-analysis

ERAP2 5q13 3p24 SP140 YDJC

2005

ICAM1/3 CCL2/7 EIF3C/CD19

2006

VAMP3 ZF36L1 SMAD3

2007

THADA DNMT3A GCR

2008

IL10 TNFSF6B PRDX5/ESRTA

2009

DENND1B UBE2D1 MTMR3

2010

IL2RA PRDX5/ESRTA

2010

MAP3K7IP1 IL18RAP FUT2 FADS1
47 Confirmed UC Loci

- IL7R
- DAP
- IL8RA/B
- SATB2
- TYK2
- 16q24
- 13q13
- 13q12
- 11q23
- ETS1
- PRKIR
- 21q11
- IL10
- IL23R
- 12q15
- 21q22
- 1q32
- Ip36
- 1p36
- LSP1
- CREM
- 2008
- 2009
- 2010

- FCGR2A
- HNF4A
- CDH1
- LAMB1
- MST1
- KIF1A
- IL2/IL21
- 12q15
- IL23R
- 1p36
- IL17REL
- MHC
- IL10
- PTGER4
- CARD9
- REL
- 21q22
- ORMDL3
- NNX2-3
- 5p15
- 7q22
- MHC
- IL12B
- PRDM1
- GNA12
- 6q23
- JAK2
- 5q31
- 5q31
- 2008
- 2009
- 2010

- MHC
- IL10
- PTGER4
IBD Genetics 2011
IBD Genetics 2012

Cumulative IBD loci

Year


0 50 100 150 200
Utility of single ‘gene’ tests for diagnosing CD

McGovern et al. Gastro 2006
IBD - A complex trait?

IBD

Lung Cancer
Car crash
Blood Group
Eye Colour
Diabetes
Cystic Fibrosis
Malaria

100% Environment
100% Genetic
IBD - A complex trait?

UC  IBDU  CD
Background: Shared genes immune-mediated diseases

Lees et al Gut 2011
Population ‘Structure’
How will genetics help in IBD?

• Diagnosis?

• Increased understanding of underlying causes
  – Novel therapeutic pathways

• Molecular classification

• Development of Biomarkers
  – Disease severity
  – Response to therapy

• ? CURE
‘An estimate, based on currently available information, on whether your genetic risk of Crohn's Disease is higher or lower than average.’

• NOD2, ATG16L1, IL23R, NKX2, IBD5, PTPN2

‘One's lifetime odds of getting Crohn's Disease range between 0% and 1%, based on genotype.’

• ? Useful in
  – General population
  – FHx
  – Symptomatic individual

‘…..sort of the modern version of genetic ‘snake oil’

Francis Collins
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Genetic heterogeneity

Epithelial integrity

CD

IL23/IL17

Innate Immunity

Autophagy
IIBDGC Meta-Analysis Identifies 30 CD Loci


<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr</th>
<th>Critical region</th>
<th>Scan</th>
<th>Replication</th>
<th>Combined</th>
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**Key Terms:**
- Autophagy
- IL23R Signaling
- Transcription Factors
- T cell Regulation
Over-Expression of TNFSF15 in Mouse Generates Severe SB/Colonic Disease with Strictures

Normal Expression  Over-Expression

Small Bowel

Colon

Is TNFSF15 a target to alter disease progression?

Barrett, R. ... Shih, D. DDW 2011, Abstract #925
TNFSF15 Antibody Healed Histologic Inflammation

Rectum
- Day 32
- Day 56
- Day 56

Mid-Colon
- Before Treatment
- Isotype Ab
- TNFSF15 Ab

Cecum
- Before Treatment
- Isotype Ab
- TNFSF15 Ab
Hypothetical TNFSF15 Trial

anti-TNFSF15 Therapeutic

Efficacy (%)

- All Subjects: 19%
- Low TNFSF15 Producers: 5%
- High TNFSF15 Producers: 50-80%

as defined by antibodies and genes
How will genetics help in IBD?

• Diagnosis?

• Increased understanding of underlying causes
  – Novel therapeutic pathways

• Molecular classification

• Development of Biomarkers
  – Disease severity
  – Response to therapy

• ? CURE
IBD – How many diseases?
“We propose to describe, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by subacute or chronic necrotizing inflammation.”

_Crohn, Ginzburg and Oppenheimer JAMA 1932_
NOD2 & ileal disease

Relative risk ileal disease

Any variant allele 4.1 (2.7-6.1)

Simple heterozygote 2.8 (1.8-4.3)

Homozygote 30.3 (7.1-129.3)

PAR ileal disease 40%

Ahmad et al Gastroenterology 2002
Crohn’s (‘Segmental’) colitis

“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…”

“Ulcerative colitis and Crohn’s disease”
Lecture delivered to the Royal College of Surgeons of England by Charles Wells, FRCS, October 1952
HLA & IBD phenotype

Colonic CD - HLA

A1B8DR3DQ2 RR=3.2

DRB1*0103 RR=5.1

Ahmad et al. Tissue Antigens 2003
Defining IBD: 1996 vs 2016?

‘Names’  vs  Molecular Mechanisms

Disease location and behavior
How will genetics help in IBD?

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Higher Risk Score Associated with need for surgery in UC (MR-UC)

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<th>Risk Score Categories</th>
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Chi-squared test for trend < 10^{-16}
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**Linkage**
- 1q24
- 1q32
- 6q21
- 7p12
- 8q24
- 10p11
- 13q14
- 19p14
- 21q21

**Initial GWAS**
- 8q24
- TAGAP
- BACH2
- 6p25
- CPEB4
- NDFIP1
- ERAP2
- CCL2/7
- EIF3/CD19
- SP140
- YDJC
- PLCL1
- SMAD3
- VAMP3
- ZF36L1
- THADA
- DNMT3A
- GCKR
- TNFRSF6B
- MTMR3
- PTNP22
- IL12B
- CDKAL1
- CCR6
- NKX2-3
- JAK2
- PTPN2
- ZNF365
- LRRK2/MUC19
- IRGM
- ORMDL3
- ZMIZ1
- MSH3
- MAP3K7IP1
- 19q13
- IL27
- ZMIZ1
- CARD9
- IL10
- UBE2D1
- IFN3/ESRRB
- IL2RA

**2008 meta-analysis**
- 1q32
- 6p21
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- 8q24
- 10p11
- 13q14
- 19p13
- 21q21
- ITLN1

**2009 meta-analysis**
- PTPN22
- IL12B
- CDKAL1
- CCR6
- NKX2-3
- JAK2
- PTPN2
- ZNF365
- LRRK2/MUC19
- IRGM
- ORMDL3
- ZMIZ1
- MSH3
- MAP3K7IP1
- 19q13
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**2010 meta-analysis**
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- MAP3K7IP1
- 19q13
- IL27
- ZMIZ1
- CARD9
- IL10
- UBE2D1
- IFN3/ESRRB
- IL2RA

**Individual GWAS/candidate gene**
- 5q31
- NOD2
- LRRK2/MUC19
- TNFRSF6B
- TNFSF11
- MTMR3
- THADA
- DNMT3A
- GCKR
- IL10
- UBE2D1
- IFN3/ESRRB
- IL2RA

**2010 meta-analysis**
- PTPN22
- IL12B
- CDKAL1
- CCR6
- NKX2-3
- JAK2
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TPMT activity

Common genetic polymorphism

- Trimodal distribution of TPMT activity
Immune Response Genes Predict Non-Response to Infliximab in UC

A human gut microbial gene catalogue established by metagenomic sequencing

Qin et al, Nature 2010
How will genetics help in IBD?

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Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor

Erik-Oliver Glocker, M.D., Daniel Kotlarz, M.D., Kaan Boztug, M.D., Fabian Michael Cortez, Ph.D., Alejandro A. Schiffer, Ph.D., Fatih Noyan, Ph.D., B.Sc., Cristina Mar, M.D., Harald F. Neurath, M.D., Harald F. Neurath, M.D., Sibylle C. Reh, M.D., Axel Schreiber, Ph.D., Boris Buchner, Ph.D., Ph.D., Ph.D.
42 year old pt, 1st surgery

Overall HR 0.36
Risk at 3 years 39.26
42 year old pt, different genetics
Same patient, now a current smoker

Overall HR 3.80
Risk at 3 years 100.00

Risk of Recurrence

Year from Present

Risk of specific recurrence: test

Personal Characteristics

Endoscopy
Input for clinical recurrence (Recurrence type = 1)
- Age at surgery
- Prior surgery
- Smoking
- Stage of endoscopic recurrence

Serologic Inputs
- ASCA

Genetic Inputs
- rs987686A
- rs844448A
- rs1014470A

Inputs for endoscopic recurrence (Recurrence type = 2)
- Sites of resection
- ASCA pos
- rs490242A

Cedars-Sinai
The environment matters too!

"It isn't pollution that's harming the environment. It's the impurities in our air and water that are doing it."
- George W. Bush

Genetic interactions with – Smoking
Bacteria
NSAIDs etc
"I can only regret that the aetiology of this condition remains in obscurity, but I trust that ere long further consideration will clear up the difficulty..."