Ulcerative colitis: GWAS to Translation

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Pediatrics, UCLA School of Medicine
What is the “best” treatment for ulcerative colitis?
Fistulae are produced... when blood accumulates in the nates near the anus, becomes putrid and spreads to the soft parts.

When you see any such formed, you must cut it open while still unripe, before it suppurates and bursts into the rectum...

But if already formed when you undertake the case, take a stalk of fresh garlic...
Further detail of ulcerative colitis

- “ulcerative colitis” defined as distinct from infectious dysentery and nervous diarrhea
  - Wilks (1859)
  - Electric sigmoidoscope for proper diagnosis

- Careful study of clinical features brought the recognition that ulcerative colitis was a unique disorder
  - Fenwick (1889), Dalziel (1913)

- Case classification at Royal Society of Medicine
  - Hawkins (1909) presented the characteristics of 300 cases collected throughout Great Britain
An Address
ON THE
NATURAL HISTORY OF ULCERATIVE COLITIS
AND ITS BEARING ON TREATMENT.*

By HERBERT P. HAWKINS, M.D., F.R.C.P.,
PHYSICIAN TO ST. THOMAS'S HOSPITAL.

The proved value of serum treatment in tropical bacillary
dysentery makes it important that the active bacterial
agents in ulcerative colitis should be known. It is the
very type of disease which should yield to serum or
vaccine treatment. The site of infection is localized,
there is no general infection, and the symptoms are mainly
local and exhaustive, though partly toxemic. If it is not
cured in an early stage, nothing remains as a rule but
such crude measures as colostomy and ileo-sigmoidostomy.
The necessity for bacterial treatment holds good, whether
the primary organism concerned should ultimately prove
to belong to the dysenteric, paratyphoid, coli or pyrogenic
group. Nothing can be done until the natural history of
the disease is understood.

The pedigree of the disease can be traced back for nearly
300 years. It was then called dysentery, or bloody flux.
In the seventeenth century epidemics were common in
this country. There were sometimes 4,000 deaths a year
from “bloody flux.” These epidemics usually occurred in
the fly season, but sporadic cases were met with also in
the spring and winter. In the eighteenth century, probably
through a safer disposal of excreta, epidemics
became less common. In the nineteenth century they
nearly disappeared in the open, except in Ireland, but
they persisted in certain institutions. Millbank Peni-
tentiary and various asylums being the chief offenders.

“dysentery,” and there should be no reversion to the
original name, unless and until it has been shown bacterio-
logically that this disease belongs to the dysenteric
group.

THE CLINICAL EVIDENCE.

This disease comes before us in varying guise, as a short
severe illness, and as a long illness continuous or inter-
mittent. To these three forms I think must be added a
simple non-necrotic diarrhoea, often the precursor of a
more severe attack. The difference between these various
forms is not a matter of symptoms and physical signs.
These are constant. The difference rests mainly on the
duration of illness and partly on the mode of onset, and—in
both these respects this disease presents greater variation
than does bacillary dysentery.

In considering a series of 85 cases (for about three-
fourths of which I am indebted to my colleagues at St.
Thomas’s Hospital) one question is kept in view—namely,
Are all these cases of the same nature, or are different
diseases mixed under one name?

If an answer to this question can be given it will allow
a definite though weak presumption, that an organism
known to be causal in one case is the cause of all the
others, and an attempt at appropriate treatment will
follow. At the same time, the subsidiary question may be
considered as to how far all or any of these cases resemble
or differ from the bacillary dysentery of tropical countries.
In all these 85 cases the disease was acquired in this
country.

A.—The Acute Continuous Disease.

Among these 85 cases (of whom 41 died and 44 survived)
we find instances both among the deaths and the sur-
vivals which, to my mind, so far as symptoms go, are
identical with bacillary dysentery. I think, if the follow-
ing cases occurred in a tropical country, no one would
think twice about the diagnosis.
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The proved value of dysentery may be due to theloser type of vaccine treatment. There is no general local and exhaustive study in an extensive survey such crude measures. The necessity is to the primary or to belong to the group. Nothing else is the disease is un

The pedigree of dysentery is 300 years. It was known in the seventeenth century, from bloody flux of the fly season, the spring and summer through the summer became less common and the autumn nearly disappeared. They persisted for most of the year and vanished during the summer.

THE CLINICAL EVIDENCE.
This disease comes before us in varying guise, as a short severe illness, and as a long illness continuous or intermittent. To these three forms I think must be added a simple non-necrotic diarrhoea, often the precursor of a more severe attack. The difference between these various forms is not a matter of symptoms and physical signs. These are constant. The difference rests mainly on the duration of illness and partly on the mode of onset, and in both these respects this disease presents greater variation than does bacillary dysentery.

In considering a series of 85 cases (for about three-fourths of which I am indebted to my colleagues at St. Thomas's Hospital) one question is kept in view—namely, Are all these cases of the same nature, or are different diseases mixed under one name?
Ulcerative Colitis Patients Differ In:

- Amount of inflammation of the lining of the colon
Ulcerative Colitis Patients Differ In:

- Amount of inflammation
- Length of colon affected
Current Pathophysiology

- **Genetic susceptibility of patient**
  - Mouse models with various genes “knocked-out” demonstrate that many genes are possible candidate genes for ulcerative colitis

- **Gut microflora**
  - Gut inflammation does not occur when mouse models of UC are raised in a germ-free environment

- **Dysregulated immune response**
  - Transfer of various combinations of inflammatory and regulatory T cells increase or decrease intestinal inflammation in mouse models
Current Treatment

- Aminosalicylates
  - Mild to moderate inflammation
- Corticosteroids
  - Moderate to severe inflammation
  - Non-responders to aminosalicylates
- Immunomodulators
  - Severe inflammation
  - Can take 6 months for full benefit
- Surgery (25-40% of patients)
Current Genetics

- 1963 reports of ulcerative colitis in families begin (groups led by Kirsner, Binder & McConnell)
- 1979 Association with Turner’s syndrome
- 1993 mouse knock-out models of UC
- 1993 association of MHC class II alleles with UC and ANCA auto-antibody (group led by Rotter)
- 2000 association of HLA-DRB1*1502 & UC
  - Molecular mapping of MHC class II
  - (Trachtenberg & Rotter)
genome wide association study of ulcerative colitis

Meta-analysis of 3 GWAS
# Subjects

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<th>Cohort</th>
<th>Population</th>
<th>UC cases</th>
<th>Controls</th>
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# replication

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<td>Total</td>
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<td>2009</td>
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Methods

• Genotyping performed by individual groups using Illumina technology
• 266,047 SNPs were common across studies
• Population correction conducted within each study using principal components
• Meta-analysis across all three studies by combining z-scores
• Replication genotyping by Sequenom technology (Broad Institute)
More significant SNPs were observed than would be expected if results were random

<table>
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<tr>
<th>P value</th>
<th>Number of snps observed</th>
<th>Excess over expected if random</th>
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<td>0.00001</td>
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<td>126</td>
<td>~5-times</td>
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<td>0.001</td>
<td>511</td>
<td>~2-times</td>
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Q-Q Plot of Observed v Expected $p$-values

genomic inflation

$= 1.036$
Major Findings I

- RNF186, OTUD3, PLA2G2E
- MHC region, BTNL2
- IFNG
- IL23R
Association with class II region of MHC
## Major Findings II

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<td>IFNG, IL26</td>
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<td>$2.7 \times 10^{-3}$</td>
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<td>rs2836878</td>
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<td>21</td>
<td>near PSMG1</td>
<td>$1.4 \times 10^{-08}$</td>
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Major Findings III

• Previously associated with UC (8)
  – IL23R, MHC, MST1, CARD9, 1q32 (near IL10), 1p36 (RNF186-OTUD3-PLA2G2E), DLD-LAMB1, 12q15 (near IFNG), 21q22

• Newly confirmed loci (4)
  – 1q21 (FCGR2A-FCGR2C), 2p16 (REL-PUS10), 5p15 (near CEP72), 17q12 (OTMDL3)

• At least 30 risk factors for UC identified that explain 10% of total variance
Gene-Gene Interaction

• Gene-gene interaction of associated loci (496 total pairs examined) demonstrated an interaction between CARD9 and REL-PUS10 SNPs
### Biology: Pathways

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<th>Gene</th>
<th>Function</th>
<th>Description</th>
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<tr>
<td>PLA2G2E</td>
<td>PhospholipaseA2 group 2e</td>
<td>Production of pro-inflammatory lipids upon endotoxin challenge</td>
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<tr>
<td>IL23R</td>
<td>IL 23 receptor</td>
<td>Differentiation of TH17 cells, also CD gene</td>
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<tr>
<td>FCGR2A/C</td>
<td>FcG receptor</td>
<td>Transport of antigen-IgG complexes in response to gut bacteria</td>
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<tr>
<td>CARD9</td>
<td>Caspase recruitment domain 9</td>
<td>Adaptor molecule required for response to pathogens, including fungi</td>
</tr>
</tbody>
</table>

✔ Focus on interaction of gut with bacteria
Biology: Mechanism

• Alteration in epithelial barrier
• Innate immunity
  – ER stress pathway
  – Response to gut microbes
  – Production of reactive oxygen species
  – NF-κB activation
• Regulation of adaptive immunity
What is the “best” treatment for ulcerative colitis?
Will SNP data help us to find better therapies?
Many ulcerative colitis patients are refractive to medical therapy—_inflammation cannot be controlled by “mild” therapies (aminosalicylates) nor “stronger” therapies (IV corticosteroids, cyclosporin, or anti-TNF biologics).

Why should we identify patients at risk of medically refractive ulcerative colitis (MR-UC)?

“Stronger” therapies would be attempted more quickly

Shorter time to surgery

Reduction in patient suffering
Treatment

- Aminosalicylates
  - Mild to moderate inflammation
- Corticosteroids
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- Immunomodulators
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AIMS

- GWAS comparing medically responsive & medically refractive UC patients
  - UC requiring colectomy for symptoms uncontrolled by medical therapy
- Identify SNPs that predict UC patients that did not respond to medical therapies
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## Subjects—Demographics

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>Responsive UC (n=537)</th>
<th>Refractive UC (n=324)</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Sex (F%)</td>
<td>47%</td>
<td>47%</td>
<td>0.89</td>
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<tr>
<td>Median Age of UC Onset</td>
<td>26</td>
<td>27</td>
<td>0.93</td>
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<tr>
<td>Extraintestinal Manifestations</td>
<td>19%</td>
<td>15%</td>
<td>0.16</td>
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<tr>
<td>Smokers</td>
<td>8%</td>
<td>6%</td>
<td>0.24</td>
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<tr>
<td>Median Disease Duration</td>
<td>95</td>
<td>48</td>
<td>7.4x10^{-9}</td>
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<tr>
<td>Extensive Disease (%)</td>
<td>64%</td>
<td>80%</td>
<td>2.7x10^{-6}</td>
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<tr>
<td>Family History of UC (%)</td>
<td>15%</td>
<td>24%</td>
<td>0.004</td>
</tr>
</tbody>
</table>
UC GWAS

- **Genotyping Data**
  - All samples genotyped with Illumina CNV370K chip
  - Samples with high rate of genotyping retained (>98%)
  - 313,720 SNPs passed quality control
    - MAF >3%; HWE ≤ 0.001; SNP failure rate <10%
    - No differences in SNP missing data between cases and controls
  - Principal component analysis used to adjust for population stratification (Eigenstrat)
  - Association tested with Logistic Regression corrected for 20 principal components (PLINK, R)
Principal Components Analysis

MR-UC Non-MR-UC

"Caucasian Axis"
MR-UC vs. Non-MR-UC: Manhattan plot
MR-UC vs. Non-IBD: Manhattan plot

-\log_{10}(P-value)

Chromosome

MHC

TNFSF15
Chromosome 6p of MHC Region
Chromosome 9q within TL1A/ TNFSF15 region
AIMS

- GWAS comparing medically responsive & medically refractive UC patients
- UC requiring colectomy for symptoms uncontrolled by medical therapy
- Identify SNPs that predict UC patients that did not respond to medical therapies
Analysis Plan – SNP Combinations

- Each SNP was independently analyzed
- **Contribution of top SNPs** to MR-UC was tested using forward logistic regression and Cox proportional hazards on time-to-surgery data (R)

MR-UC vs. Non-MR-UC
(n=324) (n=537) → Top 100 SNPs
(p < 3x10^{-4})
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MR-UC vs. Non-MR-UC
(n=324)  (n=537)
Top 100 SNPs (p < 3x10^-4) → 37 SNPs

MR-UC (<60 mo) vs. Non-MR-UC
(n=187)  (n=328)
Top 65 SNPs (p < 1x10^-4) → 9 SNPs
Each SNP was independently analyzed

**Contribution of top SNPs** to MR-UC was tested using forward logistic regression and Cox proportional hazards on time-to-surgery data (R)

MR-UC vs. Non-MR-UC

(n=324)  (n=537)

Top 100 SNPs

(p < 3x10^{-4})

37 SNPs

+ 

MR-UC (<60 mo) vs. Non-MR-UC

(n=187)  (n=328)

Top 65 SNPs

(p < 1x10^{-4})

9 SNPs

46 SNPs explaining 47.6% of risk for MR-UC (p-value $\text{Cox} < 10^{-16}$)
### 46 Risk SNPs in Model

<table>
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<th>SNP</th>
<th>Position</th>
<th>Loci *</th>
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<td>19</td>
<td>rs2967682</td>
<td>8644532</td>
<td>MYO1F</td>
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<td>19</td>
<td>rs2293683</td>
<td>12900284</td>
<td>CALR</td>
</tr>
<tr>
<td>20</td>
<td>rs6034134</td>
<td>15182479</td>
<td>MACROD2</td>
</tr>
<tr>
<td>20</td>
<td>rs10485594</td>
<td>19772393</td>
<td>RIN2</td>
</tr>
<tr>
<td>20</td>
<td>rs6059104</td>
<td>31185354</td>
<td>PLUNC</td>
</tr>
<tr>
<td>21</td>
<td>rs2831462</td>
<td>28370367</td>
<td>21q21.3</td>
</tr>
</tbody>
</table>
**Risk Score as Count of Risk Alleles**

- Score is the total number of risk alleles (each of the 46 SNPs may contribute 0, 1, or 2).
- Range of Observed Risk Score 28-60 (Possible Range 0-92).
- Higher scores associated with MR-UC.

<table>
<thead>
<tr>
<th>SCORE</th>
<th>28-38</th>
<th>39-45</th>
<th>46-52</th>
<th>53-60</th>
</tr>
</thead>
<tbody>
<tr>
<td>NON-MR-UC</td>
<td>108</td>
<td>309</td>
<td>69</td>
<td>0</td>
</tr>
<tr>
<td>MR-UC</td>
<td>1</td>
<td>64</td>
<td>199</td>
<td>50</td>
</tr>
</tbody>
</table>
Higher Risk Score Associated with MR-UC

p-value \text{ Chi-squared test for trend} < 10^{-16}

<table>
<thead>
<tr>
<th>Risk Score Categories</th>
<th>Non-MR-UC</th>
<th>MR-UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39-45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46-52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53-60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proportion (%)
Sensitivity & Specificity of Risk Score Model Following 10-fold Cross-Validation

Sensitivity/ Specificity (cut-off=0.5)
Original Data with logistic regression

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.793</td>
<td>0.858</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>0.858</td>
<td>0.793</td>
<td></td>
</tr>
</tbody>
</table>

1000 times of 10 fold Cross-Validation data sets with logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>1000</td>
<td>0.789</td>
<td>0.0067</td>
<td>0.758</td>
<td>0.793</td>
</tr>
<tr>
<td>Specificity</td>
<td>1000</td>
<td>0.859</td>
<td>0.0021</td>
<td>0.858</td>
<td>0.870</td>
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</tbody>
</table>
# Hazard Ratio Following Bootstrapping

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>Original Data</th>
<th>1000 fold Bootstrapping</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.313</td>
<td>1.314</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>1.314</td>
<td>0.017</td>
<td>1.269</td>
<td>1.372</td>
</tr>
</tbody>
</table>
Area under curve (AUC)

Receiver operating characteristic analysis (ROC; signal to noise)

AUC=0.91
Higher Score → Earlier Progression to Colectomy

Cumulative Probability of Avoiding Colectomy (MR-UC)

Time to Surgery (months)

28-38; n=109
39-45; n=373
46-52; n=268
53-60; n=50
Clinical Application: Risk Allele Score Predicts Earlier Progression to Colectomy

Cumulative Probability of Avoiding Colectomy (MR-UC)

Time to Surgery (months)

- 28-38; n=109
- 39-45; n=373
- 46-52; n=268
- 53-60; n=50
Clinical Application: Risk Allele Score Predicts Earlier Progression to Colectomy

Cumulative Probability of Avoiding Colectomy (MR-UC)

- 28-38; n=109
- 39-45; n=373
- 46-52; n=268
- 53-60; n=50

Time to Surgery (months)

- 0% (24 months)
- 8.3% (39-45 months)
- 48.4% (46-52 months)
- 84% (53-60 months)
# Potential Therapeutic Targets

<table>
<thead>
<tr>
<th>Chr</th>
<th>SNP</th>
<th>Loci</th>
<th>Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>rs17207986</td>
<td>TNXB</td>
<td>Extracellular adhesion</td>
</tr>
<tr>
<td>6</td>
<td>rs3734263</td>
<td>UHRF1BP1</td>
<td>T-cell death</td>
</tr>
<tr>
<td>6</td>
<td>rs9470224</td>
<td>MAPK13,14</td>
<td>TCR &amp; TLR signaling pathway</td>
</tr>
<tr>
<td>9</td>
<td>rs11554257</td>
<td>TNFSF15</td>
<td>Th1-Th2-Th17 activation</td>
</tr>
<tr>
<td>12</td>
<td>rs1144720</td>
<td>BICD1</td>
<td>Chlamydia inclusions; Antigen processing</td>
</tr>
<tr>
<td>17</td>
<td>rs11891</td>
<td>CANT1</td>
<td>Signal transduction</td>
</tr>
<tr>
<td>19</td>
<td>rs11085825</td>
<td>DNASE2</td>
<td>Lysosomal function</td>
</tr>
<tr>
<td></td>
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<td>CALR</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>rs4808408</td>
<td>CYP4F2</td>
<td>Leukotriene pathway</td>
</tr>
<tr>
<td>20</td>
<td>rs6039206</td>
<td>PLCB1</td>
<td>Signal transduction</td>
</tr>
<tr>
<td>20</td>
<td>rs6059101</td>
<td>C20orf186</td>
<td>Antimicrobial peptide cluster</td>
</tr>
</tbody>
</table>
Potential Therapeutic Targets: Genes from MR-UC analyses

Epithelial cell

BICD1
DNASE2
C20orf186

Innate/Myeloid

TNFSF15

T cell

UHRF1BPI   TNFSF15
MAPK13, 14  CANT1
CALR        PLCB1

T cell activation

Cytokine signaling

TNFSF15
Conclusions

- GWAS on 861 UC patients confirmed major contribution of MHC region to UC severity
- SNPs identified by GWAS may together explain a large proportion of risk
  - 46 SNPs ~48% risk of MR-UC requiring colectomy
  - Each SNP made a small contribution (OR 1.2-1.9)
- Combination of risk alleles may be useful to predict medically refractive UC
- Identified interesting pathways for further investigation of potential new therapeutic targets in MR-UC
Will SNP data help us to find better therapies?
Will SNP data help us to find better therapies?

YES
What is the “best” treatment for ulcerative colitis?
What is the “best” treatment for ulcerative colitis?

“Skip” to more aggressive therapies with higher SNP scores.