What is IBD and Why Me?

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Inflammatory Bowel Disease (IBD): Two diseases of chronic inflammation of the intestinal tract

Ulcerative Colitis (UC):
Chronic, continuous inflammation of the inside lining (mucosa) of the colon

Crohn’s disease (CD)
Chronic, inflammation involving all layers of the gut: most commonly ileum and/or colon
ULCERATIVE COLITIS (UC)

- Chronic, lifelong disease though can be stopped by colectomy
- Affects about 2/1000 Americans (~600,000 total)
- Onset at all ages
- Males = Females
- Increased in people of European Jewish ancestry

Inflammation of the inside lining (mucosa) of the colon
UC – Endoscopic Spectrum

Normal

Mild

Adapted from AGA Clinical Teaching Project: IBD. 3rd ed. 2002
Crohn’s Disease (CD)

- Chronic, lifelong disease tends to recur after surgery
- Affects about 2/1000 Americans (~600,000 total)
- Onset at all ages
- Females > Males
- Increased in people of European Jewish ancestry
- African Americans more Crohn’s than UC

Inflammation of the all layers of primarily ileum and/or colon
Crohn’s – Endoscopic Appearance

Discrete “punched out” aphthae

Longitudinal ulcer

Adapted from AGA Clinical Teaching Project: IBD. 3rd ed. 2002
Extraintestinal Manifestations/Complications:
Present in 20% of IBD, More frequent in colonic IBD
May be presenting manifestation of IBD

- **EYE**
  - Episcleritis
  - Uveitis

- **JOINTS**
  - Peripheral arthritis
  - Sacroileitis

- **SKIN**
  - Erythema nodosum
  - Pyoderma gangrenosum
  - Cutaneous Crohn’s (granulomas usually found)

- **BILE DUCTS**
  - Primary sclerosing cholangitis (related disease entity – colitis in 80%)
Inflammation Outside of the Intestine
Often Occurs (in 20%) in Inflammatory Bowel Disease
Why does IBD occur?

“as a Crohn’s sufferer . . . I am intimately acquainted with that question your brain never stops asking:

“Why do I have this disease and what caused it?”

Recent post from web site
http://www.veganreader.com
“But Doctor, didn’t I get Crohn’s ileitis because of . . .”

- **Diet?**
  - Animal protein, sugar, food additives?
- **An overly clean environment?**
  - Grew up poor, worked in a creamery, Panama canal zone, etc
- **Appendicitis?**
  - age 33 for chronic catarral appendicitis"
- **Smoking?**
  - 4 PPD till age 59
- **Risk genes?**
  - Perhaps many common genes!

Dwight D. Eisenhower, grew up poor, worked in a creamery, lived in Panama canal zone and Philippines, Crohn’s diagnosis and surgery age 66
Why do people get Crohn’s disease? Genes and Environment!

Familial Clustering of IBD

IBD most frequent in Western Industrialized Countries

- General Population
- Sibling
- Fraternal Twin
- ID Twin UC
- ID Twin Crohn

Risk of IBD

Map showing regions with high, intermediate, and low IBD frequencies.
Genetic Discoveries in IBD:
90 regions (Loci) on chromosomes 1 – 22 containing IBD disease associated variations identified

- 35 genes /gene groups identified for these loci, remainder under investigation.
- Only NOD2 alone, in the recessive state, has appreciable risk of disease - inheriting an abnormal gene from both parents leads to 5% risk of Crohn’s
- Five others have 2 to 4 times risk of CD, UC or IBD (0.6% to 1.2%)
- The remainder have a minute increase risk alone
- However, the gene variations are very common (i.e. even most healthy people carry the major IL23R and ATG16L1 risk variants)
- People with IBD carry more disease gene variants than people without IBD
Genetic Loci common to Crohn & UC
25% shared by other Autoimmune Diseases

CD 71

IBD 30

UC 49

Other AI diseases
(RA, MS, Ps, lupus, Thyroid, ASp, etc.)
over 100 loci, 20+ found in IBD

No loci found on sex chromosomes yet (X)
Genetic Research in IBD

Disease Variations: Common, Major Pathways Illuminated

Autophagy, Innate Immunity

NOD2 & ATG16L1

Crohn’s Specific Pathway

Additional Genetic Associated Components:

- TNFSF15
- IL12B
- TYK2
- JAK2
- STAT3
- NKX2-3
- CCR6

Crohn’s Controls

<table>
<thead>
<tr>
<th>Component</th>
<th>Crohn’s (%)</th>
<th>Controls (%)</th>
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<tbody>
<tr>
<td>NOD2</td>
<td>40%</td>
<td>15%</td>
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<tr>
<td>ATG16L1</td>
<td>72%</td>
<td>63%</td>
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<tr>
<td>IL23R</td>
<td>96%</td>
<td>86%</td>
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</table>

Genetic Research in IBD

Innate immune components (NOD2, ATG16L1, IRGM) specifically associated to CD

General immune pathway associated with CD, UC, MS, psoriasis
### Biological pathways or gene families implicated by GWAS

#### CD
**Innate Immunity/Autophagy**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Chromosome</th>
<th>Gene of Interest</th>
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<tbody>
<tr>
<td>CD</td>
<td>2q37</td>
<td>ATG16L1</td>
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<tr>
<td>CD</td>
<td>5q33</td>
<td>IRGM</td>
</tr>
<tr>
<td>CD</td>
<td>16q12</td>
<td>NOD2</td>
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#### IL23/Th17 Pathway

<table>
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<tr>
<td>CD, UC</td>
<td>1p31</td>
<td>IL23R</td>
</tr>
<tr>
<td>CD</td>
<td>1p31</td>
<td>IL23R</td>
</tr>
<tr>
<td>CD</td>
<td>1q32</td>
<td>IL10, IL19, IL20</td>
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</table>

#### CD and UC
**Cytokines and Cytokine Receptors**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Chromosome</th>
<th>Gene of Interest</th>
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</thead>
<tbody>
<tr>
<td>CD, UC</td>
<td>1p36</td>
<td>TNFRSF9</td>
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#### UC
**Mucosal Barrier Function**

<table>
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<tr>
<th>Phenotype</th>
<th>Chromosome</th>
<th>Gene of Interest</th>
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<tr>
<td>UC</td>
<td>7p22</td>
<td>GNA12</td>
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<tr>
<td>UC</td>
<td>7q22</td>
<td>LAMB1</td>
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<tr>
<td>UC</td>
<td>16q22</td>
<td>CDH3</td>
</tr>
<tr>
<td>UC</td>
<td>20q13</td>
<td>HNF4A</td>
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#### Transcriptional Regulation

<table>
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<th>Phenotype</th>
<th>Chromosome</th>
<th>Gene of Interest</th>
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<tbody>
<tr>
<td>CD, UC</td>
<td>2p16</td>
<td>REL</td>
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<tr>
<td>CD</td>
<td>6q15</td>
<td>IRF1</td>
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<tr>
<td>CD, UC</td>
<td>6q21</td>
<td>PDAM1</td>
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<tr>
<td>CD, UC</td>
<td>7p21</td>
<td>IRF5</td>
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<td>CD, UC</td>
<td>10p14</td>
<td>HREM</td>
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<td>CD, UC</td>
<td>10q24</td>
<td>NKKX2-3</td>
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<tr>
<td>CD</td>
<td>15q22</td>
<td>SMAD3</td>
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**Regulatory proteins for Inflammation**

- Fight against bacteria
- Sustained/Persistent Inflammation
- Inflammatory Signaling molecules and cell receptors
- Protect the colon lining
- Controls Levels of Expression of Inflammation Genes
Evidence for Major Environmental Effects:
“Modernization” IBD has been steadily increasing over time

Irvine et al., Scand J Gastro, 2001
Environmental Effect: Moving to Western Country Increases Risk of IBD
Environmental Effect: Moving to Western Country Increases Risk of IBD
Moving to more temperate climate may decrease risk
But what is it about Westernization and higher latitudes that lead to greater IBD?

• Westernized Diet?
  – Higher intake of animal protein associated 3-fold risk\(^1\)

• Hygiene Effect?
  – Crohn’s protected by Vietnam service and POW status\(^2\)
  – Helminths can protect in animal models, can decrease TH1, TH2 and TH17 response and have been used successfully in clinical trials\(^3\)

• Refrigeration (cold chain hypothesis)?

• Lack of vitamin D (Less at higher latitudes, modernization)

• Cars /Pollution /Lack of exercise / - anything that correlates !

\(^1\)Jantchou et al., Am J Gastro 2010
\(^2\)Delco and Sonnenberg, Am J Gastro 1998
\(^3\)Weinstock and Elliot, IBD Journal, 2008
Delco and Sonnenberg, 1998
Vietnam service and POW status strongly associated with Protection from IBD risk: Vietnam 0.84 risk; POW 0.60 risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>Wald’s $\chi^2$</th>
<th>p Value</th>
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<tbody>
<tr>
<td><strong>Crohn’s disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age*</td>
<td>0.85</td>
<td>0.83–0.87</td>
<td>229.48</td>
<td>0.0001</td>
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<tr>
<td>Gender</td>
<td>0.70</td>
<td>0.61–0.81</td>
<td>22.77</td>
<td>0.0001</td>
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<tr>
<td>Ethnicity</td>
<td>2.46</td>
<td>2.27–2.68</td>
<td>444.42</td>
<td>0.0001</td>
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<tr>
<td>Prisoner of war</td>
<td>0.60</td>
<td>0.41–0.87</td>
<td>7.14</td>
<td>0.0075</td>
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<td>Service in Vietnam</td>
<td>0.84</td>
<td>0.75–0.96</td>
<td>7.15</td>
<td>0.0075</td>
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<td>Exposure to Agent Orange</td>
<td>1.04</td>
<td>0.88–1.22</td>
<td>0.20</td>
<td>0.6568</td>
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<tr>
<td><strong>Ulcerative colitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age*</td>
<td>1.05</td>
<td>1.03–1.07</td>
<td>24.40</td>
<td>0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td>0.83</td>
<td>0.71–0.96</td>
<td>5.86</td>
<td>0.0155</td>
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<tr>
<td>Ethnicity</td>
<td>2.11</td>
<td>1.95–2.27</td>
<td>375.65</td>
<td>0.0001</td>
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<tr>
<td>Prisoner of war</td>
<td>0.92</td>
<td>0.71–1.18</td>
<td>0.43</td>
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<td>Service in Vietnam</td>
<td>0.91</td>
<td>0.81–1.03</td>
<td>2.42</td>
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<td>Exposure to Agent Orange</td>
<td>0.99</td>
<td>0.85–1.17</td>
<td>0.00</td>
<td>0.9443</td>
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</tbody>
</table>

* Odds ratios and confidence intervals refer to a time period of 10 yr.

Suggestion that parasite exposure reduces risk of Crohn’s disease
Pig whipworm found to be efficacious in treatment of IBD
Against hygiene hypothesis:

- Well water and unpasteurized cheese risks for familial IBD in Belgium
  
- Salmonella infection increase IBD risk 1.9 fold (1.4- 2.6) in Denmark over 15 years (excluding 1\textsuperscript{st} year)

- Tuberculosis in Cape Town, SA in 4.7\% of IBD patients, equal to or even greater than expected

Perhaps IBD needs an “infectious” trigger?

\textsuperscript{1}Van Kruiningen et al. Inflamm Bowel Dis, 2005 and J Clin Gastro 2007
\textsuperscript{2} Gradel et al., Gastroenterology 2009
\textsuperscript{3} E Deetlefs, G Watermeyer, R Seggie, D Epstein SAGES 2009
Conclusions: Why Does IBD Occur

- **ACCEPTED:**
  - DNA variations result in changes in gene function increasing risk of IBD
  - Westernization / Modernization increases risk of IBD
  - Smoking increases risk of Crohn’s disease, Decreases Risk of ulcerative colitis
  - Intestinal Bacteria appears important, especially for Crohn’s disease

Remains to be determined:

- Loss of protection from parasites that were part of all human existence until 1900s
- Infectious triggers
- High animal protein diet and refined sugars
- NSAIDs and oral contraceptives
The Ultimate Goal: IBD Prevention

- Gene Variations Defined for sporadic and familial IBD
- Avoidance of Risk Factors for those genetically at risk for IBD
- “Vaccinations” or addition of “Protective Factors” for those genetically at risk