Is genetic testing useful in the management of IBD now?

Anne Griffiths MD, FRCPC
SickKids Hospital, University of Toronto
Buenos Aires, August 15, 2014
Short answer

- Not very useful!
• Recognition of single gene disorders: Phenocopies of complex IBD

• Consider roles of genetic testing in management of complex IBD
What causes inflammatory bowel disease?

[Diagram showing the interactions between Luminal microbial antigens and adjuvants, Immune response, Environmental triggers, and Genetic susceptibility, which all contribute to IBD.]
Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease

UC and CD: Many shared genes

Total Number of Genes 162

Jostins L et al, Nature 2012
Potential benefits of identifying susceptibility genes

- Elucidate pathogenesis, help us understand cause why IBD develops
- Direct the development of new therapies
- Lead to an understanding of the genetic basis of clinical diversity…why is there so much variation within IBD?
- Enable prognostication and personalized therapy guided by genotype
Nucleotide binding oligomerization domain (NOD)2 or CARD15: intracellular bacterial sensor

LRR = leucine rich repeats

Muramyl Dipeptide

-3 major variants associated with CD
-25-30% Caucasian CD patients carry at least one variant
-(7% controls; 6% UC patients)
First Lesson from Crohn disease genetics: Innate Versus Adaptive Immunity

- Innate
  - inflammatory cytokines / chemokines
  - co-stimulatory molecules
  - cytokines to enhance phagocytosis

First line of defense, rapidly activated

- Adaptive

Diagram:
- Innate
- Adaptive
- Cytokines to enhance phagocytosis

Arrows indicate interaction between innate and adaptive immunity.
Many influential genes....but what and how microbes?

The question for the current era of research
Knowledge of genetic risk variants for disease

Specific risk variants for disease subphenotypes
"Personalized medicine"

Understanding of biological pathways of disease

Prediction of disease in general population

Adapting medical therapy to the individual patient

Development of targeted therapies

From Festen and Weersma, Best Pract Res Clin Gastro 2014
Outline

- Recognition of single gene disorders: Phenocopies of complex IBD
- Consider roles of genetic testing in management of complex IBD
Incidence of IBD in children globally

Benchimol E and Griffiths A, Inflamm Bowel Dis 2010
## Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: evidence from health administrative data

E I Benchimol, A Guttmann, A M Griffiths, L Rabeneck, D R Mack, H Brill, J Howard, J Guan and T To

<table>
<thead>
<tr>
<th>AGE (years)</th>
<th>Change in Incidence Rate</th>
<th>95% CI</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>+5.0% / year</td>
<td>0.5% - 10.5%</td>
<td>0.032</td>
</tr>
<tr>
<td>5-9</td>
<td>+7.6% / year</td>
<td>4.4% - 10.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>10-14</td>
<td>+0.63% / year</td>
<td>-0.9% - 2%</td>
<td>0.407</td>
</tr>
<tr>
<td>15-17</td>
<td>-0.21% / year</td>
<td>-1.3% - 0.9%</td>
<td>0.72</td>
</tr>
</tbody>
</table>

* By Poisson regression analysis, controlling for sex

Gut 2009; 48: 1490-1497
Continuing increasing incidence of paediatric IBD in Ontario: 1994-2009 data

Benchimol E, Guttman A, Mack D et al
NASPGHAN meeting 2013
Is IBD becoming more of a Paediatric Disease?

Shift in Incidence to Pediatric Age Group

Onset of monogenic diseases

Modified from Holm, Gut, 2013
Other Rare genetic syndromes where Crohn-like IBD develops: “phenocopies”

- Variants of Chronic Granulomatous Disease
  - Sylvester F, Can J Gastroenterol 1996

- Glycogen storage disease Ib
  - Couper RM et al, Gastroenterology 1991
Known chronic granulomatous disease genes lead to Crohn’s-like IBD

Table 2  Phagocyte NADPH oxidase defects
Data are from a registry of 368 patients with CGD [44].

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>gp91phox</td>
<td>CYBB</td>
<td>Xp21.1</td>
<td>76%</td>
</tr>
<tr>
<td>p22phox</td>
<td>CYBA</td>
<td>16p24</td>
<td>3%</td>
</tr>
<tr>
<td>p47phox</td>
<td>NCF1</td>
<td>7q11.23</td>
<td>18%</td>
</tr>
<tr>
<td>p67phox</td>
<td>NCF2</td>
<td>1q25</td>
<td>4%</td>
</tr>
<tr>
<td>Rac2</td>
<td>RAC2</td>
<td>22q13.1</td>
<td>Unknown</td>
</tr>
</tbody>
</table>


Phagocytes are unable to kill certain bacteria and fungi as a result of reduced production of superoxide and hydrogen peroxide.
Not all “IBD” is complex: identification of single gene disorders of immunedysregulation in infantile-onset colitis

Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor

Erik-Oliver Glock, M.D., Daniel Kotlarz, M.D., Kaan Boztug, M.D., E. Michael Gertz, Ph.D., Alejandro A. Schäffer, Ph.D., Fatih Noyan, Ph.D., Mario Perro, M.Sc., Jana Diestelhorst, B.Sc., Anna Allroth, M.D., Dhaarini Murugan, M.Sc., Nadine Hätscher, B.Sc., Dietmar Pfeifer, M.D., Karl-Walter Sykora, M.D., Martin Sauer, M.D., Hans Kreipe, M.D., Martin Lacher, M.D., Rainer Nustede, M.D., Cristina Woellner, M.Sc., Ulrich Baumann, M.D., Ulrich Salzer, M.D., Sibylle Koletzko, M.D., Neil Shah, M.D., Anthony W. Segal, M.D., Axel Sauerbrey, M.D., Stephan Buderus, M.D., Scott B. Snapper, M.D., Ph.D., Bodo Grimbacher, M.D., and Christoph Klein, M.D., Ph.D.

Lancet 2010; 376: 1272 (interleukin-10 gene)
Old literature: infantile “Crohn’s disease”
SickKids, Toronto infant: Evolving picture from birth

- febrile episodes as neonate
- diarrhea...periodically with visible blood
- perianal skin tag
- subsequently arthritis
- rectovaginal fistula
- folliculitis
- frequent fevers; prolonged and frequent hospitalizations
Identification of a novel IL10Rα Mutation

Laboratory of Alex Muise, SickKids Hospital

Wild type

Exon5 | splice donor site | Intron5
---|---|---
T C T C C C T C A C C A G G C A G T G T G A G T C A G C T G G G C

Patient1

Putative cryptic splice donor site

Exon5 | Intron5
---|---

Figure 3. Identification of the IL10RA nucleotide 7761 +2 T>C mutation.
Interleukin 10 inhibits secretion of pro-inflammatory cytokines
IL10/R Deficiency

- 4 case series (some overlapping patients)
  - Kotlarz et al (Gastro, 2012) – 16/66 VEOIBD patients screened had IL10/R deficiency
  - Engelhardt et al (JACI, 2013; includes 1 NEOPICS patient) – 9/40 VEOIBD patients screened had IL10/R deficiency
  - GENIUS working group – Ruemmele (IBDJ, 2013) – 10 VEOIBD patients
  - Neven et All (Blood, 2013) – 5 patients with B Cell Lymphoma

Total patients reported worldwide > 50
IL10R Pathway Lessons

- IL10/R deficiency should be considered in all infants with:
  - severe colitis, perianal disease, folliculitis, +/- joint disease
  - non-responsive to standard IBD therapy

- All patients so far (> 50) have had symptoms < 3 months of age

- Bone Marrow Transplant is definitive treatment if a IL10/IL10R mutation
NEOPICS – interNational Early Onset Pediatric IBD Cohort Study

Co-PI’s Aleixo Muise at SickKids, Scott Snapper at Boston Children’s and Christoph Klein at Children's Hospital Ludwig-Maximilians-University

Aleixo.muise@sickkids.ca
www.neopics.org
“The very young patient”

- Likelihood of “IBD” being single gene disorder (ie. “phenocopy” of complex IBD) is related to severity of phenotype in addition to age of onset

  - important to recognize!
Outline

- Single gene disorders: Phenocopies of complex IBD
- Role of genetics in management of complex IBD
What causes IBD? Does it Vary with Age?

Ruel…. Colombel, 2013
Most paediatric onset IBD shares susceptibility genes with adult onset IBD

- Genome-wide association study in exclusively paediatric onset IBD
  - International collaboration 2600 cases in total all Caucasian (Toronto SickKids ~600 cases)
  - Similar susceptibility genes to GWAS in exclusively adult IBD patients

Imielinski, Baldassano, Griffiths et al, Nature Genetics 2009
Relationship between IBD genetic burden and age at diagnosis of Crohn’s disease

Immunochip genetic data on 1105 patients

How MIGHT genetics be useful in IBD management?

Knowledge of genetic risk variants for disease

Specific risk variants for disease subphenotypes
"Personalized medicine"

Understanding of biological pathways of disease

Prediction of disease in general population

Adapting medical therapy to the individual patient

Development of targeted therapies

From Festen and Weersma, Best Pract Res Clin Gastro 2014
Understanding biologic pathways: Targeted drug development

- **IL-12B, IL-23R**: risk genes for IBD in IL23/TH17 pathway:….. Ustekinumab (anti-IL12/23 antibody) shown to have efficacy in CD

- **JAK2, STAT3, TYK2**: genes associated with IBD encode proteins involved in pro-inflammatory signaling….. Tofacitinib (a JAK kinase inhibitor) is in phase III trials in UC and CD
Personalized medicine: adapting therapy to the individual

Clinical Phenotypes

Ulcerative Colitis  Crohn Diseases
A SPECTRUM of related disorders

Can we predict clinical course and anticipated treatment responsiveness?
Clear phenotypic association of NOD2 with originally described type of Crohn’s disease: ILEITIS

Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. *JAMA* 1932;99:1323-1329
NOD2/CARD15 & phenotypic associations

- **Stricturing disease**
- **Ileal disease**

Abreu, *Gastroenterology* 2002; 123:679-88
Adler, Am J Gastro 2011; 106: 699-705
SNP13: Time to surgery in isolated ileal Crohn disease

- SNP 13 pos
  - 44% operated
  - Median 7.2 yrs

- SNP 13 neg
  - 39% operated
  - Median 6.8 yrs

Log Rank
  - p = 0.8

Sickkids, Toronto
NOD2 alleles as predictor of post-surgical recurrence

AUC = 0.638

Solon, Inflamm Bowel Dis 2013; 19: 1099-1105
To date.....lack of strong predictors of phenotype according to genetic burden

Immunochip genetic data on 1105 patients

Limitations of genotype-phenotype correlation studies to date

- > 160 IBD susceptibility loci or genes identified but accounting for only 20% of genetic risk
- Specific genes identified have small individual effect on genetic risk
- Loci identified.....susceptibility gene in the locus often not known
Personalized medicine: adapting therapy to the individual through pharmacogenomics

Dubinsky MC. Gastroenterology 2002;122:904-15

TPMT genotyping to guide thiopurine dosing
TPMT demonstrates a polymorphic distribution of activity

- Normal activity: 90%
- Very high activity: 1 in 300
- Zero activity: 1 in 10
- Intermediate activity: 1 in 10

Frequency (no. patients)

TPMT measurement allows customised strategy

- Normal dose
- Unsafe
- Alternative strategy?
- 33-50% of full dose

Personalized medicine: Prediction of disease in general population
Evidence for genetic susceptibility: Twin studies

How often are both twins affected when one is affected?....incomplete concordance

Crohn disease

monozygotic  44%

dizygotic  4%

Tysk et al, Gut 1988;29:990-996
Genetic Penetrance of NOD2

- IBD Genetics Consortium typed 1489 families (proband and parents) for NOD2/CARD15

- 79 parents homozygous for NOD2: 17 had CD (21.5%) (penetrance estimate applicable to first degree relatives)
Polymorphisms associated with IBD susceptibility are common.
Summary: Is genetic testing useful in management of IBD now?

- Not very

- Should be alert to patients with very early onset severe IBD: exclude single gene disorder
  - IL-10 and IL-10R genes
  - NADPH oxidase pathway genes
  - Referral for exome sequencing

- Personalized medicine for the majority of patients is still a future target…apart from some successes in pharmacogenomics

- Prognostic value of known genes is still very limited