GENETICS OF EARLY ONSET IBD IN YOUNG CHILDREN

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Disclosures

• Centocor
Genetic epidemiology of IBD

- 1 in 300 to 500 are affected by IBD in Caucasians from North America & Europe

<table>
<thead>
<tr>
<th>Study</th>
<th>Monozygotic</th>
<th>Dizygotic</th>
<th>Monozygotic</th>
<th>Dizygotic</th>
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</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>9/18 (50%)</td>
<td>1/26 (4%)</td>
<td>3/16 (19%)</td>
<td>0/20 (0%)</td>
</tr>
<tr>
<td>Britain</td>
<td>5/25 (20%)</td>
<td>3/46 (7%)</td>
<td>6/38 (16%)</td>
<td>1/34 (3%)</td>
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<tr>
<td>Denmark</td>
<td>5/10 (50%)</td>
<td>0/27 (0%)</td>
<td>3/21 (14%)</td>
<td>2/44 (5%)</td>
</tr>
</tbody>
</table>

CD >> UC

OBJECTIVES

- Why pediatric IBD genes? Are there any?
- Gene discovery efforts in pediatric IBD & progress to date
- Next steps
Why study pediatric IBD genes?

- Many GWAS and a subsequent meta-analysis in Crohn’s disease has determined that established 30+ loci only explain 20% of genetic risk in Crohn’s disease.

- 80% of genetic variation in Crohn’s disease is waiting to be discovered. It is important to study the heterogeneous phenotypes including early onset for more gene discoveries.
Studying early onset yielded novel risk variants in many complex diseases?

- specific genes that predisposes early onset
- Aided by enrichment of gene burden
  - Early onset form of Alzheimer’s
  - Huntington disease
    - Andrew et al. Nat Gen 1993:4;398-403
  - Myocardial infarction

Does it matter? pediatric or adult IBD genes?

- Pediatric onset IBD (both Crohn’s disease and ulcerative colitis) has unique phenotypic heterogeneity, responses to therapy and prognosis. The causal mechanisms behind these phenotypic differences are not clear.
  - Could different gene variants explain this?

- Characterizing DNA variation in early (pediatric onset) is critical – has implications for
  - Drug development / personalized medicine
  - Diagnostic testing
  - Risk stratification
Pediatric CD has unique characteristics in comparison to adult onset CD

**Pediatric**
- Colon involved
  - 80% at 8 yr of age
  - decreases with age
- Ileum involved
  - Rare at <8 yrs of age
- Positive FH in 30%
- Strictureing in 46%
- Surgery in 71%

**Adult**
- Colon only involved in <20%
- Ileum involved in 80%
- Positive FH in 14%
- Strictureing in 29%
- Surgery in 55%

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**Disease Location**
In Children & adults with UC

<table>
<thead>
<tr>
<th>Disease Location</th>
<th>Pediatric</th>
<th>Adult</th>
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</thead>
<tbody>
<tr>
<td>Distal</td>
<td>5-15%</td>
<td></td>
</tr>
<tr>
<td>Left-sided</td>
<td>10-35%</td>
<td></td>
</tr>
<tr>
<td>Pancolitis</td>
<td>65-90%</td>
<td></td>
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</table>

65-90% pancolitis in children compared to 30% in adults

Hyams et al, J Pediatrics 1996
Kugathasan et al, J Pediatrics 2003
Hendriksen C, Kreiner S, Binder V. Gut 1985;26:158-163
These important questions need answers

- Are there any pediatric (early onset) specific IBD genes?

- Are adult-identified IBD risk loci valid and with similar effect sizes in earlier onset IBD patients?

Pediatric vs. adult onset adequately powered comparison (or replications) studies are necessary
Essers J, et al. (IBD journal, 2009)

359 Pediatric CD under age 20
- Children’s Hospital Boston (CHB)
- Children’s Hospital of Wisconsin (CHW)

Sample Size
- 306 Trios
- 53 Singletons
- 312 Controls

Tests
- TDT
- 34 SNPs
- \(X^2\)

Output
- Combined Meta Z score and OR


15 Replicate in Early CD

<table>
<thead>
<tr>
<th>Chr</th>
<th>Genes of interest</th>
<th>SNP</th>
<th>Risk Allele</th>
<th>Meta Z</th>
<th>P</th>
<th>Odds Ratio</th>
<th>CI</th>
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<td>0.027</td>
<td>1.254</td>
<td>1.02,1.48</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*one-tailed p-value
# Barrett et al. 2008

Others did not replicate, because underpowered
We performed a large GWAS in exclusively pediatric IBD cases and controls

Early GWAS – 1011 pediatric onset IBD (725 CD, 261 UC)

– We identified and replicated significantly associated, previously unreported loci on chromosomes 20q13 and 21q22 located close to the TNFRSF6B and PSMG1 genes, respectively

– Gene discovery studies in childhood-onset disease have unveiled genetic factors that are less likely to surface in adult studies
Protein levels OF TNFRSF6B

- mRNA expression levels of *TNFRSF6B* are markedly elevated in IBD

Extended Pediatric GWAS in IBD

- Expanded to include Canadian, Scottish and more US samples
  - The largest GWAS to date in IBD
  - Exclusively pediatric 3426 IBD cases (all early onset) and 11,963 matched controls
More Novel Risk Variants are Identified in Pediatric Onset IBD

- Five additional novel IBD loci were identified that are genome-wide significant in CD
  - 16p11 near the cytokine gene IL27
  - loci in 22q12, 10q22, 2q37, 19q13.11

- UC with onset prior to 8 years of age
  - Toll like receptor gene cluster


More Novel Risk Variants are Identified in Pediatric Onset IBD
In addition…. 

- Replicated 21 of 30 previously reported IBD loci from an adult onset Crohn’s disease and 8 of 17 adult onset UC loci

Many more IBD Variants from all GWAS meta-analysis

- Pediatric and adult cohorts put together

International IBD consortium effort - Manuscript in preparation

Time line of confirmed IBD Loci / genes in children and adults with IBD

Year of gene discovery in chronological order
Summary & Conclusions for common variants

- Many genes/loci are common to adult onset and pediatric onset IBD highlighting the close pathogenetic relationship between early- and adult-onset IBD.

- Pediatric onset loci (may be pediatric onset specific) in IBD appears to exist, but not many.

- Joint analyses of GWAS data in young and older onset cohorts is mandatory to increase the power and identify more risk variants.

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Pediatric IBD and gene discoveries

- **Common variation of small effects**: Typically present but not typically identifiable.
- **Uncommon variation of large effect (Mendelian)**: Not typically present.
Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor


Rare variants / Mendelian

– two unrelated consanguineous families with children who have a severe, progressive, poorly treatable form of CD that occurs in the first year of life
– identified homozygous, recessive loss-of-function mutations in the interleukin-10 receptor genes, \textit{IL10RA} and \textit{IL10RB}
Defects in neutrophils NADPH oxidase and NCF4 gene mutation
Matute et al. BLOOD, 2009;111:3309-15

- 3 yr old with fevers, diarrhea, weight loss and abd pain
- History of eczema, sinusitis and croup
- Granulomatous colitis
- Defect in intracellular superoxide production during phagocytosis
- Gene Sequence – compound heterozygocity for frameshift mutation / missense R105Q in the PX domain of the NCF4 gene
- Parents / sibs are healthy heterozygous carriers
Genetic Pie of IBD

- Common variants of large effects: Identifiable by GWAS
- Common variants of small effects: Identifiable by Gene Sequencing and functional studies
- Uncommon variants of large effects: Non-Identifiable by today’s technology
- Uncommon variants of small effects: Non-Identifiable by today’s technology

Hypothetical match up with age of onset and IBD variants

- Age of Onset: 10, 20, Adult
- Common variants of small effects: OR 1.1 to 1.5
- Common variants of large effects: OR 1.5 to 4
- Uncommon variants of large effects: IL10R, NCF4
Gene discoveries may be informative in classifying disease phenotypes & behaviors in pediatric IBD

Therefore, incorporating CD and UC alleles into machine learning classification algorithms should be pursued

Speculations for future

Conclusions
common variants

- Established adult IBD risks are applicable to pediatric onset IBD. Joint meta-analysis is a priority.

- Early onset IBD risk loci more relevant to children exist at common variant levels.

- It is time to plan studies beyond GWAS in pediatric onset and adult onset IBD
  - functional studies
  - Methylation studies / markers
  - Gene-environmental interaction studies
Conclusions
Rare variants

- Early onset IBD cases offer the best opportunity to identify rare variants by sequencing and candidate gene approaches.

- It is possible these rare variants identified in very early onset can be applicable to ‘milder forms’ of adult onset IBD.

Does gene discovery mean anything to patients yet?
Gene discovery in early onset and IBD therapy; proof of principle

Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor

Acknowledgements

- International Pediatric IBD genetics efforts
  - Hakon Harkonarson, Bob Baldassano and many others
- Medical College of Wisconsin
  - Michael Stephens
- Emory
- CCFA