VEOIBD 2014

Very Early Onset Inflammatory Bowel Disease Symposium

The Hospital for Sick Children in Toronto
Thursday, October 16, 2014

Gene Discovery.

Functional Discoveries.

Novel Therapeutics.
The newly established IBD Centre at SickKids is one of the largest, busiest paediatric units in the world and provides primary clinical care for over 800 families and an estimated 2,000 annual clinic visits. Canada has among the highest incidence and prevalence rates for IBD. Most disturbingly, onset during childhood or adolescence is occurring increasingly frequently. The burden of illness imposed on these young patients and their families by ulcerative colitis and Crohn’s disease is considerable.

**Vision**
The Inflammatory Bowel Disease Centre’s vision is personalized treatment with optimal outcomes for every patient based on understanding of IBD pathogenesis

**Mission**
- To advance our understanding of the causes of IBD through focused clinical, translational, and basic research.
- To become world leaders in IBD clinical care, research and education

**Goals**
- Define the causes of IBD through state-of-the-art genetic and functional approaches.
- Develop personalized care for IBD patients based on better understanding of the genetic, immunologic, and microbial factors of IBD.
- Improve existing and emerging IBD therapies through collaboration with other specialties.
- Improve IBD clinical care in Canada and around the world through education and training.

**Leadership**
The IBD Centre is led by Co-Directors: Aleixo Muise (Translational Medicine), John Brumell (Basic Research), Anne Griffiths (Clinical Research), and Melody Hicks (Child Health Services Director, Ambulatory Care).
# AGENDA

## Very Early Onset Inflammatory Bowel Disease Symposium

**Thursday, October 16, 2014 at The Hospital for Sick Children**  
**Peter Gilgan Centre for Research & Learning (PGCRL)**  
**686 Bay Street, 3rd floor auditorium**

### MORNING

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>8:30 am</td>
<td><strong>Registration on the main floor. Refreshments in the Gallery on the 2nd floor</strong></td>
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<tr>
<td>9:30 am</td>
<td><strong>WELCOME &amp; INTRODUCTIONS</strong> by Dr. Peter Durie in the Auditorium</td>
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<tr>
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<td><strong>GENETICS OF IBD</strong></td>
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<td>9:45 am</td>
<td><strong>Overview of IBD Genetics: A look at Phenotype-Genotype Correlations</strong></td>
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<tr>
<td>10:45 am</td>
<td><strong>Insight into the Genetics of IBD: Lessons from Ashkenazi Jewish Crohn’s Disease</strong></td>
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<tr>
<td>11:15 am</td>
<td><strong>Break in the Gallery on the 2nd floor.</strong></td>
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<td><strong>WHAT IS VEOIBD?</strong></td>
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<tr>
<td>11:30 am</td>
<td><strong>Spectrum and Treatment Challenges in Complex IBD developing in the Very Young</strong></td>
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<tr>
<td>12:00 pm</td>
<td><strong>The Epidemiology and Burden of VEOIBD: Are Age of Onset and Outcomes Changing?</strong></td>
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<tr>
<td>12:15 pm</td>
<td><strong>Lunch served in the Gallery on the 2nd floor.</strong></td>
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**Dermot McGovern, MD, PhD**  
Director of Translational Medicine, Inflammatory Bowel Disease Center and Immunology Research Institute, Cedars-Sinai Medical Center.  
Associate Professor of Medicine, University of California, Los Angeles David Geffen School of Medicine

**Judy Cho, MD,**  
Professor, Departments of Medicine and Genetics & Genomic Sciences  
Icahn School of Medicine at Mount Sinai, New York

**David C Wilson, MD, PhD**  
Professor, Paediatric Gastroenterology and Nutrition,  
Child Life and Health, College of Medicine and Veterinary Medicine, University of Edinburgh, United Kingdom

**Eric Benchimol, MD, PhD, FRCP**  
Principal Investigator, Children’s Hospital of Eastern Ontario (CHEO) Research Institute  
Physician, Division of Gastroenterology, Hepatology and Nutrition, CHEO  
Assistant Professor, Department of Pediatrics, Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa
**AGENDA**

**Very Early Onset Inflammatory Bowel Disease Symposium**

*Thursday, October 16, 2014 at The Hospital for Sick Children*

*Peter Gilgan Centre for Research & Learning (PGCRL)*

*686 Bay Street, 3rd floor auditorium*

**AFTERNOON**

<table>
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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
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<tbody>
<tr>
<td>1:15 pm</td>
<td><strong>NOVEL APPROACHES TO STUDY IBD</strong></td>
<td><strong>Moderated by Dr. Neil Warner, University of Michigan Health System</strong></td>
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|        | **Insight into Inflammatory Disease using Animal Models: the ACE2 Story**| **Professor Josef Martin Penninger, MD**  
Senior Scientist and Scientific Director, IMBA, Institute for Molecular Biotechnology of the  
Austrian Academy of Sciences, Vienna, Austria                                                   |
| 1:45 pm| **Organoids as Model System to Study VEOIBD**                            | **Robert Vries, PhD**  
Managing Director, Hubrecht Organoid Technology foundation  
Senior Scientist, Hubrecht Institute, Developmental Biology and Stem Cell Research               |
| 2:15 pm| **Humanized Mice as a Model to Understand the Pathogenesis of VEOIBD**   | **Scott Snapper, MD, PhD**  
Division of Gastroenterology, Hepatology & Nutrition, Boston Children's Hospital  
Director, Inflammatory Bowel Disease Center  
Professor of Medicine, Harvard Medical School                                                   |
| 2:45 pm| **Break**                                                                |                                                                                                |
| 3:00 pm| **GENETICS OF VEOIBD**                                                   | **Moderated by Dr. Eytan Wine, Stollery Children's Hospital and University of Alberta**         |
| 3:00 pm| **Known VEOIBD genes and a Clinical Approach to VEOIBD**                 | **Holm Uhlig, MD, PhD**  
Senior Clinical Research Fellow, Pediatric Gastroenterology and Mucosal Immunology Hon  
Consultant  
Pediatrics, Translational Gastroenterology Unit, University of Oxford                         |
| 3:30 pm| **The First VEOIBD Gene: IL10R**                                        | **Christoph Klein, MD, PhD**  
Director, Department of Paediatrics, Dr. von Hauner Children's Hospital Ludwig-Maximilians-  
University Munich                                                                             |
| 4:00 pm| **New Candidate Genes in VEOIBD**                                       | **Aleixo Muise, MD, PhD, FRCP**  
Co-Director, SickKids Inflammatory Bowel Disease Centre  
Clinician-Scientist, Division of Gastroenterology  
The Hospital for Sick Children                                                                    |
| 4:30 pm| **CLOSING REMARKS**                                                     | **by Dr. Anne Griffiths**                                                                         |
A brief overview of VEOIBD
Definitions of VEO-IBD

- **VEO-IBD:** Very Early Onset Inflammatory Bowel Disease.
- Patients with VEO-IBD are a unique subset within IBD.
- These young children with IBD have a distinct disease regarding disease location, disease extension over time, and are often challenging to treat.
- Recent Paris Modification of the Montreal Classification system defined children diagnosed under age 10 as a distinct phenotype (A1a).
- However, a definition of VEO is perhaps most appropriate for children diagnosed under age 6 (versus under age 10)?
- Children diagnosed under age 1 are further distinct and defined as infantile IBD.

Clinical Features of VEO-IBD

**VEO-IBD**
- Colon involved:
  - 80% in those with onset <10 years of age.
  - Decreases with age
- Ileum involved:
  - Rare at <10 years of age
- Positive FH: 40-50%
- Stricturing disease: 20-46%
- Surgery: up to 71%
- Extension of disease: up to 40%

**Adult onset IBD**
- Colon only involved
  - <20%
- Ileum involved:
  - Up to 80%
- Positive FH: 14-20%
- Stricturing disease: 29-40%
- Surgery: up to 55%
- Extension of disease: up to 16%
What causes VEO-IBD?

Causes of IBD are complex:
- Environmental factors
- Gut Bacteria
- Abnormal immune response
- Genetics

VEO-IBD patients:
- Genetics are generally considered to play a more important role in VEO-IBD.


Incidence of Paediatric IBD in Canada

<table>
<thead>
<tr>
<th></th>
<th>USA (WI)</th>
<th>UK</th>
<th>Norway</th>
<th>Netherlands</th>
<th>BC, Canada</th>
<th>NS, Canada</th>
<th>ON, Canada</th>
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<tbody>
<tr>
<td>Sample Size</td>
<td>199</td>
<td>739</td>
<td>48</td>
<td>188</td>
<td>473 (prevalence)</td>
<td>473 (prevalence)</td>
<td>3169</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;18</td>
<td>&lt;16</td>
<td>&lt;16</td>
<td>&lt;18</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;18</td>
</tr>
<tr>
<td>Inc CD (per 100k)</td>
<td>4.6</td>
<td>3.0</td>
<td>2.8</td>
<td>2.1-4.1</td>
<td>5.4</td>
<td>12.0</td>
<td>6.2-7.0</td>
</tr>
<tr>
<td>Inc UC (per 100k)</td>
<td>2.4</td>
<td>2.2</td>
<td>2.8</td>
<td>1.6-2.6</td>
<td>3.2</td>
<td>5.7</td>
<td>4.4-4.8</td>
</tr>
</tbody>
</table>

There is a 30% increase in incidence over a decade.


1Kugathasan et al., J Pediatr, 2003
2Sawczenko & Sandhu, Arch Dis Child, 2003
3Henriksen et al., Inflamm Bowel Dis, 2006
4van der Zaag-Loonen, J Pediatr Gastroenterol, 2004
5Bernstein et al., Am J Gastroenterol, 2006
Changes in IBD Incidence Rates By Age

<table>
<thead>
<tr>
<th>Age</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>
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</table>

*By Poisson regression analysis, controlling for sex

- In Canada, VEO-IBD has an incidence of 4.37/100,000 and a prevalence of 14/100,000 (~0.3/2,000).
- These are the highest rates in the world.


Challenges of VEO-IBD

- **Diagnosis** at a very young age requires that other causes of colitis are also ruled out—especially immunodeficiency.
- **Treatment options**: disease in VEO-IBD is often severe at diagnosis and there are no treatment guidelines for children at these very early ages, only a few small case studies. Surgery may not always be a viable option as extensive colonic disease has a tendency to extend to the small bowel.
- **Long term outcomes** including growth and cancer risk are poorly understood.
Personalized Patient Care Model For VEO-IBD

1. Phenotype and Genotype
   (immunology, cell biology, functional testing)

2. Discovery
   (genomics, transcriptomic, proteomics, metabolomics, microbiome, organoids, environmental assessment)

3. Computational Biology & Integrative Analysis
   (pathway discovery, drug target identification)

4. Experimental Validation
   (model systems – e.g., cells, organoids, iPS cells, mice, fish)

5. Therapeutic Platform
   (organoid/gene therapy/pharmacological therapy)

6. Treatment
   BMT/bowel transplant/pharmacological therapy

*P4Care = Pediatric (VEO-IBD) Portal for Personalized Patient Care

The Very Early Onset Inflammatory Bowel Disease Initiative
Summary of NEOPICS Genetic Efforts

- **Recent Advances**
  - IL10/R
  - NADPH oxidase
  - NOS2

- **NEOPICS Completed**

- **NEOPICS**

- **Never done in**
  - VEO-IBD

Variants not captured with current technology

Rare and uncommon coding variants (targeted and exome sequencing)

Common variants (fine mapping and immunochip)

Common variants (GWAS)

www.neopics.org
SPEAKER PROFILES
Dermot McGovern  MD, Ph.D, FRCP  
*Cedars-Sinai Medical Center and University of California, Los Angeles David Geffen School of Medicine*

Dermot McGovern is the Director of Translational Medicine and Professor of Medicine at Cedars-Sinai Medical Center in Los Angeles. Dr McGovern serves on the Steering Committee of the NIDDK IBD Genetics Consortium, the Management Committee of the International IBD Genetics Consortium, and the National Scientific Advisory Board of the Crohn's and Colitis Foundation of America (CCFA). Dr McGovern completed his clinical training with a focus on Crohn's disease and ulcerative colitis in Oxford, UK and holds a doctorate from the University of Oxford on IBD Genetics. Dr McGovern’s research group receive funding from the NIH, the European Union, The Leona M. and Harry B. Helmsley Charitable Trust, and the CCFA. The group's research has focused in identifying IBD susceptibility genes and also the functional consequences of these genes as well as the way genetic variation interacts with environmental factors including the microbiome. As an IBD clinician Dr McGovern is particularly interested in translating these basic science findings to the clinic through the development of models that predict disease behavior and response to therapy, as well as identifying new areas for the development of treatments for both Crohn's disease and ulcerative colitis.

“Overview of IBD Genetics: A look at Phenotype-Genotype Correlations”
Judy Cho MD
*Icahn School of Medicine at Mount Sinai, New York*

Dr. Judy Cho is the Ward-Coleman Professor of Translational Genetics and Medicine, Vice-Chair of Translational Genetics and Gastroenterology and Director of Cedared at the Icahn School of Medicine at Mount Sinai. She is the Principal Investigator and chair of the Steering Committee of the NIDDK IBD Genetics Consortium. She is a member of the American Association of Physicians (AAP) and will receive the Basic Science Award in IBD from the CCFA in 2014. Her research interest is in defining pathophysiologic mechanisms of IBD, leading efforts in identifying associations to *NOD2, IL23R* and most recently, 163 loci to IBD. Her laboratory is presently investigating the role of less common variation contributing to IBD in the Ashkenazi Jewish population.

“Insight into the Genetics of IBD: Lessons from Ashkenazi Jewish Crohn’s Disease”
David C Wilson  MB, BCh (Hons); MD; FRCP; FRCPCH
Royal Hospital for Sick Children and University of Edinburgh

Current Appointment:
Professor of Paediatric Gastroenterology and Nutrition, Child Life and Health, University of Edinburgh (formerly Senior Lecturer then Reader from 08.97) and Consultant in Paediatric Gastroenterology and Nutrition, Royal Hospital for Sick Children, Edinburgh (08.97 to date)

Clinical and research profile:
Clinical – Lead for paediatric IBD in SE Scotland region.
Research - Lead of paediatric gastroenterological and nutritional research in University of Edinburgh; lead for Scottish paediatric IBD collaborative research – clinical and translational including biologicals registry, IBD genetics, epidemiology and environmental studies (funders including Wellcome Trust, MRC, Scottish Government Health Department, IBD charities).
Academic collaborations – Member of International IBD genetics consortium, paediatric lead in UK IBD GC, founder of UK and Irish paediatric IBD genetics group, co-investigator in COLORS in IBD project, member of NEOPICS, member of Porto ESPGHAN IBD WG, UK paediatric lead for GEM project.
Publications - 125 papers (>60% on IBD); 1 Cochrane review (in IBD).

Other confession:

“Spectrum and Treatment Challenges in Complex IBD developing in the Very Young”

Learning Objectives:
- Review changes in Paediatric-onset (PIBD) phenotyping
- Evaluate whether the concept of VEOIBD as an entity is supported by natural history (phenotypic progression)
- Assess the spectrum of VEOIBD by different PIBD centre models
- Determine the spectrum of treatment challenges in VEOIBD
Eric Benchimol MD PhD FRCPC
Children’s Hospital of Eastern Ontario (CHEO) and University of Ottawa

Eric Benchimol is an Assistant Professor of Pediatrics and Epidemiology and the University of Ottawa. He is also a pediatric gastroenterologist in the Division of Gastroenterology at the Children’s Hospital of Eastern Ontario (CHEO), a scientist at the CHEO Research Institute, and an adjunct scientist at The Institute for Clinical Evaluative Sciences (ICES) uOttawa. He received his MD from University of Western Ontario, completed fellowships in pediatric gastroenterology and inflammatory bowel diseases at SickKids, and completed a PhD in clinical epidemiology at the University of Toronto. He conducts epidemiology, outcomes, and health services research in patients with inflammatory bowel disease (IBD) using health administrative data, as well as in children with other chronic diseases. His previous work created The Ontario Crohn’s and Colitis Cohort, the world’s largest ongoing surveillance cohort of IBD patients. Dr. Benchimol was recently awarded the CIHR/CAG/CCFC New Investigator Award to examine burden and variation of care for children with IBD in Canada.

“The Epidemiology and Burden of VEOIBD: Are Age of Onset and Outcomes Changing?”
Holm Uhlig MD, PhD
Children’s Hospital Oxford and University of Oxford

Holm Uhlig is an Associate Professor in the Translational Gastroenterology Unit, University of Oxford and Honorary Consultant in Paediatric Gastroenterology, Children’s Hospital Oxford. After his medical training at Leipzig University in Germany, Holm joined Fiona Powrie’s group at the Sir William Dunn School of Pathology in Oxford for his DPhil working on the role of IL23 and regulatory T cells in models of intestinal inflammation. Holm completed his training as a paediatrician and paediatric gastroenterologist in Germany before returning back to Oxford. Holm Uhlig’s group investigates monogenic disorders that are associated with very early onset of inflammatory bowel disease.

“Known VEOIBD genes and a Clinical Approach to VEOIBD”
Josef Penninger MD
Institute for Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria

Josef Penninger studied Medicine, Immunology, and History of Arts in Innsbruck, Austria. After his graduation in 1990 he left Austria to pursue postgraduate studies at the Ontario Cancer Institute in Toronto. From 1994 to 2002, Josef Penninger worked as a lead researcher at the Amgen Research Institute in Toronto. In 2002, he accepted the appointment as founding director of the newly established Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA) in Vienna. Scientifically, his basic approach is to genetically manipulate and change genes in mice and to determine the effects of these mutations in the development of the whole organism and in diseases. His group has also developed the first haploid embryonic stem cells for functional genetics. Josef Penninger has received various prizes, such as the EU Excellence Award (2004), Elected Young Global Leader by the World Economic Forum (2005), Ernst Jung Prize for Medicine (highest endowed medicine prize in Europe, 2007), Descartes Prize (highest EU research prize, 2007), Carus Medal (2008), ESCI Award for Excellence in Biomedical Investigation, ASMR-Medal of the Australian Society for Medical Research (2009), the Award as Elected Fellow of the American Association for the Advancement of Science (2011), in 2012 the Innovator Award from Era of Hope/DOD, in 2013 he received a second ERC Advanced grant and in 2014 he received the Wittgensteinprize.

“Insight into Inflammatory Disease using Animal Models: the ACE2 Story”

Learning Objectives:

- Description of the renin-angiotensin system, including ACE2
- In vivo functions for ACE2
- ACE2 and intestinal inflammation – diet and gut health
Robert Vries PhD

Hubrecht Institute, The Netherlands

Dr Robert Vries studied biology in Utrecht (the Netherlands) and Kent University (UK) to obtain his MSc in 1997. Subsequently, he earned his PhD from Leiden University Medical Center (The Netherlands) for the study of gene regulation during oncogenic transformation. Subsequently, he did his Post Doc studies on Neural stem cells at Stanford University (USA). In 2007 he returned to the Netherlands to the lab of Prof Dr Hans Clevers to continue the study of stem cells during development.

The group of Dr Clevers identified adult stem cells in the intestine and technology to expand them in vitro. This system formed the basis of protocols that were subsequently developed for other organs such as liver and pancreas but also different diseases such as prostate cancer. Robert Vries studied adult stem cells in the brain and the stem cell culture methods. In 2011, Robert became the manager of the Clevers group. At the same time he initiated the establishment of a spin of entity to translate the organoid technology towards clinical applications. The foundation Hubrecht Organoid Technology (HUB) was established in 2013 with the aim to generated patient and disease specific organoid biobanks to create a novel disease platform for drug development and testing. Robert is currently the managing director of the HUB foundation for organoids.

“Organoids as Model System to Study VEOIBD”
Scott B. Snapper  
**MD, PhD** 
*Boston Children’s Hospital and Harvard Medical School*

Scott B. Snapper is a physician-scientist whose research focuses on understanding the role of the immune system in maintaining health in the intestine with a concentration on inflammatory bowel diseases in very young children and human immunodeficiencies. Dr. Snapper is the Wolpow Family Chair and Director of the Center for Inflammatory Bowel Disease and Director of Basic and Translational Research at Boston Children’s Hospital. In addition, Dr. Snapper is the Director of IBD Research within the Gastroenterology Division at Brigham & Women’s Hospital (BWH) where he maintains a joint clinical appointment. He is an Associate Professor of Medicine at Harvard Medical School (HMS). Dr. Snapper currently serves as Chair on the CCFA Senior Research Awards Grant Committee and is Chair Elect of the National Science Advisory Committee of the CCFA.

For the last decade, his laboratory has been investigating how the “adaptive” and “innate” arms of the immune system maintain health in the intestine. In particular his laboratory is trying to understand how a defective immune system can contribute simultaneously to both immunodeficiency and intestinal inflammation with some focus on human immunodeficiencies. Currently, his laboratory is characterizing new genes that are associated with IBD and testing novel treatment strategies to manipulate immunoregulatory circuits in mice and man for IBD disease prevention and therapy. A major goal of his recent activities is to identify the genetic, immunological, microbiological and other environmental causes that lead to very early onset inflammatory bowel disease (VEO-IBD) and to develop novel personalized therapeutic options based on these findings. Together with Dr. Aleixo Muise in Toronto, and Dr. Christoph Klein in Munich, Dr. Snapper has started an international consortium focused on this effort.

“**Humanized Mice as a Model to understand the Pathogenesis of VEOIBD**”
Klein Christoph, Prof. Dr. med. Dr. sci. nat.
Dr. von Hauner University Children’s Hospital Ludwig-Maximilians-University Munich, Germany

Christoph Klein is a clinical pediatric immunologist and hematologist/oncologist and the director of the Department of Pediatrics at the Dr. von Hauner University Children’s Hospital Ludwig-Maximilians-University Munich. His main research interest is to study developmental aspects of the blood and immune system. His laboratory is interested in defining genetic mutations in children with inherited disorders of the immune system and to use genetic model organisms to identify their pathophysiological implications. Furthermore, his lab develops innovative gene- and cell-based therapeutic strategies for patients with disorders of the immune system. He has received numerous national and international awards such as the William-Dameshek Prize by the American Society of Hematology and the Gottfried-Wilhelm- Leibniz Award by the German Research Foundation. Christoph Klein is currently the spokesman of 12 National Research Networks on Rare Diseases. In line with his commitment towards children with rare diseases he has founded the international Care-for-Rare Foundation, a non-profit organization dedicated to improve care for children with rare diseases – regardless of their nationality, ethnicity and financial resources.

“The First VEOIBD Gene: IL10R”
Aleixo Muise, MD PhD, FRCPC  
*The Hospital for Sick Children and University of Toronto*

Dr. Muise is a Clinician-Scientist and Pediatric Gastroenterologist at the Hospital for Sick Children, Toronto. He is the co-Lead of the SickKids IBD Centre and Associate Professor of Pediatrics at the University of Toronto. His clinical work and laboratory research has focused on understanding the genetic susceptibility and function of identified genes in pathogenesis of Inflammatory Bowel disease, in particular very early onset IBD (VEOIBD; diagnosed prior to 6 years of age) including infantile disease. This has led to a number of high impact publications from his laboratory, describing novel genetic and functional studies in IBD and VEOIBD. Moreover, his genetic analysis has also led to curative treatments in patients with VEOIBD, and brought forth very promising development of further treatment modalities. He has created one of the largest repositories of DNA from well phenotyped VEOIBD patients by establishing (a) a clinic at Sickkids to ascertain, treat, and follow infants and young children with VEOIBD, and (b) founding the interNational Early Onset Pediatric IBD Cohort Study (NEOPICS; [www.NEOPICS.org](http://www.NEOPICS.org)) consortium. His Canadian and international collaborations with leading experts in IBD genetics and immunology have led to a greater understanding of the genetic factors associated with VEOIBD and changed treatment of these young patients.

“New Candidate Genes in VEOIBD”
Selected VEOIBD Publications


Mutations in Tetratricopeptide Repeat Domain 7A Result in a Severe Form of Very Early Onset Inflammatory Bowel Disease

Yaron Avitzur,1,2,3,§ Conghui Guo,2,* Lucas A. Mastropaolo,2 Ehsan Bahrami,4 Hannah Chen,5 Zhen Zhao,2 Abdul Eldakdr2,3,6 Sandeep Dhillon,2 Ryan Murchie,2 Ramzi Fattouh,2 Hien Huynh,7 Jennifer L. Walker,8 Paul W. Wales,1 Ernest Cutz,9 Yoichi Kakuta,10 Joel Dudley,11 Jochen Kammermeier,12 Fiona Powrie,13 Neil Shah,12 Christoph Walz,14 Michaela Nathrath,15 Daniel Kotlarz,4 Jacek Puchaka,4 Jonathan R. Krieger,2 Tomas Racek,14 Thomas Kirchner,14 Thomas D. Walters,2,3 John H. Brumell,2,3,6 Anne M. Griffiths,2,3 Nima Rezaei,16,17 Parisa Rashtian,18 Mehr Najafi,18 Maryam Monajemzadeh,19 Stephen Pelsue,8 Dermot P. B. McGovern,10 Holm H. Uhlig,5 Eric Schadt,11 Christoph Klein,4,8 Scott B. Snapper,20,21,§ and Aleixo M. Muise2,3,6,§

1Group for Improvement of Intestinal Function and Treatment (GIFT), Hospital for Sick Children, Toronto, Ontario, Canada; 2SickKids Inflammatory Bowel Disease Center and Cell Biology Program, Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada; 3Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada; 4Department of Pediatrics, Dr von Hauner Children’s Hospital, Ludwig-Maximilians-University, Munich, Germany; 5Translational Gastroenterology Unit and Paediatric Gastroenterology, Translational Gastroenterology Unit, Nuffield Department of Pediatrics, Dr von Hauner Children’s Hospital, Ludwig-Maximilians-University, Munich, Germany; 6Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 7Division of Pathology, The Hospital for Sick Children, London, UK; 8Department of Immunology and Molecular Biology, University of Southern Maine, Portland, Maine; 9Division of Pathology, The Hospital for Sick Children, London, UK; 10F. Widjaja Foundation Institute for Genomics and Multiscale Biology, Department of Genetics and Genomics Sciences at Mount Sinai, New York, New York; 11Icahn Institute for Genomics and Multiscale Biology, Department of Genetics and Genomics Sciences at Mount Sinai, New York, New York; 12Gastroenterology Department, Great Ormond Street Hospital, London, UK; 13Translational Gastroenterology Unit, Nuffield Department of Medicine-Experimental Medicine Division, University of Oxford, Oxford, UK; 14Institute for Pathology, Ludwig-Maximilians University, Munich, Germany; 15Department of Pediatric Oncology, Kassel and CCG Osteosarcoma, Heilmoltz Center Munich, Munich, Germany; 16Research Center for Immunodeficiencies, Children’s Medical Center, Tehran University of Medical Sciences, Tehran, Iran; 17Institute for Pathology, Ludwig-Maximilians University, Munich, Germany; 18Department of Pediatrics, Children’s Medical Center, Tehran University of Medical Sciences, Tehran, Iran; 19Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, Children’s Hospital Boston, Massachusetts; and 20Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, Harvard Medical School, Boston, Massachusetts

See Covering the Cover synopsis on page 876.

BACKGROUND & AIMS: Very early onset inflammatory bowel diseases (VEOIBD), including infant disorders, are a diverse group of diseases found in children younger than 6 years of age. They have been associated with several gene variants. Our aim was to identify the genes that cause VEOIBD. METHODS: We performed whole exome sequencing of DNA from 1 infant with severe enterocolitis and her parents. Candidate gene mutations were validated in 40 pediatric patients and functional studies were carried out using intestinal samples and human intestinal cell lines. RESULTS: We identified compound heterozygote mutations in the Tetratricopeptide repeat domain 7 (TTC7A) gene in an infant from non-consanguineous parents with severe exfoliative apoptotic enterocolitis; we also detected TTC7A mutations in 2 unrelated families, each with 2 affected siblings. TTC7A interacts with EFR3 homolog B to regulate phosphatidylinositol 4-kinase at the plasma membrane. Functional studies demonstrated that TTC7A is expressed in human enterocytes. The mutations we identified in TTC7A result in either mislocalization or reduced expression of TTC7A. Phosphatidylinositol 4-kinase was found to co-immunoprecipitate with TTC7A; the identified TTC7A mutations reduced this binding. Knockdown of TTC7A in human intestinal-like cell lines reduced their adhesion, increased apoptosis, and decreased production of phosphatidylinositol 4-phosphate. CONCLUSIONS: In a genetic analysis, we identified loss of function mutations in TTC7A in 5 infants with VEOIBD.

*Authors share co-first authorship; §Authors share co-senior authorship.

Abbreviations used in this paper: co-IP, co-immunoprecipitate; EFR3B, EFR3 homolog B; MIA, multiple intestinal atresia; PI4KIIα, phosphatidylinositol 4-kinase IIα; SCID, severe combined immunodeficiency; shRNA, short hairpin RNA; TPR, tetratricopeptide repeat; TTC7A, tetratricopeptide repeat domain 7; VEOIBD, very early onset inflammatory bowel diseases; WT, wild type.

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Variants in Nicotinamide Adenine Dinucleotide Phosphate Oxidase Complex Components Determine Susceptibility to Very Early Onset Inflammatory Bowel Disease

Sandeep S. Dhillon,1,2 Ramzi Fattouh,1 Abdul Elkadri,1,2,3 Wei Xu,4 Ryan Murchie,1 Thomas Walters,1,3 Conghui Guo,1 David Mack,5 Hien Q. Huynh,6 Shiraz Baksh,6 Mark S. Silverberg,2,7 Anne M. Griffiths,1,3 Scott B. Snapper,8 John H. Brumell,1,2,9 and Aleixo M. Muise1,2,3

1SickKids Inflammatory Bowel Disease Center and Cell Biology Program, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada; 2Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 3Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada; 4Princess Margaret Hospital and Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada; 5Division of Pediatric Gastroenterology, Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada; 6 Division of Pediatric Gastroenterology, Stollery Children’s Hospital, Edmonton, Alberta, Canada; 7Mount Sinai Hospital Inflammatory Bowel Disease Group, University of Toronto Group, Zane Cohen Center for Digestive Diseases, Toronto, Ontario, Canada; 8Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Medicine, Children’s Hospital Boston; Division of Gastroenterology and Hepatology, Brigham & Women’s Hospital, Department of Medicine, Harvard Medical School, Boston, Massachusetts; and 9Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada

BACKGROUND & AIMS: The colitis observed in patients with very early onset inflammatory bowel disease (VEOIBD; defined as onset of disease at younger than 6 years of age) often resembles that of chronic granulomatous disease (CGD) in extent and features of colonic inflammation observed by endoscopy and histology. CGD is a severe immunodeficiency caused by defects in the genes that encode components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. We investigated whether variants in genes that encode NADPH oxidase components affect susceptibility to VEOIBD using independent approaches. METHODS: We performed targeted exome sequencing of genes that encode components of NADPH oxidases (cytochrome b light chain and encodes p22phox protein; cytochrome b-245 or NADPH oxidase 2, and encodes Nox2 or gp91phox; neutrophil cytosol factor 1 and encodes p47phox protein; neutrophil cytosol factor 2 and encodes p67phox protein; neutrophil cytosol factor 4 and encodes p40phox protein; and Ras-related C3 botulinum toxin substrate 1 and 2) in 122 patients with VEOIBD diagnosed at The Hospital for Sick Children, University of Toronto, from 1994 through 2012. Gene variants were validated in an independent International Early Onset Pediatric IBD Cohort Study cohort of patients with VEOIBD. In a second approach, we examined Tag single nucleotide polymorphisms in a subset of patients with VEOIBD in which the NOX2 NADPH oxidase genes sequence had been previously analyzed. We then looked for single nucleotide polymorphisms associated with the disease in an independent International Early Onset Pediatric IBD Cohort Study cohort of patients. We analyzed the functional effects of variants associated with VEOIBD. RESULTS: Targeted exome sequencing and Tag single nucleotide polymorphism genotyping identified 11 variants associated with VEOIBD; the majority of patients were heterozygous for these variants. Expression of these variants in cells either reduced oxidative burst or altered interactions among proteins in the NADPH oxidase complex. Variants in the noncoding regulatory and splicing elements resulted in reduced levels of proteins, or expression of altered forms of the proteins, in blood cells from VEOIBD patients. CONCLUSIONS: We found that VEOIBD patients carry heterozygous functional hypomorphic variants in components of the NOX2 NADPH oxidase complex. These do not cause overt immunodeficiency, but instead determine susceptibility to VEOIBD. Specific approaches might be developed to treat individual patients based on their genetic variant.

Keywords: VEOIBD; CGD; Genetics; Phagocytes.

Chronic granulomatous disease (CGD) is a severe immunodeficiency caused by genetic defects in components of the NOX2 nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex (Figure 1). The mutations identified in the NADPH oxidase gene in CGD patients mostly result in the complete loss of phagocytes’ ability to mount the sufficient respiratory burst required to kill invading pathogens, leading to a severe immunodeficiency with

Abbreviations used in this paper: CGD, chronic granulomatous disease; CYBA, cytochrome b light chain and encodes p22phox protein; CYBB, cytochrome b-245 or NADPH oxidase 2 and encodes Nox2 or gp91phox; GFP, green fluorescent protein; IBD, inflammatory bowel disease; MSMD, Mendelian susceptibility to mycobacterial disease; NADPH, nicotinamide adenine dinucleotide phosphate; NBT, nitroblue tetrazolium; NCF1, neutrophil cytosol factor 1 and encodes p47phox protein; NCF2, neutrophil cytosol factor 2 and encodes p67phox protein; NCF4, neutrophil cytosol factor 4 and encodes p40phox protein; PID, primary immunodeficiency; RAC1 and 2, Ras-related C3 botulinum toxin substrate 1 and 2; ROS, reactive oxygen species; SNP, single nucleotide polymorphism; VEOIBD, very early onset inflammatory bowel disease; VEOUC, very early onset ulcerative colitis.
Incidence, Outcomes, and Health Services Burden of Very Early Onset Inflammatory Bowel Disease

Eric I. Benchimol,1,2,3,4 David R. Mack,1,2 Geoffrey C. Nguyen,4,5,7 Scott B. Snapper,8,9 Wenbin Li,4 Nassim Mojaverian,4 Pauline Quach,1,4 and Aleixo M. Muise6,10

1Children’s Hospital of Eastern Ontario Inflammatory Bowel Disease Centre, Division of Gastroenterology, Hepatology and Nutrition, Children’s Hospital of Eastern Ontario, Ottawa, Canada;2Department of Pediatrics, 3Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Canada;4Institute for Clinical Evaluative Sciences, Toronto, Canada;5Department of Medicine, 6Department of Paediatrics, University of Toronto, Toronto, Canada;7Mount Sinai Centre for Inflammatory Bowel Disease, Toronto, Canada;8Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Children’s Hospital Boston, Boston, Massachusetts;9Department of Medicine, Harvard University, Boston, Massachusetts;10SickKids Inflammatory Bowel Disease Centre, Division of Gastroenterology Hepatology and Nutrition, Cell Biology Program, Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada

This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of this exam, successful learners will be able to understand the differences in epidemiology, outcomes, and health services burden of children with very early onset IBD (VEO-IBD), compared with patients with older-onset pediatric IBD.

BACKGROUND & AIMS: The Paris pediatric modification of the Montreal classification defines very early onset inflammatory bowel disease (VEO-IBD) as a form of IBD distinct from that of older children. We compared the incidence and outcomes of VEO-IBD with those of IBD in older children.

METHODS: We performed a population-based retrospective cohort study of all children diagnosed with IBD in Ontario, Canada, from 1994 through 2009. Trends in standardized incidence were calculated using Poisson regression. We compared outpatient and emergency department visits, hospitalizations, and surgeries among children diagnosed with IBD when they were younger than age 6, ages 6–9.9, and older than age 10 years. Multivariable models were adjusted for income and stratified by sex.

RESULTS: The incidence of IBD increased from 9.4 per 100,000 children (95% confidence interval [CI], 8.2–10.8/100,000 children) in 1994 to 13.2 per 100,000 children (95% CI, 11.9–14.6/100,000 children) in 2009 (P < .0001). The incidence increased by 7.4% per year among children younger than 6 years old and 6.9–9.9 years old, and by 2.2% per year among children 10 years old. IBD-related outpatient visits were less frequent among children <6 years old than ≥10 years old (odds ratio for female patients, 0.67; 95% CI, 0.58–0.78; odds ratio for male patients, 0.86; 95% CI, 0.75–0.98). Hazard ratios [HRs] for hospitalization were lower for children <6 years old (female HR, 0.70; 95% CI, 0.56–0.87; male HR, 1.12; 95% CI, 0.94–1.33) than for older children. HRs for surgery among children <6 years old with Crohn’s disease were 0.35 for female patients (95% CI, 0.16–0.78) and 0.59 for male patients (95% CI, 0.34–0.99). HRs for children <6 years old with ulcerative colitis were 0.88 for female patients (95% CI, 0.47–1.63) and 0.42 for male patients (95% CI, 0.21–0.85). There was no difference in hospitalization or surgery rates among children 6–9.9 years old vs those ≥10 years old.

CONCLUSIONS: Based on a retrospective cohort study, the incidence of VEO-IBD increased from 1994 through 2009. Children diagnosed with IBD before they were 6 years old used fewer health services and had lower rates of surgery than children diagnosed when they were 10 years or older.

Keywords: Pediatrics; Epidemiology; Health Administrative Data; Disease Progression.

Watch this article’s video abstract and others at http://bit.ly/1q51BIW.

The incidence of childhood-onset inflammatory bowel disease (IBD) is increasing internationally,1 with the most striking increase in Ontario, Canada, described in children younger than 10 years of age.2 A small number of unique genetic mutations3–5 have been identified in children with a diagnosis of IBD at a very young age, but genome-wide association studies have not detected large differences between adult-onset and early onset disease.6–8 However, the phenotype of children with onset of Crohn’s disease (CD) occurring younger than the age of 10 is predominantly colonic, with a lower risk of ileal disease.9–12 In children with earlier onset of ulcerative colitis (UC), the requirement for second-line therapy (biologics or colectomy) was reported to be lower than for those diagnosed in the second decade of life.13 These findings led to a change in the classification of pediatric patients with IBD. Although the Montreal classification of IBD previously denoted all children diagnosed at younger than 17 years as having

Abbreviations used in this paper: CD, Crohn’s disease; CI, confidence interval; ED, emergency department; HR, hazard ratio; IBD, inflammatory bowel disease; OHIP, Ontario Health Insurance Plan; VEO, very early onset; UC, ulcerative colitis.

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The Diagnostic Approach to Monogenic Very Early Onset Inflammatory Bowel Disease

Holm H. Uhlig, 1,2 Tobias Schwerd, 1 Sibylle Koletzko, 3 Neil Shah, 4,5 Jochen Kammermeier, 4 Abdul Elkadri, 6,7 Jodie Ouahed, 8,9 David C. Wilson, 10,11 Simon P. Travis, 1 Dan Turner, 12 Christoph Klein, 3 Scott B. Snapper, 8,9 and Aleixo M. Muise, 6,7 for the COLORS in IBD Study Group and NEOPICS

Patients with a diverse spectrum of rare genetic disorders can present with inflammatory bowel disease (monogenic IBD). Patients with these disorders often develop symptoms during infancy or early childhood, along with endoscopic or histological features of Crohn’s disease, ulcerative colitis, or IBD unclassified. Defects in interleukin-10 signaling have a Mendelian inheritance pattern with complete penetrance of intestinal inflammation. Several genetic defects that disturb intestinal epithelial barrier function or affect innate and adaptive immune function have incomplete penetrance of the IBD-like phenotype. Several of these monogenic conditions do not respond to conventional therapy and are associated with high morbidity and mortality. Due to the broad spectrum of these extremely rare diseases, a correct diagnosis is frequently a challenge and often delayed. In many cases, these diseases cannot be categorized based on standard histological and immunologic features of IBD. Genetic analysis is required to identify the cause of the disorder and offer the patient appropriate treatment options, which include medical therapy, surgery, or allogeneic hematopoietic stem cell transplantation. In addition, diagnosis based on genetic analysis can lead to genetic counseling for family members of patients. We describe key intestinal, extra-intestinal, and laboratory features of 50 genetic variants associated with IBD-like intestinal inflammation. In addition, we provide approaches for identifying patients likely to have these disorders. We also discuss classic approaches to identify these variants in patients, starting with phenotypic and functional assessments that lead to analysis of candidate genes. As a complementary approach, we discuss parallel genetic screening using next-generation sequencing followed by functional confirmation of genetic defects.

Inflammatory bowel diseases (IBDs) are a diverse group of complex and multifactorial disorders. The most common subtypes are Crohn’s disease (CD) and ulcerative colitis (UC). 1,2 There is increasing evidence that IBD arises in genetically susceptible people, who develop a chronic and relapsing inflammatory intestinal immune response toward the intestinal microbiota. Disease development and progression are clearly influenced by environmental factors, which have contributed to the rapid global increase in the incidence of IBD in recent decades. 3

Developmental, Genetic, and Biological Differences Among Age Groups

IBD location, progression, and response to therapy have age-dependent characteristics. 4–10 The onset of intestinal inflammation in children can affect their development and growth. Age of onset can also provide information about the

Abbreviations used in this paper: CD, Crohn’s disease; CGD, chronic granulomatous disease; CVID, combined variable immunodeficiency; EOIBD, early-onset inflammatory bowel disease; HSCT, hematopoietic stem cell transplantation; IBD, inflammatory bowel disease; Ig, immunoglobulin; IL, interleukin; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NEMO, nuclear factor B essential modulator protein; NK, natural killer; PID, primary immunodeficiency; SCID, severe combined immunodeficiency; UC, ulcerative colitis; VEOIBD, very early onset inflammatory bowel disease; WAS, Wiskott-Aldrich syndrome; WES, whole-exome sequencing.

Keywords: Inflammatory Bowel Disease; Crohn’s Disease; Ulcerative Colitis; Unclassified Colitis; Indeterminate Colitis; Immunodeficiency; Pediatrics; IBD Unclassified; Genetics; Next-Generation Sequencing; Whole Exome Sequencing.
type of IBD and its associated genetic features. For example, patients with defects in interleukin (IL)-10 signaling have a particularly early onset of IBD, within the first few months of life. Our increasing understanding of age-specific characteristics has led to changes in the classification of pediatric IBD. Based on disease characteristics, several age subgroups have been proposed that correspond largely to the generally accepted age stages defined by National Institute of Child Health and Human Development pediatric terminology.11

Five major subgroups of pediatric IBD can be summarized according to age (Table 1). The Montreal classification12 originally defined patients with age of onset younger than 17 years as a distinct group of patients with pediatric-onset IBD (A1). The Pediatric Paris modification13 of the Montreal classification12 later defined the pediatric-onset group of IBD as A1 but subdivided those with a diagnosis before 10 years of age as subgroup A1a and those with a diagnosis between 10 and <17 years of age as subgroup A1b.13 This reclassification was based on several findings indicating that children with a diagnosis of IBD before 10 years of age develop a somewhat different disease phenotype compared with adolescents or adults. Particular differences that supported the modification were paucity of ileal inflammation and predominance of pancolonic inflammation as well as a low rate of anti–Saccharomyces cerevisiae antibodies in A1a patients with CD, with an increased risk of surgery (colectomy) and biological therapy in A1a patients with UC.13

In this review, we refer to the A1a group as having early-onset IBD (EOIBD). Very early onset IBD (VEOIBD), the subject of this review, represents children with a diagnosis before 6 years of age.14 This age classification includes neonatal, infantile, toddler, and early childhood groups. Proposing an age group between infantile IBD and A1a EOIBD makes sense when taking account that the age of onset is often older than 2 years in multiple relevant subgroups of patients with monogenic IBD (such as those with XIAP deficiency, chronic granulomatous disease [CGD], or other neutrophil defects). On the other hand, from the age of 7 years, there is a substantial rise in the frequency of patients with a diagnosis of conventional polygenic IBD, particularly CD.5,15 This leads to a relative enrichment of monogenic IBD in those with age of onset younger than 6 years. Approximately one-fifth of children with IBD younger than 6 years of age and one-third of children with IBD younger than 3 years of age are categorized as having IBD unclassified (or indeterminate colitis),16 reflecting the lack of a refined phenotyping tool to categorize relevant subgroups of patients with VEOIBD and a potential bias due to incomplete diagnostic workup in very young children.15 The enrichment of monogenic defects in EOIBD and VEOIBD becomes apparent when relating the approximately 1% of patients with IBD younger than 6 years of age and <0.2% younger than 1 year of age to reports that the majority of monogenic disorders can present at younger than 6 years of age and even younger than 1 year of age (Figure 1).

Although it is generally accepted that many patients with VEOIBD have low response rates to conventional anti-inflammatory and immunomodulatory therapy, there is a paucity of well-designed studies to support this hypothesis. Infantile (and toddler) onset of IBD was highlighted in the Pediatric Paris classification because of higher rates of affected first-degree family relatives, indicating an increased genetic component, severe disease course, and high rate of resistance to immunosuppressive treatment.13 Features of autoimmunity with dominant lymphoid cell infiltration are frequently found in infants and toddlers.17 Such patients are likely to have pancolitis; subgroups of patients develop severely ulcerating perianal disease, and there is a high rate of resistance to conventional therapy, a high rate of first-degree relatives with IBD, and increased lethality.4–8 Recent guidelines and consensus approaches on the diagnosis and management of IBD16,19 highlight that children with infantile onset of IBD have a particular high risk of an underlying primary immunodeficiency. An extreme early subgroup, neonatal IBD, has been described with manifestations during the first 27 days of life.4,5,8

**Guidelines on the diagnosis and classification of IBD in pediatric patients**13,18–22 have addressed the need to recognize monogenic disorders and immunodeficiencies in particular, because these require a different treatment strategy than conventional IBD. Current guidelines do not, however, cover the spectrum of these rare subgroups of monogenic IBD. The identification of an underlying genetic defect is indeed challenging, owing to the orphan nature of these diseases, the wide phenotypic spectrum of disorders, and the limited information available on most genetic defects. This review and practice guide provides a comprehensive summary of the monogenic causes of IBD-like intestinal inflammation and a conceptual framework for the diagnostic evaluation of patients with suspected monogenic IBD. We categorize known genetic defects into functional subgroups and discuss key intestinal and extraintestinal findings. Based on the enrichment of known causative mutations as well as extreme phenotypes in very young children, we have focused on a practical approach to detect monogenic disorders in patients with VEOIBD and infantile IBD in particular. Because there is only modest biological evidence to support age-specific categorization of IBD above infantile IBD and within the EOIBD subgroup, we also discuss disease- and gene-specific ages of onset of intestinal inflammation (Figure 1).

### Table 1. Subgroups of Pediatric IBD According to Age

<table>
<thead>
<tr>
<th>Group</th>
<th>Classification</th>
<th>Age range (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric-onset IBD</td>
<td>Montreal A1</td>
<td>Younger than 17</td>
</tr>
<tr>
<td>EOIBD</td>
<td>Paris A1a</td>
<td>Younger than 10</td>
</tr>
<tr>
<td>VEOIBD</td>
<td></td>
<td>Younger than 6</td>
</tr>
<tr>
<td>Infantile (and toddler)</td>
<td></td>
<td>Younger than 2</td>
</tr>
<tr>
<td>onset IBD</td>
<td></td>
<td>First 28 days of age</td>
</tr>
</tbody>
</table>

**Epidemiology of Pediatric IBD**

Approximately 20% to 25% of patients with IBD develop intestinal inflammation during childhood and adolescence.
IBD in children younger than 1 year of age has been reported in approximately 1% and VEOIBD in approximately 15% of pediatric patients with IBD.\(^6\) VEOIBD has an estimated incidence of 4.37 per 100,000 children and a prevalence of 14 per 100,000 children.\(^22\) The incidence of pediatric IBD is increasing.\(^22,23\) Some studies have reported that the incidence of IBD is increasing particularly rapidly in young children,\(^24,25\) although not all studies have confirmed this observation.\(^9\)

**Polygenic and Monogenic Forms of IBD**

Twin studies have provided the best evidence for a genetic predisposition to IBD, which is stronger for CD than UC. Conventional IBD is a group of polygenic disorders in which hundred(s) of susceptibility loci contribute to the overall risk of disease. Meta-analyses of (genome-wide) association studies of adolescent- and adult-referral-based IBD cohort, \(n = 1605\) patients comprising CD, UC, and IBD unclassified (IBDU), Symbols represent individual patients. Bars represent the age range of case series if individual data were not available. The age ranges of infantile IBD, VEOIBD, EOIBD, and Montreal classification A1a, A1b, A2, and A3 are shown for reference. Age of onset data refer to references provided in Table 2. Additional references for disease subgroups are provided in Supplementary Information for Figure 1.
important to consider that these 163 loci individually contribute only a small percentage of the expected heritability in IBD.\textsuperscript{26} This suggests that IBD, including CD and UC, can be regarded as a classic polygenic disorder. Findings from initial genome-wide pediatric association studies focused on adolescents and confirm a polygenic model.\textsuperscript{27,28}

There are no well-powered genome-wide association studies of patients with EOIBD or VEOIBD.

Although most cases of IBD are caused by a polygenic contribution toward genetic susceptibility, there is a diverse spectrum of rare genetic disorders that produce IBD-like immunopathology.\textsuperscript{29} The genetic variants that cause these disorders have a large effect on gene function. However, these variants are so rare in allele frequency (many private mutations) that those genetic signals are not detected in genome-wide association studies of patients with IBD. With recent advances in genetic mapping and sequencing techniques and increasing awareness of the importance of those “orphan” disorders, approximately 50 genetic disorders have been identified and associated with IBD-like immunopathology (for a partial summary, see Uhlig\textsuperscript{30}). For simplicity, we refer to these disorders in the following text as monogenic IBD, even if there is a spectrum of penetrance of the IBD phenotype. We will compare those monogenic forms of IBD with polygenic conventional IBD.

All data suggest that the fraction of monogenic disorders with IBD-like presentation among all patients with IBD correlates inversely with the age of onset. Despite a growing genotype spectrum, monogenic disorders still account for only a fraction of VEOIBD cases. The true fraction is unknown. In a study of 66 patients who developed IBD at ages younger than 5 years, 5 patients were found to carry mutations in \textit{IL10RA}, 8 in \textit{IL10RB}, and 3 in \textit{IL10}.\textsuperscript{30} All patients developed symptoms within the first 3 months of life.\textsuperscript{30} A recent study detected 4 patients with presumed pathogenic \textit{XIAP} mutations in a group of 275 patients with pediatric IBD (A1A/A1B Paris classification) and 1047 patients with adult-onset CD (A2 and A3 Montreal classification).\textsuperscript{31} Because all patients with \textit{XIAP} variants were infantile to adolescent male patients with CD, this could suggest an approximate prevalence of 4% among young male patients with IBD. However, studies like these focus on specific genes and may have strong selection bias toward an expected clinical subphenotype. They might therefore overestimate the frequency of specific variants. Analysis of large, multicenter, population-based cohorts is needed to determine the proportion of cases of VEOIBD caused by single gene defects and to estimate penetrance.

Monogenic defects have been found to alter intestinal immune homeostasis via several mechanisms (Table 2). These include disruption of the epithelial barrier and the epithelial response as well as reduced clearance of bacteria by neutrophil granulocytes and other phagocytes. Other single-gene defects induce hyperinflammation or autoinflammation or disrupt T- and B-cell selection and activation. Hyperactivation of the immune response can result from defects in immune inhibitory mechanisms, such as defects in IL-10 signaling or dysfunctional regulatory T-cell activity.

### Epithelial Barrier and Response Defects

Genetic disorders that affect intestinal epithelial barrier function include dystrophic epidermolysis bullosa,\textsuperscript{32} Kindler syndrome,\textsuperscript{33} familial diarrhea caused by dominant activating mutations in guanylate cyclase \textit{C},\textsuperscript{33} X-linked ectodermal dysplasia and immunodeficiency,\textsuperscript{34} and ADAM17 deficiency.\textsuperscript{35}

X-linked ectodermal dysplasia and immunodeficiency, caused by hypomorphic mutations in \textit{IKBKG} (encodes nuclear factor \(\kappa B\) essential modulator protein [NEMO])\textsuperscript{34} and \textit{ADAM17} deficiency\textsuperscript{35} cause epithelial and immune dysfunction. Recently, \textit{TTC7A} deficiency was described in patients with multiple intestinal atresia, with and without severe combined immunodeficiency (SCID) immunodeficiency.\textsuperscript{36,37} Hypomorphic mutations in \textit{TTC7A} without intestinal stricturing or severe immunodeficiency, most likely due to a defect in epithelial signaling.\textsuperscript{38}

### Dysfunction of Neutrophil Granulocytes

Variants in genes that affect neutrophil granulocytes (and other phagocytes) predispose people to IBD-like intestinal inflammation. Chronic granulomatous disease is characterized by genetic defects in components of the phagocyte reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (phox) complex. Genetic mutations in all 5 components of the phagocyte NADPH oxidase (phox)—\textit{gp91-phox} (\textit{CYBB}), \textit{p22-phox} (\textit{CYBA}), \textit{p47-phox} (\textit{NCF1}), \textit{p67-phox} (\textit{NCF2}), and \textit{p40-phox} (\textit{NCF4})—are associated with immunodeficiency and can cause IBD-like intestinal inflammation.

As high as 40% of patients with CGD develop CD-like intestinal inflammation.\textsuperscript{39–41} Multiple granulomas and the presence of pigmented macrophages can indicate the group of defects histologically. Missense variants in \textit{NCF2} that affect RAC2 binding sites have recently been reported in patients with VEOIBD.\textsuperscript{42} Recently, several heterozygous functional hypomorphic variants in multiple components of the \textit{NOX2} NADPH oxidase complex were detected in patients with VEOIBD that do not cause CGD-like immunodeficiency but have a moderate effect on reactive oxygen species production and confer susceptibility to VEOIBD.\textsuperscript{43}

Tumor necrosis factor \(\alpha\) inhibitors can resolve intestinal inflammation in patients with CGD but could increase the risk of severe infections in patients with CGD.\textsuperscript{44} Allogeneic hematopoietic stem cell transplantation (HSCT) can cure CGD and resolve intestinal inflammation.\textsuperscript{44–46} Monocytes produce high levels of IL-1 in patients with CGD, and an IL-1 receptor antagonist (anakinra) has been used to treat noninfectious colitis in those patients.\textsuperscript{47}

In addition to CGD, a number of other neutrophil defects are associated with intestinal inflammation. Defects in glucose-6-phosphate translocase (\textit{SLC27A4})\textsuperscript{48,49} and glucose-6-phosphatase catalytic subunit 3 (\textit{G6PC3})\textsuperscript{50} are associated with congenital neutropenia (and other distinctive features) but also predispose people to IBD. Leukocyte adhesion deficiency type 1 is caused by mutations in the gene encoding CD18 (\textit{ITGB2}) and is associated with
### Table 2. Genetic Defects and Phenotype of Monogenic IBD

<table>
<thead>
<tr>
<th>Group</th>
<th>Syndrome/disorder</th>
<th>Gene</th>
<th>Inheritance</th>
<th>CD-like Granuloma</th>
<th>UC-like Epithelial defect (apoptosis)</th>
<th>Disease location (1-5)</th>
<th>Perianal fistula/abscess</th>
<th>Penetrating fistulas</th>
<th>Strictures</th>
<th>Skin lesions</th>
<th>Autoimmunity, inflammation</th>
<th>HLH/ MAS</th>
<th>Neoplasia</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Epithelial barrier</td>
<td>Dystrophic bullousa</td>
<td>COL7A1</td>
<td>AR</td>
<td>+</td>
<td>+</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>eb</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>32 (A. Martinez)</td>
</tr>
<tr>
<td>2 Kindler syndrome</td>
<td></td>
<td>FERMT1</td>
<td>AR</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>32, 149</td>
</tr>
<tr>
<td>3 X-linked ectodermal</td>
<td>immunodeficiency</td>
<td>IKBKG</td>
<td>X</td>
<td>+</td>
<td>+</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ A, Vasc</td>
<td></td>
<td></td>
<td></td>
<td>34, 150, 151</td>
</tr>
<tr>
<td>4 TTC7A deficiency</td>
<td></td>
<td>TTC7A</td>
<td>AR</td>
<td>+</td>
<td>+</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>5 ADAM17 deficiency</td>
<td></td>
<td>ADAM17</td>
<td>AR (+)</td>
<td>+</td>
<td>+</td>
<td>3</td>
<td>+</td>
<td>n, h</td>
<td>+</td>
<td>+</td>
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References

1. Uhlig et al. Gastroenterology Vol. 147, No. 5
2. Reviews and Perspectives
3. 994
Table 2. Continued

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NOTE. Genetic defects are grouped according to functional subgroups. Gene names refer to HUGO gene nomenclature. CD-like and UC-like were marked only when patient characteristics in the original reports were described as typical CD or UC pathologies. Unclassified or indeterminate colitis is the not specified default option. Disease location is classified as follows: 1, mouth; 2, enteropathy; 3, enterocolitis; 4, isolated ileitis; 5, colitis; 6, perianal disease. Epithelial defects refer in particular to finding of epithelial lining nonadherent at the basal membrane or increased epithelial apoptosis and epithelial tufting. Key laboratory findings are provided in Supplementary Table 1, and examples of additional defects of possible or unclear relevance are listed in the Supplementary Information for Table 1. HLH, hemophagocytic lymphohistiocytosis; AR, autosomal recessive; eb, epidermolysis bullosa; X, X-linked; A, arthritis; vasc, vasculitis; n, nail; h, hair; AD, autosomal dominant; e, eczema; f, folliculitis/pyoderma; SJ, Sjögren syndrome; p, psoriasis; AIHA, autoimmune hemolytic anemia; AN, autoimmune neutropenia; PSC, primary sclerosing cholangitis; HT, Hashimoto thyroiditis; AIH, autoimmune hepatitis; TID, type 1 diabetes mellitus; MAS, macrophage activation syndrome; NSIP, non-specific interstitial pneumonitis; S, serositis.

9aPersonal information and communication.
defective transendothelial migration of neutrophil granulocytes. Patients typically present with high peripheral granulocyte counts and bacterial infections, and some present with IBD-like features.

CD-like disease is a typical manifestation of glycogen storage disease type Ib, characterized by neutropenia and neutrophil granulocyte dysfunction. Granulocyte colony-stimulating factor has been used to treat neutropenia and colitis in some patients with glycogen storage disease type Ib.

In addition to neutrophil defects, defects in several other genes, including WAS, LRBA, BTK, CD40LG, and FOXP3, can lead to autoantibody-induced or hemophagocytosis-induced neutropenia. These multidimensional mechanisms of secondary immune dysregulation indicate the functional complexity of some seemingly unrelated genetic immune defects and the broad effects they might have on the innate immune system.

**Hyperinflammatory and Autoinflammatory Disorders**

VEOIBD has been described in a number of hyperinflammatory and autoinflammatory disorders such as mevalonate kinase deficiency, phospholipase C-γ2 defects, familial Mediterranean fever, Herman-sky–Pudlak syndrome (type 1, 4, and 6), X-linked lymphoproliferative syndrome type 1 and type 2, or familial hemophagocytic lymphohistiocytosis type 5. Among these, mevalonate kinase deficiency is a prototypic autoinflammatory disorder, characterized by increased activation of caspase-1 and subsequent activation of IL-1β. Inhibiting IL-1β signaling with antibodies that block IL-1β or IL-1 receptor antagonists can induce complete or partial remission in patients, including those with VEOIBD.

X-linked lymphoproliferative syndrome 2 is caused by defects in the XIAP gene. At least 20% of patients with XIAP defects develop a CD-like immunopathology with severe fistulizing perianal phenotype. In these patients, Epstein–Barr virus infections can lead to life-threatening hemophagocytic lymphohistiocytosis. Originally associated with a poor outcome after HSCT, less toxic induction regimens could improve the prognosis and cure this form of IBD.

**Complex Defects in T- and B-Cell Function**

IBD-like immunopathology is a common finding in patients with defects in the adaptive immune system. Multiple genetic defects that disturb T- and/or B-cell selection and activation can cause complex immune dysfunction, including immunodeficiency and autoimmunity as well as intestinal inflammation. Disorders associated with IBD-like immunopathology include B-cell defects such as common variable immunodeficiency (CVID), hyper-immunoglobulin (Ig) M syndrome, and agammaglobulinemia. Several other primary immune deficiencies, such as Wiskott-Aldrich syndrome (WAS) and atypical SCID or Omenn syndrome, can also cause IBD-like intestinal inflammation.

**CVID, Agammaglobulinemia, and Hyper IgM Syndrome**

Patients with CVID have clinical features of different types of IBD, spanning CD, UC, and ulcerative proctitis-like findings. Although CVID is largely polygenic, a small proportion of cases of CVID have been associated with specific genetic defects. CVID type 1 is caused by variants in the gene encoding the inducible T-cell costimulator (ICOS), whereas CVID type B is caused by variants in LRBA. Patients with these mutations can present with IBD-like pathology. Recently, IBD and CVID-like disease was described in a family with IL-21 deficiency.

Patients with agammaglobulinemia, caused by defects in BTK or PIK3RI, as well as patients with subtypes of hyper IgM syndrome caused by defects in CD40LG, AICDA, or IKKBG can develop IBD-like immunopathology. It is worth considering that several other immunodeficiencies, not regarded as primary B-cell defects, are similarly associated with low numbers of B cells and/or Iggs (such as those caused by variants in SKIV2L and TTC37; see Table 2 and Supplementary Table 1).

**WAS**

WAS is a primary immunodeficiency. Many patients with WAS present with UC-like noninfectious colitis during early infancy. The syndrome is caused by the absence or abnormal expression of the cytoskeletal regulator WASP and is associated with defects in most immune subsets (effector and regulatory T cells, natural killer [NK] T cells, B cells, dendritic cells, macrophages, NK cells, and neutrophils). In addition to features of UC, patients develop many other autoimmune complications. Allogeneic bone marrow transplantation is the standard of care for those patients. Patients who are not candidates for bone marrow transplantation have been successfully treated with experimental gene therapy approaches.

**Atypical SCID Defects**

Patients with atypical SCID defects have residual B- and T-cell development and oligoclonal T-cell expansion. VEOIBD is commonly observed in patients with atypical SCID due to hypomorphic defects in multiple genes such as DCLRE1C, ZAP70, RAG2, IL2RG, LIG4, ADA, and CD3G. This list of genes is likely not complete, and it seems reasonable to assume that most genetic defects that cause T-cell atypical SCID also cause IBD.

A subset of patients with SCID present with severe eczematosus rash (Omenn syndrome). It is not clear whether residual lymphocyte function in patients with hypomorphic TTC7A mutations is a precondition for IBD or contributes to VEOIBD. Intestinal and skin lesions also develop in patients with SCID due to graft-versus-host disease in response to maternal cells.
**Hoyeraal–Hreidarsson Syndrome**

Hoyeraal–Hreidarsson syndrome is a severe form of dyskeratosis congenita characterized by dysplastic nails, lacy reticular skin pigmentation, and oral leukoplakia. It is a multiorgan disorder. Patients with mutations in RTEL1 or DKC1 can develop SCID and intestinal inflammation.

**Regulatory T Cells and IL-10 Signaling**

Loss-of-function defects in IL-10 and its receptor (encoded by IL10RA and IL10RB) cause VEOIBD with perianal disease and folliculitis within the first months of life. All patients with loss-of-function mutations that prevent IL-10 signaling develop IBD-like immunopathology, indicating that these defects are a monogenic form of IBD with 100% penetrance. The anti-inflammatory cytokine IL-10 is secreted by natural and induced regulatory T cells (in particular, intestinal CD4+FOXP3+ and Tr1 cells), macrophages, and B cells. Many intestinal and extraintestinal cell types express the IL-10 receptor and respond to IL-10. Defects in IL-10 receptor signaling affect the differentiation of macrophage M1/M2, shifting them toward an inflammatory phenotype. Defects in IL-10 signaling are associated with extraintestinal inflammation such as folliculitis or arthritis and predispose to B-cell lymphoma. Conventional therapy options are largely not effective in patients with IL-10 signaling defects, but allogeneic matched or mismatched HSCT can induce sustained remission of intestinal inflammation.

X-linked immune dysregulation, polyendocrinopathy, enteropathy syndrome (IPEX) is caused by mutations in the transcription factor FOXP3. Those mutations affect natural and induced regulatory T cells, causing autoimmunity and immunodeficiency but also enteropathy in a large percentage of patients with colitis. The intestinal lesions that develop in patients with IPEX can be classified as graft-versus-host disease–like changes with small bowel involvement and colitis, celiac disease–like lesions, or enteropathy with goblet cell depletion.

Antibodies against enterocytes and/or antibodies against goblet cells can be detected in the serum of patients with IPEX. IPEX-like immune dysregulation with enteropathy can also be caused by defects in IL-2 signaling in patients with defects in the IL-2 receptor α chain (IL2RA, encoding CD25) or a dominant gain of function in STAT1 signaling.

**Other Disorders and Genes**

IBD or IBD-like disorders have been described in patients with several other disorders. In some disorders, there is no well-defined plausible functional mechanism. For example, patients with trichobezoar syndrome have presumed defects in epithelial cells that lead to intractable diarrhea. However, an adaptive immune defect might also cause this disorder, because the patients have Ig deficiencies that require Ig substitution.

Several genes, described in the Supplementary Information for Table 1, are associated with a single or less well-defined case report of patients who developed IBD-like features. Some of these patients might happen to have intestinal inflammation by coincidence, and even several case reports cannot exclude a publication bias.

Heterozygous defects in the PTEN phosphatase are associated not only with multiple tumors but also immune dysregulation and autoimmunity. Inflammatory polyps are common among patients with PTEN hamartoma tumor syndrome and indeterminate colitis, and ileitis is a rare complication. The functional mechanism involved in intestinal inflammatory polyps and intestinal inflammation is not clear because heterozygous mutations in PTEN are not associated with conventional immunodeficiency and affect multiple cell types.

Very early onset enteropathies and intestinal infections are described in several monogenic immunodeficiency and/or autoinflammation disorders, including defects in the itchy E3 ubiquitin ligase activity encoded by the ITCH gene, defects in E3 ubiquitin ligase HOIL-1 encoded by HOIL1, and gain of function defects in IKBA encoded by NFκBIA (see Supplementary Information for Table 1). It is not clear what activates the inflammatory events in those patients; it could be pathogenic microbes in the intestine, food, or IBD-like intestinal inflammation induced by the commensal microbiota.

Additional disorders are associated with intestinal inflammation without immunodeficiency or without known epithelial mechanisms. For example, some patients with Hirschsprung disease, an intestinal innervation and dysmotility disorder, develop enterocolitis associated with dominant germline mutations in RET. One possible pathomechanism could be increased bacterial translocation due to bacterial stasis leading to subsequent inflammation.

Despite multiple reports of complement system deficiencies and IBD, this group of disorders is not clearly defined. MASP2 deficiency has been reported in a patient with pediatric-onset IBD. However, reports of intestinal inflammation in several other complement defects are much harder to interpret because those patients present with inconsistent disease phenotypes; some are less well documented and could be simple chance findings (see Supplementary Information for Table 1).

**Why Should We Care About Monogenic Defects?**

It is a challenge to diagnose the rare patients with monogenic IBD, but differences in the prognosis and medical management argue that a genetic diagnosis should not be missed. As a group, these diseases have high morbidity and subgroups have high mortality if untreated. Based on their causes, some require different treatment strategies than most cases of IBD.

Allogeneic HSCT has been used to treat several monogenic disorders. It is the standard treatment for patients with disorders that do not respond to conventional treatment, those with high mortality, or those that increase susceptibility to hematopoietic cancers (eg IL-10 signaling defects, IPEX, WAS, or increasingly XIAP deficiency). Introduction of HSCT as a potentially curative treatment option
for intestinal and extraintestinal manifestations of these disorders has changed clinical practice.\textsuperscript{30,73,74,107,111}

However, there is evidence from mouse models and clinical studies that patients with epithelial barrier defects are less amenable to HSCT, because this does not correct the defect that causes the disease (eg, \textit{NEMO} deficiency or possibly \textit{TTC7A} deficiency). For example, severe recurrence of multiple intestinal atresia after HSCT in patients with \textit{TTC7A} deficiency\textsuperscript{16,37} indicates a contribution of the enterocyte defect to pathogenesis. Due to the significant risk associated with HSCT, including graft-versus-host disease and severe infections, it is important to determine the genetic basis of each patient’s VEOIBD before selecting HSCT as a treatment approach.

Understanding the pathophysiology of a disorder caused by a genetic defect can identify unconventional biological treatment options that interfere with specific pathogenic pathways. Patients with mevalonate kinase deficiency or CGD produce excess amounts of IL-1\(\beta\), so treatment with IL-1\(\beta\) receptor antagonists has been successful.\textsuperscript{54,55} This treatment is not part of the standard therapeutic repertoire for patients with conventional IBD. Access to individualized genotype-specific therapies is particularly important, because it might avoid both surgery (including colectomy) and the adverse effects of medical therapy in patients who are unlikely to benefit from conventional IBD therapies in the long term.

A further incentive to establish a specific genetic diagnosis is the ability to anticipate complications. Some patients should be screened for infections (such as for Epstein–Barr virus infection status in \textit{XIAP} defects) or cancer (including B-cell lymphomas in patients with IL-10 receptor deficiency\textsuperscript{109} or skin and hematopoietic malignancies in Hoyeraal–Hreidarsson syndrome). Genetic information can also identify patients who should be screened for extraintestinal manifestations such as idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune neutropenia, or autoimmune hepatitis (Table 2).

Knowledge of the genetic predisposition can reduce the time to detect associated complications. Families who are aware of the genetic basis of their disease can receive genetic counseling.

### When Should We Suspect Monogenic IBD?

The timely diagnosis of monogenic IBD requires assessments of intestinal and extraintestinal disease phenotypes in conjunction with the histopathology and appropriate laboratory tests to exclude allergies or infections.\textsuperscript{18,19} Classification of clinical, endoscopic, histological, and imaging findings into CD-like and UC-like phenotypes can be helpful but is not sufficient to differentiate patients with a monogenic disorder from conventional idiopathic CD (such as discontinuous, transmural inflammation affecting the entire gastrointestinal tract, fistulizing disease, or granuloma formation) or UC (a continuous, colonic disorder with crypt abscess formation and increases in chronic inflammatory cells, typically restricted to the lamina propria). Histopathologists use nonspecific terms such as IBD unclassified in a relevant proportion of patients with VEOIBD, including monogenic forms of IBD. In the absence of highly specific and sensitive intestinal histological markers of monogenic forms of IBD, extraintestinal findings and laboratory test results are important factors to focus the search for monogenic forms of IBD (Table 3 and Figure 2). A phenotypic aide-mémoire summarizing the key findings to ensure that a careful clinical history for VEOIBD and examination to narrow the search for an underlying monogenetic defect is YOUNG AGE MATTERS MOST (YOUNG AGE onset, Multiple family members and consanguinity, Autoimmunity, Thriving failure, Treatment with conventional medication fails, Endocrine concerns, Recurrent infections or unexplained fever, Severe perianal disease, Macrophage activation syndrome and hemophagocytic lymphohistiocytosis, Obstruction and atresia of intestine).

### Table 3. Pivotal Prompts for Suspecting Monogenic IBD

<table>
<thead>
<tr>
<th>Key points</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early age of onset of IBD-like immunopathology</td>
<td>Likelihood increases with very early onset, particularly in those younger than 2 years of age at diagnosis</td>
</tr>
<tr>
<td>Family history</td>
<td>In particular consanguinity, predominance of affected males in families, or multiple family members affected</td>
</tr>
<tr>
<td>Atypical endoscopic or histological findings</td>
<td>For example, extreme epithelial apoptosis or loss of germinal centers</td>
</tr>
<tr>
<td>Resistance to conventional therapies</td>
<td>Such as exclusive enteral nutrition, corticosteroids, and/or biological therapy</td>
</tr>
<tr>
<td>Skin lesions, nail dystrophy, or hair abnormalities</td>
<td>For example, epidermolysis bullosa, eczema, folliculitis, pyodermia or abscesses, woolen hair, or trichorrhexis nodosa</td>
</tr>
<tr>
<td>Severe or very early onset perianal disease</td>
<td>Fistulas and abscesses</td>
</tr>
<tr>
<td>Lymphoid organ abnormalities</td>
<td>For example, lymph node abscesses, splenomegaly</td>
</tr>
<tr>
<td>Recurrent or atypical infections</td>
<td>Intestinal and nonintestinal</td>
</tr>
<tr>
<td>Hemophagocytic lymphohistiocytosis</td>
<td>Induced by viral infections such as Epstein–Barr virus or cytomegalovirus or macrophage activation syndrome</td>
</tr>
<tr>
<td>Associated autoimmunity</td>
<td>For example, arthritis, serositis, sclerosing cholangitis, anemia, and endocrine dysfunction such as thyroiditis, type 1 diabetes mellitus</td>
</tr>
<tr>
<td>Early development of tumors</td>
<td>For example, non-Hodgkin lymphoma, skin tumors, hamartoma, thyroid tumors</td>
</tr>
</tbody>
</table>
Skin lesions and dental and hair abnormalities, and Tumors). An important component of management is to solicit advice from a specialist in VEOIBD.

Very early age of onset of intestinal symptoms and IBD-like endoscopic and histological changes are strong indicators of monogenic IBD as a group (Figure 1). However, there are clear gene-specific differences in the age of onset. The reported time of onset of IBD-like immunopathology in subgroups with, for example, IL-10 signaling defects, WAS, or IPEX, is infancy and early childhood. However, atypical late onset of IBD has been reported in patients with WAS122,123 as well as IPEX.124–126 The age is variable in neutrophil defects, B-cell defects, and XIAP deficiency. Indeed, XIAP deficiency caused by identical genetic defects within families can be associated with VEOIBD or adult-onset IBD.68,73,127 Other diseases, such as GUCY2C deficiency, typically develop during adulthood (Figure 1). Phenotypes of many monogenic forms of IBD change over time; gastrointestinal problems can present as an initial or a later finding.

Some candidate disorders will be recognized by their pathognomonic symptom combinations. Because there are no specific and fully reliable endoscopic and histological features of monogenic VEOIBD, patients with VEOIBD and multiple other features (listed in Table 3) should be considered to have increased likelihood to carry disease-causing mutations. The degree of suspicion should dictate the extent of functional and genetic exploration for an underlying cause. This fraction of causative defects will increase as our knowledge expands and with a growing number of patients undergoing whole-exome sequencing (WES). Although young age of IBD onset is a strong indicator, a strong suspicion for a monogenic cause should lead to limited functional or genetics screening irrespective of age.

**Laboratory Tests and Functional Screens**

Laboratory tests, upper and lower gastrointestinal endoscopy with histological analysis of multiple biopsy specimens, and imaging should be performed for every patient with VEOIBD according to guidelines.13,16–21,128 Histological investigation is paramount not only to differentiate IBD-like features but also to exclude other established pathologies such as eosinophilic or allergic gastrointestinal disease and infection.
Cowie’s milk protein allergy is common and can cause severe colitis that resembles UC and even requires hospitalization. It manifests typically within the first 2 to 3 months of exposure to cow’s milk protein. This may be apparent with breast-feeding or only after introducing formula feeding. Colitis resolves after cow’s milk is removed from the diet, so a trial of exclusive feeding with an amino acid–based infant formula is a customary treatment strategy for all VEOIBD diagnosed when the patient is younger than 1 year of age. However, improvement of symptoms or inflammation does not exclude the possibility that a patient could have a monogenic IBD disorder, because food intolerance and allergy can be secondary to the disorder and allergen avoidance by exclusive enteral nutrition with elemental formula could also alleviate the inflammation of classic IBD.

High levels of IgE and/or eosinophilia are also found in patients with monogenic disorders caused by defects in FOXP3, IL2RA, IKBKG, WAS, or DOCK8 (Table 2 and Supplementary Table 1). It should also be standard practice to exclude infectious causes such as bacteria (Yersinia spp, Salmonella spp, Shigella spp, Campylobacter spp, Mycobacterium tuberculosis, Clostridium difficile), parasites (Entamoeba histolytica, Giardia lamblia), and viral infections (cytomegalovirus or human immunodeficiency virus), remembering that some infections can mimic IBD. However, most of these pathogens do not cause bloody diarrhea for more than 2 to 3 weeks. In addition, monogenic disorders (such as B- or T-cell defect immunodeficiencies or familial HLH type 5, caused by STXBP2 deficiency) predispose patients to intestinal infections.69 Celiac disease should be considered as a differential diagnosis for patients with suspected autoimmune enteropathy presenting with villous atrophy (such as IPEX or IPEX-like patients).

To detect possible causes of monogenic IBD-like immunopathology, we propose additional laboratory screening for all children diagnosed before 6 years of age. The limited set of laboratory tests includes measurements of IgA, IgG, and IgM; flow cytometry analysis of lymphocyte subsets (CD3, CD4, CD8, CD19/CD20, NK cells); and analysis of oxidative burst by neutrophils (using the nitro blue tetrazolium test or flow cytometry–based assays such as the dihydrorhodamine fluorescence assay).

When placed in the context of clinical, histopathologic, and radiological data, these tests can guide the diagnosis toward the more prevalent defects of neutrophil, B-cell, or T-cell dysfunction. Further tests are necessary to characterize particular subgroups, such as those who develop the disease when they are younger than 2 years of age, those with excessive autoimmunity, or those with severe perianal disease. Those tests include flow cytometry analysis of XIAP expression by lymphocytes and NK cells129,130 or FOXP3 expression in CD4+ T cells, which can diagnose a significant proportion of patients with XLP2 and IPEX. Flow cytometry can detect functional defects in MDP signaling in patients with XIAP deficiency.131 IL10RA and IL10RB defects can be detected by assays that determine whether exogenous IL-10 will suppress lipopolysaccharide-induced peripheral blood mononuclear cell cytokine secretion or IL-10–induced STAT3 phosphorylation.30,103,107 Increased levels of antibodies against enterocytes can indicate autoimmune enteropathy, in particular in patients with IPEX.

In contrast to measurements of IgGs, flow cytometry, and oxidative burst assays (which are largely standardized), other tests such as IL-10–mediated suppression of LPS-induced peripheral blood mononuclear cell activation and detection of antibodies against enterocytes are nonroutine assays. Similarly, additional tests for extremely rare genetic defects might be appropriate but are only available at specialized laboratories, often as part of research projects. The clinical utility of the algorithm to use a limited set of laboratory tests to differentiate between conventional and monogenic VEOIBD, as suggested in Figure 2, is based on experience, case reports, and case series of individual disorders. It has not been validated in prospective studies of patients with all forms of VEOIBD.

**Diagnosis via Sequencing of Candidate Genes**

The classic approach to detect monogenic forms of IBD, as described in the preceding text and summarized in Figure 2, is based on careful phenotypic analysis and candidate sequencing to confirm a suspected genetic diagnosis. Due to the increasing number of candidate genes, sequential candidate sequencing can be costly and time consuming. It is therefore not surprising to propose that this strategy of functional screening followed by genetic confirmation will increasingly be complemented by early parallel genetic screening using next-generation sequencing followed by functional confirmation. The US Food and Drug Administration has recently granted marketing authorization for the first next-generation genomic sequencer, which will further pave the way for genome, exome, or other targeted parallel genetic tests in routine practice.132,133 WES or even whole-genome sequencing will increasingly become part of the routine analysis of patients with suspected genetic disorders including subtypes of IBD.79,134,135 This has several important implications for selecting candidate gene lists, identification of disease-causing variants, and dealing with a large number of genetic variants of unknown relevance. In research and clinical settings, WES has been shown to reliably detect genetic variants that cause VEOIBD in genes such as XIAP,67 IL10RA,136,137 G6PC3,138 MEFV,59 LRBA,66 FOXP3,126 and TTC7A.38

There are several reasons to propose extended parallel candidate sequencing for patients with suspected monogenic IBD. Immune and gastrointestinal phenotypes of patients evolve over time, whereas the diagnosis needs to be made at the initial presentation to avoid unnecessary tests and treatment. IBD-like immunopathology can be linked to nonclassic phenotypes of known immunodeficiencies, such as hypomorphic genetic defects in SCID patients (in genes such as ZAP70, RAG2, IL2RG, IL14, ADA, DCLRE1C, CD3G, or TTC7A; see Table 2) with residual B- and T-cell development,68,81,82 glucose-6-phosphatase 3 deficiency with lymphopenia,50 or FOXP3 defects without the classic IPEX phenotype.126 WES has revealed unexpected known causative variants even after workup in centers with specialized
immunologic and genetic clinical and research facilities. This all demonstrates that current knowledge about the disease phenotype spectrum is incomplete, which means that a pure candidate approach is not reliable and genetic screening may have advantages. The 50 monogenic defects associated with IBD provide an initial filter to identify patients with monogenic disorders.

Because of the greatly reduced costs of next-generation sequencing, it is probably cost effective in many cases to perform multiplex gene sequencing, WES, or whole-genome sequencing rather than sequential Sanger sequencing of multiple genes. A big advantage of WES is the potential to identify novel causal genetic variants once the initial candidate filter list of known disease-causing candidates has been analyzed. The number of gene variants associated with VEOIBD is indeed constantly increasing, largely due to the new sequencing technologies, so data sets derived from WES allow updated analysis of candidates as well as novel genes. Because multiple genetic defects can lead to spontaneous or induced colitis in mice, assuming homology, it is likely that many additional human gene variants will be associated with IBD.

Targeted sequencing of genes of interest is an alternative approach to exome-targeted sequencing. Initial studies to perform targeted next-generation parallel sequencing showed the potential power of this approach. Targeted next-generation sequencing of the 170 primary immunodeficiency (PID)-related genes accurately detected point mutations and exonic deletions. Only 9 of 170 PID-related genes analyzed showed inadequate coverage. Four of 26 patients with PID without an established prescreening genetic diagnosis, despite routine functional and genetic testing, were diagnosed, indicating the advantage of parallel genetic screening. Because a major group of VEOIBD-causing variants is associated with PID-related genes, it is obvious how this approach can be adapted and extended to monogenic IBD genes.

Genetic approaches also offer practical advantages. Specialized functional immune assays are often only available in research laboratories and are not necessarily validated; functional tests often require rapid processing of peripheral blood mononuclear cells or biopsy specimens in specialized laboratories. This means that handling of DNA and sequencing seems far less prone to error or variation.

However, relying solely on genetic screening can be misleading, because computational mutation prediction can fail to detect functional damaging variants. For example, variants in the protein-coding region of the IL10RA gene were misclassified as “tolerated” by certain prediction tools, whereas other prediction tools and functional analysis reported defects in IL-10 signaling. Although most studies report variants in protein-coding regions in monogenic diseases, there could be selection bias. It is indeed far more difficult to establish the biological effects of variants that affect processes such as splicing, gene expression, or messenger RNA stability. It should go without saying that novel genetic variants require appropriate functional validation.

The increased availability of sequencing data sets highlights the role of mutation-specific IBD-causing variants that illustrate the functional balance of gene products affected by gain or loss of function variants as well as gene dosage effects. Inherited gain-of-function mutations in guanylyl cyclase cause diarrhea and increase susceptibility to IBD, whereas loss-of-function mutations lead to intestinal obstruction and meconium ileus. Gain-of-function mutations in STAT1 cause an IPEX-like syndrome with enteropathy, whereas loss-of-function mutations are found in patients with autosomal dominant chronic mucocutaneous candidiasis. Loss of TTC7A activity results in multiple intestinal atresia and SCID, whereas hypomorphic mutations cause VEOIBD. Similarly, loss-of-function variants cause classic SCID defects, whereas hypomorphic variants in the same genes allow residual oligoclonal T-cell activation and are associated with immunopathology, including colitis.

Performing next-generation sequencing exome-wide or genome-wide will identify (in each patient) genetic variants of unknown relevance and, in some patients, known variants that are associated with incomplete penetrance or variable phenotype severity. Increasing use of DNA sequencing technologies will lead to detection of hypomorphic variants that cause milder phenotypes and/or later onset of IBD. The increased availability of genotype-phenotype data sets in databases such as ClinVar (http://www.ncbi.nlm.nih.gov/clinvar) or commercial databases will increase our ability to differentiate variants that cause IBD from those without biological effects. WES analysis of patients with pediatric onset of IBD, including VEOIBD, has revealed multiple rare genetic variants in those IBD susceptibility genes that were discovered by association studies. Similarly, WES analysis of patients with genetically confirmed mevalonate kinase deficiency identified multiple variants in IBD-related genes outside of the MVK gene. It is currently not clear how strongly these rare variants influence the genetic susceptibility to IBD as additive or synergistic factors. In particular, in patients with nonconventional forms of IBD, the identification of variants of unknown relevance can lead to the therapeutic dilemma of whether to wait for the disease to progress or start early treatment. Because some of the disease-specific treatment options have potentially severe adverse effects, careful evaluation of genetic variants is required not only to validate sequence data and statistical association but to provide functional evidence that those variants cause disease.

Conclusion

Rare monogenic disorders that affect intestinal immune and epithelial function can lead to VEOIBD and severe phenotypes. These disorders are diagnosed based on clinical and genetic information. Accurate genetic diagnosis is required for assessing prognosis and proper treatment of patients. We summarized phenotypes and laboratory findings for more than 50 monogenic disorders and suggest a diagnostic strategy to identify these extremely rare diseases, which have large effects on patients and their families.
Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org and at http://dx.doi.org/10.1053/j.gastro.2014.07.023.

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Reprint requests
Address requests for reprints to: Dr Holm H. Uhlig, Translational Gastroenterology Unit, Experimental Medicine Division and Department of Paediatrics, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, England. e-mail: holm.uhlig@ndm.ox.ac.uk.

Conflicts of interest
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Other NEOPIGS/VEOIBD Papers


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