The Age of Gene Discovery in Very Early Onset Inflammatory Bowel Disease

See "Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy," by Kotlarz D, Beier R, Murugan D, et al on page 347.

The onset of inflammatory bowel diseases (IBD) peaks in adolescents and young adults, but clinicians are increasingly aware that IBD can occur in very young children, including infants. Infantile and very early onset (VEO)-IBD (diagnosed at <than 6 years of age) forms a poorly defined group of children with IBD that is often classified as 'indeterminate colitis' owing to atypical presentation, severe growth failure, extensive colonic inflammation with lack of small bowel disease, and poor responsiveness to conventional therapies. Given the lack of clear definition(s), it is difficult to estimate the prevalence of infantile and VEO-IBD. Data emerging from several multicenter observational, cohort studies from North America and Europe indicate an increasing prevalence of patients with this unique phenotype.[1] Although genetic determinants have long been considered more important in the pathogenesis of VEO-IBD,[2–6] only recently have genetic mutations including those in interleukin (IL)10RA/B,[7] IL10,[8] XIAP,[9] ADAM17,[10] and the reduced nicotinamide adenine dinucleotide phosphate oxidase genes NCF2/RAC2[11] and NCF4[12] have been identified in VEO-IBD patients. These studies have renewed emphasis in understanding these very young IBD patients with extreme phenotypes and have been providing critical new insights into the pathogenesis of IBD and hopefully pointing to personalized treatment strategies.

In this issue of Gastroenterology, Kotlarz et al[13] screened 66 children diagnosed with IBD at <5 years of age and identified 16 patients with IL-10 or IL-10R deficiency, including 3 patients with IL-10 mutations, 5 with IL-10R1 (encoding IL-10RA) mutations, and 8 with IL-10R2 (encoding IL-10RB) mutations. Interestingly, 2 patients had grossly impaired IL-10 signaling causing disease, despite having mutations in the IL-10RA that were predicted to be tolerated by computational analysis. Also, in addition to missense coding mutations, 1 patient had an IL-10RB 3′ untranslated region mutation, which presumably reduced the level of receptor expression. These studies imply that genetic screening for mutations that are predicted to be damaging alone may not be sufficient to diagnose this form of IBD and further functional studies, including STAT3 phosphorylation, may be required for more accurate diagnosis.

The authors also provide the first detailed clinical phenotypes of a case series of 16 patients with defects in IL-10 signaling.[13] Most strikingly, all 16 patients with IL-10 signaling pathway defects developed progressive colitis before 3 months of age and all had perianal disease. An accurate diagnosis of IBD often lagged behind clinical presentation (13 years in 1 patient). All patients with IL-10RA/B mutations had folliculitis and 4 had arthritis; no patient with an IL-10 mutation had extra-intestinal manifestation of the disease. This paper clearly sends a take-home message to pediatric gastroenterologists and other clinicians: an infant with colitis and perianal disease should be screened for IL-10 signaling defects. What is not clear is the utility of such screening in older children with severe perianal disease who are refractory to treatment, as proposed by the authors. Recent studies demonstrating that polymorphisms in IL-10RA gene are associated with susceptibility with colitis in very young children show that the IL-10/IL-10R pathway may play an important role in the pathogenesis of VEO-IBD and point to a subgroup of patients that may benefit from IL-10 therapy.[14,15]

It is interesting to speculate about the overall contribution of IL-10 and IL-10R mutations in the susceptibility of infantile and VEO-IBD. Thirteen of the 16 patients identified were from consanguineous parents. However, it is unclear how many of the patients in the original cohort of 66 were diagnosed as infants and did not have defects in IL-10R or IL-10.[13] The majority of infantile IBD patients, at least in North America (Moran et al[15]; Muise and Snapper, personal communication), are not from consanguineous marriages and the identification of these mutations has not been as apparent as reported by Kotlarz et al.[13] It will also be important to consider whether IL-10 signaling is associated with other forms of IBD. This may include VEO-ulcerative colitis as recently reported[15] and early onset and adult-onset disease, as suggested by recent pediatric[16,17] and adult genome-wide association studies (GWAS).[18,19]

This study also reports the outcomes of 5 patients after hematopoietic stem cell transplantation (HSCT) with 2-year follow-up on 4 patients.[13] The authors used a highly immunosuppressive conditioning regimen that also resulted in depletion of myeloid cells including dendritic cells in conjunction with intense gut decolonization. HSCT in this patient population was remarkably well tolerated and led to complete clinical remission in 4 out of 5 patients. Although successful, it will be interesting to determine whether HSCT will result in a permanent "cure" for the colonic, joint, and skin

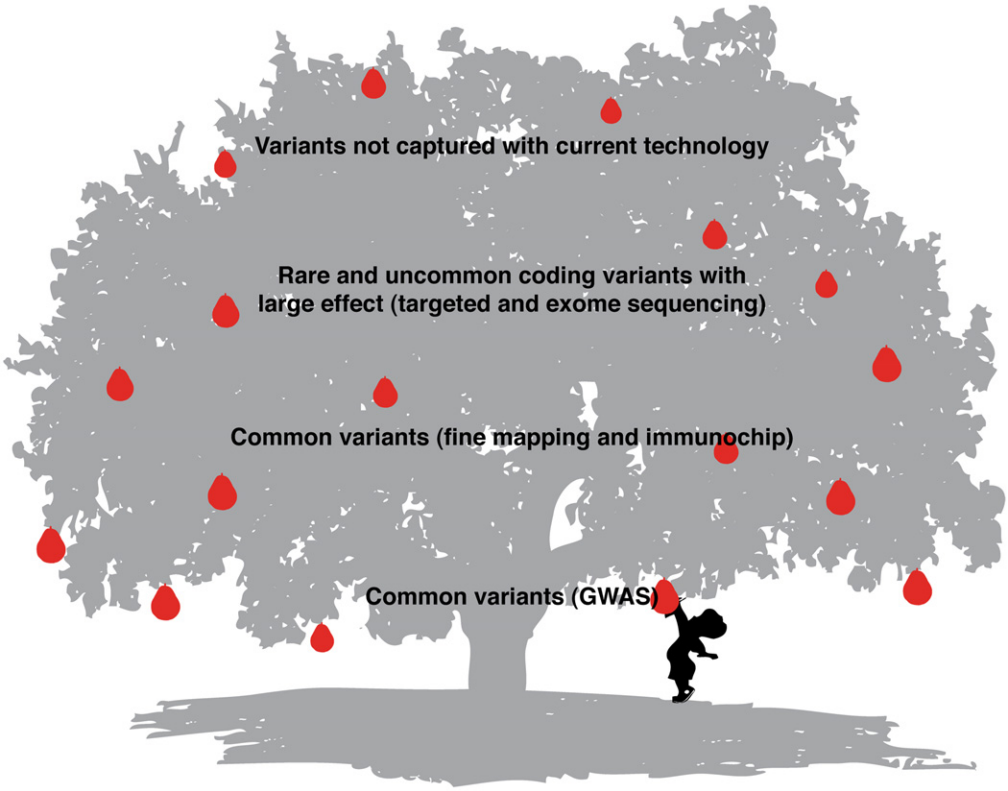

Figure 1. Gene discovery efforts of the past, present, and future in IBD and their degree of difficulty are compared with "fruit harvest." GWAS and fine mapping (immunochip) has only identified appropriately 30% of IBD heritability, mainly discovering common variants (low-hanging fruit). Innovative and newer approaches such as deep sequencing in extreme phenotypes such as VEO-IBD is expected to fill some of the missing heritability in IBD. However, a large proportion of IBD susceptibility may not be discovered any time soon as sophisticated and newer methods are needed to uncover genes of small effects, gene-gene, gene-environmental, and gene-microbiota interactions (high-hanging fruit).

disease in patients with IL-10RB mutations, because this receptor is widely expressed in these tissues and presumably the deficiency would persist after HSCT. Variable results in HSCT ability to establish long-term remission in adult-onset IBD patients (reviewed by Anderson et al[20]) points to cautious interpretation of these promising short-term HSCT results. This study also leads to another important question regarding the role of HSCT in all infantile IBD. As the authors correctly point out, there is a strong possibility that some infant and VEO-IBD patients may have gene defects in the non-hematopoietic cells, including epithelial barrier genes and, therefore, HSCT for all infantile IBD cannot be recommended at this time, unless a hematopoietic gene mutation that is functionally linked to disease can be identified.

A decade of progress in gene discovery efforts in adult IBD, one of the largest involving common complex diseases, have yielded numerous results and uncovered >100 loci,[18,19] substantially more than reported for any other complex disease. However, these common variants involving the pathways of genes in innate immunity, autophagy and T-cell differentiation found with GWAS and subsequent immunochip experiments explains only 30% of the heritability at its best. Because most of these variants are not in the protein coding regions of the gene and the exact function is not known, it is unlikely that these discoveries will lead to therapeutic targets any time soon in IBD. Alternative approaches to find the missing heritability in IBD is urgently needed, and deep and exome sequencing to discover rare coding variants with large effects will be the next 'low-hanging fruit' ripe for harvest (Figure 1). This study[13] identifies defective IL-10 signaling in a number of VEO-IBD patients and demonstrates long-term remission achieved by HSCT offering the much needed 'proof-of-principle' that discoveries can lead to 'cure' in IBD. The best way to develop individualized and targeted treatments in IBD is to precisely understand the pathophysiologic mechanisms. Recent technological advances may make it now possible to identify the missing heritability in IBD by identifying rare variants with large effects. Rare genetic variants are predicted to vastly outnumber common variants in the human genome.[21] By capturing and sequencing all protein-coding exons (the exome comprises 1%–2% of the human genome), exome sequencing is a powerful approach for discovering rare variation and has facilitated the genetic dissection of heritable disorders. Furthermore, rare and low-frequency variants (major allele frequency of 0.5%–1.0%) have been hypothesized to explain a substantial fraction of common complex diseases.[22] We propose that gene discovery efforts focusing on the discovery of rare and low-frequency coding variants, especially in VEO-IBD, and the subsequent functional studies will lead to impor-

tant advances and more personalized therapy for children with IBD.

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.

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A Tale of Two Cohorts: Are We Overestimating the Risk of Colorectal Cancer in Inflammatory Bowel Disease?

See "Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years," by Jess T, Simonsen J, Jørgensen KT, et al, on page 375; and "Incidence and mortality of colorectal adenocarcinoma in persons with inflammatory bowel disease from 1998 to 2010," by Herrinton LJ, Liu L, Levin TR, et al, on page 382.

Colorectal cancer (CRC) has been widely accepted as a long-term complication of inflammatory bowel disease (IBD). A meta-analysis from 2001 showed that the cumulative risks of colon cancer among those with longstanding ulcerative colitis (UC) after 10 years was 2% and as high as 18% after 30 years.[1] A subsequent meta-analysis 5 years later suggested that the cumulative risk of colon cancer in those with Crohn's disease (CD) approaches 3% at 10 years and 8% at 30 years and was similar to that of UC.[2] Factors that may accentuate the risk of IBD-associated CRC include extent of colonic involvement, duration of disease, disease activity, age of IBD onset, family history of colon cancer, and presence of primary sclerosing cholangitis.[3] The association of IBD with increased risk of colon cancer has led to North American consensus statements that recommend regular surveillance with colonoscopy every 1–3 years for those with either UC or CD with colonic disease of >8 years' duration.[4,5] Although there have been no clinical trials that demonstrate surveillance leads to reduced mortality, there is indirect evidence from observational studies that suggests it may lead to earlier detection of cancer and improved prognosis.[6] Another approach to reducing the burden of IBD-associated colon cancer has been chemoprevention. Data from observational studies suggest that long-term use of 5-aminosalicylates may reduce the relative risk of CRC by half in individuals with longstanding IBD, although these effects were inconsistent and less convincing in population-based studies.[7,8]

In this issue of GASTROENTEROLOGY, Jess et al[9] present population-based data from Denmark suggesting that the risk of colon cancer is not as high as previously estimated and in fact may have declined with calendar time. Overall, the investigators found no association between UC and CRC (incidence rate ratio, 1.07; 95% confidence interval [CI], 0.95–1.21). More interestingly, the risk CRC associated with UC seems to have decreased with calendar time. The adjusted relative risk of colon cancer compared to non-IBD patients was 1.34 (95% CI, 1.13–1.58), 1.09 (95% CI, 0.90–1.33), and 0.57 (95% CI, 0.41–0.80) for UC patients diagnosed during 1979–1988, 1989–1998, and 1999–2008, respectively. There were no such temporal trends in CRC observed for CD, which was never at any point greater than that of the general population. Among this study's key strengths is the minimization of selection and referral bias because of the high completeness of Denmark's nationwide IBD registry and the inclusion of all non-IBD individuals as the reference population. These temporal trends may be explained by several potential factors: Dysplasia surveillance, use of chemoprevention, optimization of medical therapy to control disease activity, implementation of colectomy, and UC phenotype. Because colectomy rates were stable in Denmark between 1962 and 2005, they do not likely explain the reduction in risks of CRC.[10] During the same time period, the median age of UC diagnosis increased over time, but this was accounted for in this current study through multivariate analysis. Moreover, the proportion of UC patients with pancolitis at diagnosis has increased with calendar time and would not account for the time trends in CRC.[10] One of the unique attributes of this study population is that, during the study period, there was minimal implementation of dysplasia surveillance in Denmark. Thus, the temporal changes in CRC risk reflect secular changes that are independent of surveillance programs. As noted by the authors, the decrease in IBD-associated CRC may be attributable to more optimal management of UC. Interestingly, those diagnosed with UC during 1999–2008 experienced lower risk of CRC than the general population. Denmark does not have a national colon cancer screening program for the general population. Thus, it is possible that increased utilization of symptom-related colonoscopy among UC patients may have led to earlier detection of premalignant lesions.

The findings from this study may have implications for current paradigms and recommendations for dysplasia surveillance in IBD patients. Decision analyses have previously shown that the cost-effectiveness and life expectancy gained from surveillance is highly dependent on cumulative risk of CRC.[11,12] Therefore, we need to con-