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Pediatric Inflammatory Bowel Disease

Third Edition

Springer

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We dedicate this book…

To our families.

To Gordana-Dana, to Melissa, to Joanne, and to Kay. For their love, understanding, and encouragement.

To Niko; to Alex and Matthew; to Julie, Steven, Chris, Linda, William, and Andrew; and to Jack, Leo, and Benjamin. For helping us believe the best is yet to come.

To our colleagues everywhere, past and present. For working hard each day to make a difference.

To our patients. For constantly inspiring us.

Petar, Andrew, Bob, Judith, and Jon

Foreword

Pediatric inflammatory bowel diseases (IBD) are the most common and most significant chronic disorders in pediatric gastroenterology. The onset of Crohn disease and ulcerative colitis in the first two decades of life presents a number of diagnostic and therapeutic challenges that are unique to pediatric patients. Although the studies available for pediatric diagnosis have improved dramatically in the past three decades, the improvement in technology alone cannot account for the increased frequency of IBD recognized in early childhood. While therapy for older patients has improved dramatically with the use of immunomodulators and the development of exciting biologic strategies, rarely if ever have comprehensive studies of the pharmacokinetics, safety, and efficacy of any of the IBD medications been performed in pediatric patients. A number of excellent medications are not available in liquid preparations that can be swallowed by children, and others, such as timed-release formulations, are developed for delivery to an adult gastrointestinal tract. It is unfortunate that the care we provide to children is often an extrapolation of what is known about and available for adults with IBD.

Pediatric patients with IBD face a number of unique challenges. The onset of disease before puberty can be devastating. Growth failure is a particularly difficult problem with potentially permanent consequences. Much of the pediatric specific research has focused on the role of nutritional therapy to treat growth failure and induce remission. Strategies such as nocturnal nasogastric administration of supplements are widespread in most pediatric centers and are surprisingly well tolerated even by the youngest patients, particularly when the value of nutritional therapy is presented in advance to both the family and the child. Nutrition must be strongly advocated for pediatric patients, as it has great therapeutic value and it is the only therapy for which there are no serious potential complications.

The long-term consequences of medical and surgical therapy are particularly troubling for pediatric patients. The complications of corticosteroids in childhood and adolescence can seem worse than the disease itself. While most of the cosmetic side effects are reversible, the psychological trauma to an adolescent can be overwhelming. We are only beginning to understand and address the long-term consequences of therapy given at an early age. Bone mass accumulation and linear growth are critical processes that are age dependent, with peaks in early adolescence. Failure of therapy at this stage will have permanent and possibly debilitating consequences. In order to spare cumulative steroid exposure, there has been a marked shift in the last two decades to immunomodulator and biologic therapies, often initiated in the first decade of life. Most recently, biologic therapies have resulted in a dramatic shift in therapeutic armamentarium and the sequence of its administration. In adults, the "therapeutic pyramid" has been turned on all of its sides, with a resulting dramatic improvement in quality of life and a decrease in overall corticosteroid exposure, but with a new set of adverse events from therapy. While pediatric patients undoubtedly benefit from the adult data supporting the "top-down" strategies, the data in adults does not necessarily predict the optimal strategies for children. The effects of more "aggressive" therapy are being recognized for their positives and negatives, and the risks and benefits are undoubtedly different in children and adolescents. Whether it is the state of the immature immune system, the effect of rapid growth, or the background susceptibility to different malignancies at different ages, the incidence of profound problems such as hepatosplenic T-cell lymphomas reminds all practitioners that we do not understand the unique aspects of the younger patient that may confer increased susceptibility.

The rate of advance in the science and the understanding of the causes of and the therapies for IBD are truly astounding and fully warrant a third edition of this book. In the decades since the first IBD gene association was discovered, another 200 loci have been identified, and the individual characteristics and functions of these sites are increasingly understood. This is only the beginning of the synergy that can be achieved from the combination of the human genome project results and the availability of genome-wide arrays. The increased focus on the unique aspects and causes of very early onset IBD has led to an exciting and new group of diseases that are more likely to be monogenic and are unlikely to be identified by genome-wide array analysis. These high-impact variants can cause devastating disease in infancy, and some will have entirely novel causes and therapies. Whole exome sequencing will provide a better understanding of the role of individual genes at important loci, and the potential for the "thousand-dollar genome sequencing" is actually within reach, providing not only a true potential for "personalized medicine" but also for predictive identification of "at-risk" children who then might be enrolled in "prevention" studies (as are ongoing in GI allergic diseases and celiac disease) rather than merely treatment protocols. To complement these advances, there is incredible progress in the technology available to study the microbiome, its role in immunomodulation, and the effects of prebiotic, probiotic, antibiotic, and nutritional therapy for gastrointestinal diseases. This work has given insight into the complex relationship between the human immune system and the enteric inhabitants that reside within us. This work will likely identify one important group of environmental triggers that comprise part of the cause of IBD, and through that understanding, we may have one more route for the prevention of IBD in genetically susceptible individuals. A better understanding of the resident microbiota will undoubtedly inform better enteric therapy for IBD.

There is no better care than that given by a well-educated and experienced practitioner who considers all aspects of a patient's problems. This book is designed for those practitioners who care for children. IBD therapy must be customized for each individual patient. There is no more ultimate "individual" patient than a child or adolescent with IBD. The many challenges of growth, nutrition, psychology, and adaptation weigh heavily upon the profound challenges of pediatric Crohn disease and ulcerative colitis. In addition to the need for induction and maintenance of remission, the pediatric gastroenterologist must be obsessed not only with the benefits of early achievement of mucosal healing but also with the long-term consequences of therapy, not just a decade away, but hopefully a half century or more hence. Although these patients will move on to adult gastroenterologists, the problems may only accumulate and multiply. "Above all else, do no harm" is a wise admonition for pediatric IBD, where therapies are rapidly improving and there is a great potential for a cure of these devastating illnesses. These therapies and ultimate cures for Crohn disease and ulcerative colitis will come from the extraordinary advances in immunology and immunogenetics that are well detailed in this book. Until that time, we must rely on the conventional approaches developed in adults, but with the conviction to verify their efficacy for children with IBD.

This book is a landmark step toward better understanding of pediatric IBD and the challenges of IBD therapy in children. The editors are highly respected clinical scientists who have each contributed substantially to the knowledge about pediatric IBD. In addition, the knowledge gained from their extensive clinical experience is reflected in this book. They have assembled a truly extraordinary group of authoritative leaders whose contributions to this volume will guarantee that this will be a reference for all who care for pediatric IBD. The book is a tribute to those authors, but is dedicated to the children and adolescents with Crohn disease and ulcerative colitis. It is remarkable how far we have come since the first edition, yet sobering how far the journey is yet to go. It is a sign of the times that increased focus at every level is directed toward children, and this book is one significant step along that road toward improving care for the hundreds of thousands of children and adolescents with inflammatory bowel diseases. It should be a required reading for all those who care for these children.

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Preface

We are pleased to present the third edition of *Pediatric Inflammatory Bowel Disease.* Since the publication of the last edition, there has continued to be an explosion of discoveries and advances in the areas of genetics, immunology, pharmacogenomics, microbiome, optimization of therapeutic delivery, and epidemiologic knowledge, particularly regarding our youngest pediatric patients afflicted with inflammatory bowel disease. These advances have resulted in improved understanding of the etiology and pathogenesis of inflammatory bowel disease and have provided mechanisms to optimize therapeutic management of our patients.

The focus of the textbook remains unchanged. We hope to provide a reference that assists clinicians from multiple disciplines, including primary care, pediatric, and internal medicine gastroenterology – all healthcare providers who care for children with inflammatory bowel disease. This textbook will augment other utilized references, focusing on pediatrics while also incorporating the adult evidence and experience that has informed and influenced the care of children.

The format of the textbook is similar to the last edition, with sections dedicated to etiology and pathogenesis, epidemiology and clinical features, diagnosis, medical and nutritional therapy, surgical therapy, research, and special considerations – a section that includes topics which have become increasingly important and challenging for the experienced clinician, including addressing the psychological aspects of pediatric inflammatory bowel disease, legislative advocacy, transition from pediatric to adult care, and quality improvement. We are pleased to offer topical new chapters regarding immune dysregulation in very early onset pediatric inflammatory bowel disease, fecal markers of disease activity, therapeutic drug monitoring, dietary therapies, complementary and alternative therapies, management of intra-abdominal complications, postoperative surveillance, and fostering self-management and patient activation, coauthored by two parents of patients with pediatric inflammatory bowel disease.

As with the previous two editions, we are indebted to the internationally recognized experts who contributed to this book, inculcating the latest research- and evidence-based clinical opinion to the updated chapters. This edition would not have been possible if not for their generous contributions and dedication.

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Part VII Special Considerations

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Part I

Etiology and Pathogenesis

Genetics of Inflammatory Bowel Diseases

1

Christopher J. Cardinale and Hakon Hakonarson

Introduction

The inflammatory bowel diseases (IBD), Crohn disease and ulcerative colitis, are immune-mediated disorders resulting in chronic, relapsing inflammation of the gastrointestinal tract. The etiology of IBD is multifactorial, influenced by both genes and environmental factors. It has been hypothesized that environmental factors and maladaptive immune responses to gastrointestinal flora generate a dysregulated inflammatory cascade creating mucosal injury in genetically susceptible individuals. Over the last two decades, considerable interest and research have focused on the genetic aspect of IBD. The identification of linkage between Crohn disease and the pericentromeric region of chromosome 16 (*IBD1*) by Hugot et al. in 1996 spawned a series of genome scans and linkage analyses in search of susceptibility and phenotypic modifier genes [1]. In 2001, the discovery that specific polymorphisms in the *CARD15/NOD2* gene at the *IBD1* locus were associated with Crohn disease introduced a new era of genotype-phenotype investigations [2, 3]. The advent of genome-wide association studies has resulted in the successful identification of new, well-replicated disease associations, now encompassing 200 independent loci [4]. This abundance of associations shows that IBD is highly polygenic with a complex mode of inheritance.

The field of IBD genetics is of special interest to pediatric gastroenterologists for both practical and investigational reasons. From a clinical practice standpoint, pediatric gastroenterologists are often faced with questions from concerned parents regarding the risk of IBD among current or future siblings, as well as the eventual offspring of the affected child. Understanding genetic associations of IBD can provide patients and their families with useful information that may help them cope with the disease. Furthermore, as our knowledge of genotype-phenotype associations grows, it is anticipated that genotyping at the onset of disease may enable physicians to predict disease course and tailor medical therapies specific for each patient. Insofar as advancing the field of gastroenterology through research, studies of pediatric IBD genetics are significant because children have been exposed to fewer environmental confounders of disease than their adult counterparts. Examining the disease in young individuals could provide us with keys to unlock intrinsic genetic mechanisms in IBD that may not otherwise be detected in adult studies. This may be especially important in individuals with very early-onset IBD (<5 years), whose disease course and phenotypes are the most discordant with those of adult-onset IBD.

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Crohn Disease and Ulcerative Colitis: Genetic Epidemiology

Ethnic and Racial Variations of Disease

The genetic underpinnings of IBD are supported by ethnic and racial variations in disease prevalence. The highest rates of IBD are found in Caucasian individuals, especially those of Jewish heritage. Among Jewish subgroups, Ashkenazi Jews have a two- to ninefold greater prevalence of IBD over non-Jewish counterparts [5]. This increased occurrence has been noted to be stable over time and geographic distribution, substantiating the important role of genetics in IBD. While the vast majority of genetic investigations in IBD have been conducted in Caucasians, it is apparent that it can occur in all racial and ethnic groups. African Americans and Asians are believed to have a lower risk of IBD, although there appears to be a trend toward growing prevalence in these populations. Basu et al. reported that African Americans and whites were more likely to have Crohn disease, whereas

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ulcerative colitis predominated among Mexican Americans [6]. While intestinal manifestations did not appear to vary based upon race or ethnicity, there were differences in extraintestinal manifestation between groups. Among Crohn patients, African Americans were more likely to develop arthritis and uveitis than whites, whereas joint symptoms and osteoporosis were more common among whites with UC than Mexican Americans.

Family Studies

The concept that IBD may, in part, be hereditary has been well established through observations of familial disease aggregation. Family studies have demonstrated that 5–30% of probands with Crohn disease and ulcerative colitis identify the presence of IBD in a family member [5]. This association appears to be stronger for Crohn disease than ulcerative colitis. Phenotypically, relatives of probands with IBD are more likely to develop the same form of disease as the affected family member, with a concordance between family members in terms of localization of disease but not disease severity. With regard to age of disease onset, patients with a family history of IBD are thought to be more likely to develop disease at an earlier age than affected individuals lacking a family history [7]. Among family members, the risk of developing IBD is greatest among first-degree relatives, especially siblings. The relative risk (RR) for a sibling of a Crohn patient developing disease is 13–26; for ulcerative colitis patients, the RR for a sibling is 7–17 [8]. Orholm et al. reported that 6.2% of children born to a parent with ulcerative colitis developed IBD and 9.2% of children born to a parent with Crohn disease developed IBD [9]. In the rare instance that both parents have IBD, studies estimate that their children have a 33% chance of developing IBD by age 28 [8]. While second- and third-degree relatives of IBD probands have a lower likelihood of disease, their risk is still elevated compared to the background population.

Twin Studies

Investigations of monozygotic and dizygotic twins have provided strong evidence that genetics play an integral role in the etiology of IBD. Twin studies are based upon the premise that in the setting of a similar environmental milieu, rates of disease concordance between twins correlate with the influence of genetic factors. To date, three large studies of twin pairs with IBD from Scandinavia and the UK have consistently identified higher concordance rates among monozygotic twins with Crohn disease and ulcerative colitis than dizygotic twins [10–12]. The influence of genetics appears to be greater in Crohn disease than ulcerative colitis with reported cumulative monozygotic concordance rates of 30 and 15%, respectively [13]. Concordance rates for dizygotic twins are approximately 4% in both Crohn disease and ulcerative colitis. Co-twins with IBD are more likely to develop the same disease type, although mixed pairs of dizygotic twins with ulcerative colitis and Crohn disease have been reported. With regard to disease-specific characteristics, Scandinavian twin registries demonstrated concordance of 40–77% for disease location; however, there appeared to be no association of disease behavior or extent among co-twins [10, 12]. A trend toward concordance for age at diagnosis was identified with 40–67% receiving a diagnosis of IBD within 2 years of one another. Thus, the concordance data from twin studies provide strong evidence that genetic influences are important in the development of IBD. However, monozygotic concordance is not 100%, and the low concordance between dizygotes suggests that genotype alone is not sufficient for disease evolution.

Identifiable Gene Variants in Crohn Disease

NOD2/CARD15 Gene and Crohn Disease

The *NOD2/CARD15* gene located on the *IBD1* locus of chromosome 16 is associated with an increased susceptibility to Crohn disease but not ulcerative colitis. Among the more than 30 known amino acid polymorphisms identified in the *NOD2* gene [14], the most common variants are two missense mutations, R702W and G908R, and one frameshift mutation L1007fsinsC. From a disease pathogenesis perspective, NOD proteins (NOD1 and NOD2) are mammalian pattern recognition receptors which serve the innate immune system as bacterial sensing molecules. NOD2 is a cytosolic protein found in a variety of cells including monocytes, macrophages, B and T lymphocytes, dendritic cells, and intestinal epithelial cells. Stimulation of NOD2 by its ligand, muramyl dipeptide (MDP), propagates signal transduction pathways leading to nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) activation. These three polymorphisms impair activation of NF-κB, suggesting that deficiencies in innate immune cell function play a role in the development of Crohn disease [15].

Epidemiology of *NOD2* Mutations

A *NOD2* risk allele confers a two- to threefold relative risk of developing Crohn disease; this risk is increased to 17-fold if two alleles are present [16]. Ten to thirty percent of patients with Crohn disease are heterozygous for one of the three mutations, while 3–15% are homozygous or compound heterozygotes [17]. Although these variants are associated with

an increased risk of Crohn disease, 8–15% of the healthy population possesses at least one of these mutations, and 1% of healthy individuals are homozygous or compound heterozygotes. That genotypic variants are found in individuals without known Crohn disease suggests phenotypic expression of disease is subject to polygenic factors, variable penetrance, and other environmental mediators.

Studies of patients with Crohn disease worldwide have revealed that the association of *NOD2* polymorphisms with Crohn disease varies between different ethnic populations. North American adult Caucasian cohorts report carriage rates of 10–30% for the three common *NOD2* variants, while minority groups were found to have lower allele frequencies. A North American, multicenter study of pediatric patients with Crohn disease identified *NOD2* polymorphisms among 25% White, 1.6% African American, and 1.6% Hispanic participants [18]. Significant diversity in allele carriage has been described among Crohn patients in European countries and background control populations. *NOD2* variants are virtually absent in Japanese, Korean, Chinese, and sub-Saharan African individuals. High rates of *NOD2* mutations have been seen in the Jewish Ashkenazim with one Israeli group reporting the presence of variants in 51% of pediatric and 37.5% of adult Crohn patients studied [19].

HLA Type and IBD Susceptibility

The major histocompatibility complex (MHC) locus on chromosome 6p encodes genes in the human leukocyte antigen (HLA) family which serve an immunoregulatory function through their role in antigen presentation to T cells. Associated polymorphisms between HLA types and IBD have included HLA-B, HLA-DRB1, HLA-DQB1, HLA-DP, tumor necrosis factor (TNF), heat shock protein (HSP)-70, and MICA [20]. The polymorphic nature of the HLA region as well as its complex linkage disequilibrium has resulted in heterogeneous findings among investigators. Of the greater than 100 association studies of IBD and HLA performed to date, stronger evidence exists for an association with class II alleles than class I alleles.

Class II alleles DRB1*0103, DRB*1502, and DRB*401 have been consistently associated with ulcerative colitis [21]. Phenotypic analyses have identified DRB1*0103 to be predictive of a more aggressive form of ulcerative colitis with shorter time to colectomy than those without the allele. In Crohn patients, a particular link between DRB1*0103 and isolated colonic disease has been reported [22]. The correlation of DRB1*0103 with both colonic Crohn disease and ulcerative colitis has been postulated to provide a unifying molecular mechanism for colonic involvement in IBD. HLA associations with extraintestinal manifestations of IBD have also been evaluated. One small study of both ulcerative colitis and Crohn disease identified a connection between TNF promoter variants and erythema nodosum [23]. HLA-B*27, HLA-B*35, and HLA-DRB*103 have been associated with type I peripheral arthropathy, whereas HLA-B*44 is associated with type II peripheral arthropathy [24, 25]. Symptoms of uveitis have been linked with HLA-B27 and DRB*0103.

High-density genotyping in the MHC region has reinforced the primacy of HLA-DRB1*0103 in both Crohn disease and ulcerative colitis in a study by Goyette et al. Their study genotyped 7,406 single nucleotide polymorphisms in 32,000 IBD cases and an equal number of controls [26], finding that DRB1*0103 gave by far the strongest signal. The fine resolution of mapping allowed localization to specific amino acid substitutions in the MHC molecule which revealed that the causal variants are located within the peptide-binding groove and thereby influence antigen presentation directly [26].

Genome-Wide Association Studies in IBD

A major new development in the field of complex human genetics has been the capacity to perform dense genotyping across the genome on microarrays. This technological development has made possible the performance of genome-wide association studies (GWAS). These studies have the capacity to assay a large fraction of the common human genetic variation and have the potential to markedly increase understanding of the genetic basis for complex, polygenic disorders. GWAS tests each of millions of single nucleotide polymorphisms (SNPs) for direct association with the trait of interest by comparing the population allele frequency between IBD cases and healthy controls [27]. This direct association testing approach has the advantage of greater power to detect small effects. Risch and Merikangas estimated that 17,997 affected sibling pairs would be necessary to detect a risk allele with 50% frequency and odds ratio of 1.5 by linkage analysis [28]. By contrast, direct association analysis would require only 484 cases and controls. The early GWAS studies detected only dozens of associations, but with the introduction of meta-analysis combining case-control data from many cohorts along with large-scale genotyping on the Immunochip and trans-ancestry analysis, the number of associated loci has risen to 200 [4].

Association of *IL23R* (Interleukin 23 Receptor) Polymorphisms to Crohn Disease and Ulcerative Colitis

A genome-wide association study in a North American Crohn disease cohort identified multiple new gene associations, notably including multiple polymorphisms within the

IL23R gene on chromosome 1p31 [29]. In particular, an amino acid polymorphism, Arg381Gln, located in the cytoplasmic domain of the *IL23R* protein, demonstrated highly significant evidence for association. The less common glutamine allele conferred significant protection against developing IBD in non-Jewish and Jewish Crohn disease cohorts, as well as in non-Jewish ulcerative colitis cohorts. Additional independent association signals were observed indicating the presence of multiple associations within the *IL23R* gene [29]. Since the initial report, the *IL23R* associations have been replicated in a childhood-onset IBD cohort from Scotland [30], as well as in a Belgian CD cohort [31]. The functional IL-23 heterodimeric receptor is comprised of the *IL23R* (chromosome 1p31) and *IL12RB2* (chromosome 19p13) [32] subunits, with the latter subunit shared with the functional IL-12 receptor. Similarly, the IL-23 cytokine is comprised of a unique subunit, p19 (chromosome 12q13), as well as the p40 subunit which is common to the IL-12 functional cytokine. Additional support for the role of the IL12/IL23 pathway in mediating end-organ inflammation has been generated in mouse models demonstrating requirement for IL-23 in murine colitis [33–36], experimental autoimmune encephalitis [37], and collagen-induced arthritis. Similar *IL23R* gene associations have been reported in human psoriasis [38]. Collectively, these findings would suggest that blocking the IL-23 pathway may be efficacious in the treatment of IBD. In support of this, anti-p40 antibodies (which would block both IL-12 and IL-23 pathways) [39] have been effective in the treatment of Crohn disease. Whether specific targeting of the p19 pathway to achieve IL-23-specific effects [40] will be more efficacious will be the focus of future studies.

Association of the *ATG16L1* Autophagy Gene to Crohn Disease

A GWAS focusing on coding region polymorphisms identified association of the amino acid polymorphism Thr300Ala with Crohn disease. The *ATG16L1* gene is part of the autophagosome pathway and has been implicated in the processing of intracellular bacteria [41]. *ATG16L1* is expressed in intestinal epithelial cells, as well as in $CD4^+$, $CD8^+$, and $CD19^+$ primary human lymphocytes [42]. This association has been confirmed in multiple independent cohorts, including Belgian [31] and North American cohorts [42]. Of interest is that no association was observed to ulcerative colitis, suggesting that *ATG16L1*, like the NOD2/CARD15 associations, represents CD-specific risk alleles. The *ATG16L1* association suggests that autophagy and host cell responses to intracellular microbes are involved in the pathogenesis of CD. Before the discovery of this genetic association, the role of autophagy in IBD was not well appreciated, and this example demonstrates how genetic investigation can advance new treatment approaches and understanding of disease pathophysiology.

Association of *TNFRSF6B* and *IL27* to Pediatric Age of Onset IBD

Pediatric-age-onset IBD is an attractive target for GWA studies for several reasons. Early-onset IBD is characterized by unique phenotypes [43, 44], and increased severity, suggesting the possibility of loci specific to early-onset disease. Early-onset IBD also has a stronger association with family history of IBD, and the childhood population may also be less affected by exogenous factors implicated in adult-onset IBD, such as diet, smoking, and medication [45]. Therefore, GWA studies in children may provide additional power to reveal genetic risk variants with only modest effects relevant in pediatric-age- and adult-onset IBD.

Two GWAS have been performed focusing exclusively on pediatric cases. The most recent of these, conducted by Imielinski et al. in 2009 [46], built on the initial study by Kugathasan et al. in 2008[47] and involved 3,426 affected individuals and 11,963 genetically matched controls. These studies nominally replicated 29 of 32 loci previously associated with adult-onset Crohn disease, as well as 13 of 17 adult-onset ulcerative colitis loci. Further, these studies identified seven new regions associated with childhood IBD susceptibility.

Two of the newly identified loci present immediate insight regarding the pathogenic mechanisms implicated in pediatric-age-onset IBD. Kugathasan et al. found an association located on chromosome 20q13, a block which contains multiple genes, most interestingly *TNFSFR6B* [47]. This locus has since been replicated in an independent pediatric study [48]. The protein product of *TNFSFR6B*, decoy receptor 3 (DcR3), is a member of the tumor necrosis factor receptor superfamily. DcR3 binds to and neutralizes signaling by pro-inflammatory cytokines LIGHT, TL1A, and Fas ligand [49–52]. Serum DcR3 levels were elevated in pediatric cases of IBD relative to controls, most dramatically in patients harboring the 20q13 minor allelic variants [47].

The second locus of interest is in the 16p11 region, in an LD block containing several genes including *IL27*. The IL-27 cytokine regulates T-cell differentiation in adaptive immune responses, influencing the balance between pathogenic Th17 cells and inflammation-suppressing T-cell subsets. Identification of *IL27* as a candidate gene thus provides further support for involvement of the Th17 pathway in pathogenesis of Crohn disease, corroborating gene findings from other genome-wide scans (*IL23R*, *STAT3*, *JAK2*, *IL12B*) [53, 54]. Figure 1.1 shows association results for IL12/IL23 pathway genes (left panel) and IL27/TH17 pathway genes

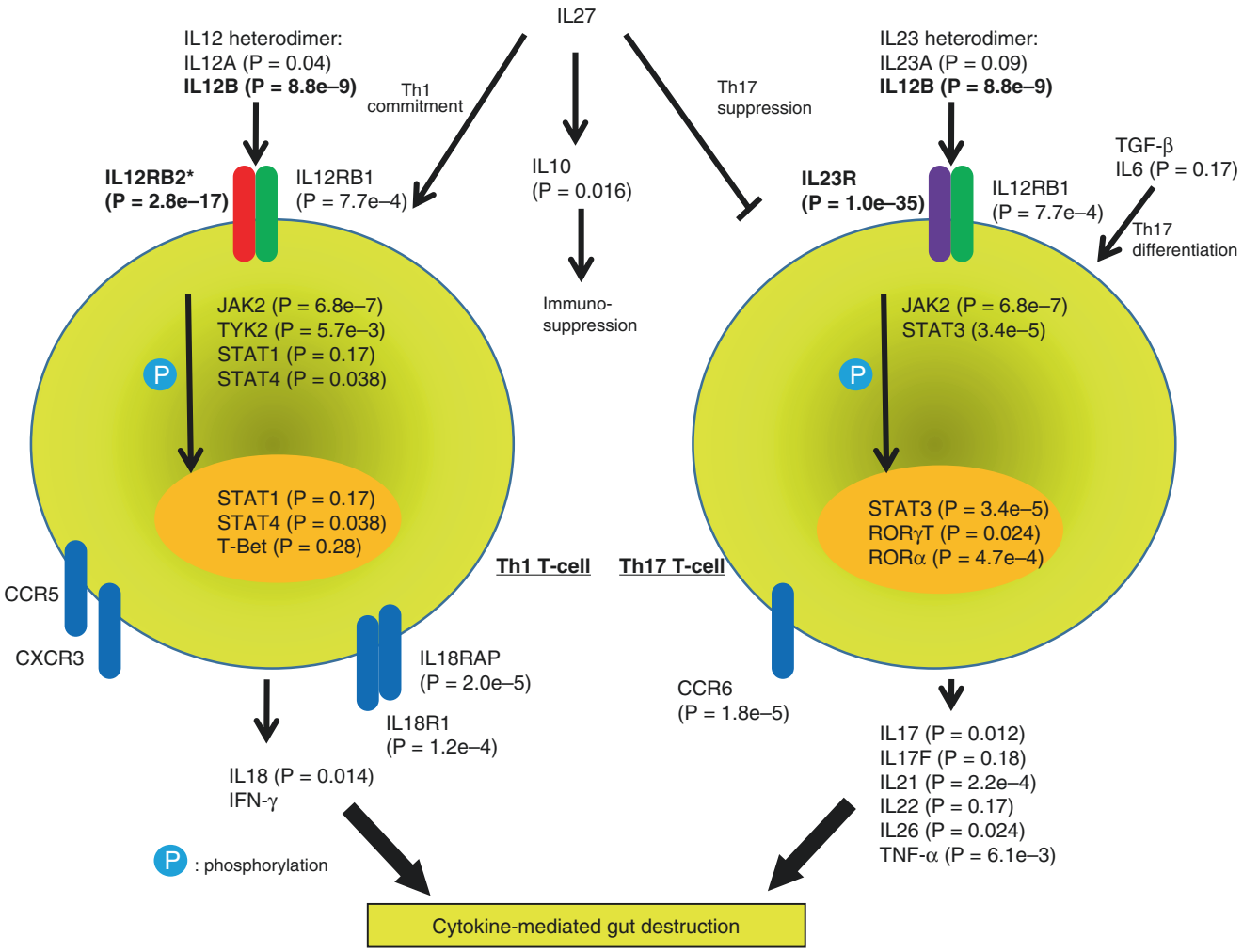

Fig. 1.1 Associations of the IL12/IL23- and IL27-regulating genes with IBD in keeping with the TH1 and TH2/TH17 theory (Wang et al. [96]). Only the main proteins in these pathways are shown. For each gene, the most significant P value among SNPs closest to the gene was annotated

(right panel) in pediatric-age-onset IBD, lending support to the relevance of these two opposing signaling pathways, with multiple associated genes, in the pathogens of IBD.

Meta-analysis

The associated common variants identified by single GWAS usually have modest individual effects, often with odds ratios of smaller than 1.2 for binary traits or with explained variance of less than 1% for quantitative traits [55]. To discover common variants with even smaller effects, a sample size larger than that of single studies is required. Meta-analysis combines large data sets and is an economical way to improve sample size. An early meta-analysis of three genome-wide Crohn scans identified 21 new Crohn susceptibility loci. It increased the number of independent loci conclusively associated with Crohn to 32, explaining approximately 20% of Crohn disease heritability [56]. Including three additional GWAS scans, a recent meta-analysis added 39 new confirmed Crohn disease susceptibility loci [57]. These 39 new loci increase the proportion of explained heritability to only 23.2%, indicating their rather modest effects. While some of these newly identified loci contain a single gene, others contain multiple genes or none at all. Some functionally interesting candidate genes in the implicated regions including *STAT3*, *JAK2*, *ICOSLG*, *ITLN1*, and *SMAD3* are briefly described below.

STAT3 (signal transducer and activator of transcription 3) and JAK2 (Janus kinase 2) both come from the JAK-STAT pathway. This major signaling pathway transmits information from cell surface receptors stimulated by cytokine and growth factors to the nucleus to regulate transcription of various genes. STATs play a central role in Th17 differentiation [58] while both contribute to IL23R signaling [32]. ICOSLG (inducible T-cell co-stimulator ligand) is a co-stimulatory molecule expressed on intestinal (and other) epithelial cells. It has been suggested that ICOSLG