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Recent Insights Into the Genetics of Inflammatory Bowel Disease

Judy H. Cho[*] and **Steven R. Brant**[‡]

[*]Departments of Medicine and Genetics, Yale University, New Haven, Connecticut [‡]Harvey M. and Lyn P. Meyerhoff Inflammatory Bowel Disease Center, Department of Medicine, School of Medicine, Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland

Abstract

Inflammatory bowel diseases (IBDs) are complex, multifactorial disorders that comprise Crohn's disease (CD) and ulcerative colitis (UC). Genome-wide association studies have identified approximately 100 loci that are significantly associated with IBD. These loci implicate a diverse array of genes and pathophysiologic mechanisms, including microbe recognition, lymphocyte activation, cytokine signaling, and intestinal epithelial defense. Consistent with epidemio-logic predictions, many IBD-associated loci demonstrate genome-wide significant associations to both CD and UC, notably, genes whose products function in the interleukin-23 pathway, and transcription factors, including NK2 transcription factor related, locus 3 (NKX2-3), SMAD3, STAT3, ZMIZ1, and c-REL. Although CD and UC are both associated with genomic regions that implicate products of genes involved in leukocyte trafficking, there is evidence for association patterns that are distinct between CD and UC. CD-predominant associations include *NOD2* and genes that regulate autophagy. In UC, the predominant association signal is on chromosome 6p21, in the major histocompatibility complex region, near HLA class II genes. UC-predominant loci have also implicated genes mediating epithelial defense function. There is a striking overlap of loci between diseases, which could provide comparative insight into mechanisms of disease pathogenesis. Genes that encode factors that function in the interleukin-23 pathway have been associated with a number of chronic inflammatory diseases, notably psoriasis and anky-losing spondylitis. Distinct genetic associations indicate that the colitis associated with primary sclerosing cholangitis is pathophysiologically distinct from UC that is not associated with primary sclerosing cholangitis. As many as 14 susceptibility loci are shared between IBD and celiac disease, indicating significant overlap in pathophysiology. Future genetic studies will be directed toward identifying un common variations with potentially greater statistical effects, defining population differences, and more completely accounting for familial transmission of disease.

Reprint requests Address requests for reprints to: Judy H. Cho, MD, Departments of Medicine and Genetics, 333 Cedar Street, LMP 1080, New Haven, Connecticut 06520. judy.cho@yale.edu; fax: (203) 785-5673.

Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are available online only with the electronic version of the article. Visit the online version of Gastroenterology at www.gastrojournal.org, and at doi:10.1053/j.gastro.2011.02.046.

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Genetic Epidemiology

Population-based studies have provided compelling evidence that genetic factors contribute to the pathogenesis of inflammatory bowel disease (IBD); they demonstrated an 8- to 10-fold greater risk of IBD among relatives of ulcerative colitis (UC) and Crohn's disease (CD) probands[1]; that Ashkenazi Jews have an increased risk for IBD[2]; and, most importantly, that there is concordance between twins. Overall, rates of concordance between twins are more modest for CD (30.3% in monozygotic vs 3.6% in dizygotic twins) and are somewhat greater for UC (15.4% in monozygotic vs 3.9% in dizygotic twins) than shown previously.[3] The significantly greater concordance for CD vs UC in monozygotic twins indicates that genetic factors make a larger contribution to CD than UC. However, it is also clear that environmental and developmental factors are required for most cases of IBD to develop.

Exceedingly rare, autosomal, recessive mutations in the gene encoding interleukin (IL)-10 receptor[4] and the IL-10 cytokine[5] have been associated with severe forms of CD in infants born to consanguinous parents. The IL-10 receptor is a tetramer comprising the products of the *IL10RA* (chromosome 11q21) and *IL10RB* (chromosome 21q22) genes. Loss-of-function, autosomal, recessive mutations in either receptor subunit are sufficient to cause disease.[4] IL-10 inhibits expression of proinflammatory cytokines and increases expression of anti-inflammatory cytokines. These findings demonstrate that loss of IL-10 or IL-10R function can result in a severe CD phenotype without any apparent environmental trigger. Patients with the mutations in the IL-10 receptor[4] or cytokine[5] have been successfully treated by bone marrow transplantation.

A few genetic disorders, such as those that affect neutrophil function (X-linked chronic granulomatous disease from mutations in cytochrome b-245, β polypeptide) and glycogen storage disease type 1B (from mutations in glucose-6-phosphate transporter *SLC37A4*), have very high rates of IBD.[6,7] The extent to which Mendelian and non-Mendelian forms of IBD share pathogenesis is not known. However, significant associations at chromosome 1q32 near the *IL10* gene have been observed in common, non-Mendelian forms of CD[8] and UC.[9] For the most part, the non-Mendelian forms of IBD have been associated with common (often defined as those polymorphisms where the less common minor allele is present in >5% of chromosomes), relatively low-penetrance genetic variations. Among the >100 IBD genes and loci defined, only nucleotide binding oligomerization domain protein 2 (NOD2) (5% penetrance or ~ 20-fold risk in mutation homozygotes)[10] has a meaningful contribution to [CD] risk alone. Nearly all remaining genes and loci contribute modestly to IBD risk, having a relative risk of <1.5-fold and marginal increase in disease penetrance (Figure 1). We have not comprehensively identified genes and variants that mediate familial IBD, found in up to 30% of IBD probands.

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Gene Mapping Approaches

Of the numerous candidate gene studies tested before linkage and genome-wide association studies (GWAS) were performed, only major histocompatibility complex class II alleles were consistently associated with IBD.[11] Linkage mapping studies identified segments of human chromosomes shared among affected relatives, greater than expected by chance, and described the *IBD1* CD locus on chromosome 16 in 1996, where the *NOD2* gene was later identified. GWAS began in 2005, with a modest-sized Japanese case-control cohort of patients with CD and a relatively low-density genome-wide panel of small nucleotide polymorphisms (SNPs).[12] This study mapped the region that confers the highest risk for CD among Pacific Asian populations; it contains *tumor necrosis factor* [TNF] *superfamily [ligand] member 15 (TNFSF15)* that encodes TNF ligand related molecule 1 (TL1A). Distinct patterns of association have been observed in IBD patients of European ancestry, and studies of Asian and European ancestry-associated polymorphisms indicate that disease-associated haplotypes might affect expression of *TNFSF15*.[13,14] GWAS in North American and European white populations have used arrays of several hundred thousand SNP markers, which comprehensively tag common SNPs throughout the human genome. By combining large datasets, meta-analyses powered to identify loci that have even smaller effects on IBD risk than those identified through individual GWAS have been performed.[9,15]

With few exceptions, the precise functional allele, or even the causative genes in the GWAS-identified association regions, have not been defined. Many of the loci associated with IBD by GWAS contain multiple genes and some contain no genes. Missense polymorphisms conserved between species and predicted to alter protein structure and/or function are strong candidates for functional, disease-associated polymorphisms. Many of the observed associations are believed to mediate individual differences in messenger RNA expression: the SNPs that have the highest levels of association with IBD may cause significant differences in messenger RNA expression, supporting their role in pathogenesis. Although it is logical to prioritize the potential pathogenic role of expressed transcripts contained within regions of maximal genetic association, it is important to remember that regulatory domains are often distant from the protein-coding regions of genes. Table 1 lists the genetic regions most significantly associated with CD and UC, and select loci that demonstrate genome-wide significance in association with CD and UC.

Genes That Affect Microbe Recognition by the Innate Immune System—*NOD2*

The most common mutations in *NOD2* that are associated with CD (Arg702Trp [rs2066844], Gly908Arg [rs2066845], and Leu1007fsinsC [rs41450053]) lie either within or near the C-terminal, leucine-rich repeat domain, which is required for microbial sensing.[16,17] NOD2 is expressed by many leukocytes, including antigen presenting cells, macrophages, and lymphocytes, as well as ileal Paneth cells, fibroblasts, and epithelial cells. Activation of NOD2 by microbial ligands activates the transcription factor nuclear factor–κB (NF-κB) and mitogen-activated protein kinase signaling, and functions as a positive regulator of immune defense. Studies in primary human cells stimulated with muramyl

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dipeptide (a ligand of NOD2 and a bioactive component of a peptidoglycan in cell walls of gram-positive and gram-negative bacteria) demonstrated that homozygous or compound heterozygous mutations in *NOD2* reduced activation of NF-κB, compared to wild-type *NOD2*.[18]

In individuals of European ancestry, heterozygous carriage of one of the major risk alleles confers a 2.4-fold increase in risk for CD; homozygous or compound heterozygous carriage confers a 17.1-fold increase in risk for CD.[19] *NOD2* mutations are consistently associated with ileal location and stricturing disease.[19,20] In African Americans, *NOD2* mutations are much less common and only heterozygous, occurring at 20% the frequency observed in Americans of European ancestry—proportionate to the degree of European admixture.[21,22] However, risk for CD among carriers of heterozygous mutations is similar (odds ratio = 4.1) to that observed in European ancestry cohorts.[22] The *NOD2* mutations associated with CD are not observed in Asian or sub-Saharan African populations.[22–24] Loss-of-function mutations in *NOD2* alone are not sufficient to cause CD. However, *NOD2*-deficient mice express lower levels of antimicrobial defensins and have increased colonization by commensal bacteria and reduced capacity to clear pathogens. These findings indicate that one major pathogenic mechanism of *NOD2* mutations may involve impaired clearance of bacteria that increases their invasion and contributes to the deeper, often transmural inflammation observed with ileal CD.

The NOD2 ligand muramyl dipeptide is ubiquitous, indicating that broad classes of bacteria are capable of activating NOD2. However, the N-glycolyated form of muramyl dipeptide found in mycobacteria and actinomycetes more potently activates NOD2 compared to the N-acetylated form, found more frequently in gram-positive and gram-negative bacteria.[25] Particular patterns of bacterial colonization might therefore contribute to CD. A recent Chinese GWAS of leprosy (Mycobacterium leprae) made an interesting association with CD. Whereas major histocompatibility complex genes were most significantly associated with leprosy, genes in the region of *NOD2* were also significantly associated, although the SNPs identified were distinct from the variants associated with CD in patients of European ancestry. Receptor interactive protein 2, which is required for NOD2 activation of NF-κB, has not been genetically associated with CD in patients of European ancestry, but SNPs in its gene (*RIP kinase 2*) were associated with leprosy, as were SNPs in *TNFSF15*.[26]

Genes That Regulate Autophagy

Autophagy degrades damaged organelles and proteins, in homeostasis and as a response to starvation, and is important for the clearance of pathogens (xenophagy), which is required for immunity to multiple different types of bacteria. *Autophagy 16-like 1* (*ATG16L1*) has been strongly associated with CD and encodes a protein component of the autophagy complex.[27] ATG16L1 is broadly expressed, including in small intestinal Paneth cells[28] where it mediates exocytosis of secretory granules that contain antimicrobial peptides. A single Thr300Ala substitution in *ATG16L1* has been associated with CD. Thr300Ala (notably, the major allele in European ancestry cohorts) has reduced ability to capture bacteria.[29] Mice that are hypomorphic for ATG16L1 and infected with the intestinal pathogen norovirus develop Paneth-cell abnormalities, aberrant responses to injury, and

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increased susceptibility to ileal injury.[30] Despite the demonstration of a functional interaction between NOD2 and ATG16L1,[31,32] statistical risks to CD are additive, not synergistic.

Genes that encode immunity-related guanosine triphosphatase M (IRGM) and leucine-rich repeat kinase 2 (LRRK2), which also regulate autophagy, have been associated with CD in GWAS.[33,34] Genetic polymorphisms in *IRGM* that were associated with CD appear to reduce its expression; they include a 20-kb deletion polymorphism 1.6 kb upstream of the *IRGM* promoter[35] and a recently described tetranucleotide insertion.[36] Interestingly, although both variants are several-fold more frequent among Japanese people, compared with people of European ancestry, neither variant was associated with CD in Japanese cohorts. *Leucine-rich repeat kinase 2 (LRRK2)*, which has also been associated with Parkinson's disease,[37] is located in the CD-associated region on chromosome 12q12,[33] along with *MUC19* (encodes mucin 19). Mice deficient in LRRK2 have impairments in shuttling of autophagosomes to lysosomes and have increased apoptosis, inflammatory responses, and oxidative damage.[38] Alterations in autophagy therefore have important roles in pathogenesis of CD, possibly because of the close apposition of microbial components with high cellular turnover of the intestinal environment.

Lymphocyte Activation, Survival, and Growth

HLA class II genes have been significantly associated with UC. HLA genes are frequently associated with chronic inflammatory genetic disorders, probably because of the enormous genetic and functional diversity contained within this region and its role in regulating interactions between host cells and pathogens. A comprehensive meta-analysis of HLA candidate gene studies reported that *DRB1*0103* (odds ratio = 4.6) and *DRB1*1502* (odds ratio = 3.3) conferred the greatest risk for UC, whereas *DRB1*0410* (odds ratio = 3.9), *DQB*0401* (odds ratio = 2.8), and *DRB1*0103* (odds ratio = 2.07) conferred the greatest risk for CD among HLA class II variants.[39] Among HLA class I genes, *B52* conferred the greatest risk for UC (odds ratio = 3.3), whereas *Cw8* and *B21* (odds ratios = 3.4 and 2.3, respectively) conferred the greatest risk for CD.[39] Overall, genes associated with UC confer greater risk with greater consistency than those associated with CD. GWAS studies have highlighted the importance of the HLA region in IBD, with greater association evidence of HLA variations to risk with UC than CD. A recent meta-analysis of nearly 7000 cases of UC and 20,000 controls reported the strongest association with SNP rs9268853, near HLA DR9 ($P = 1.4 \times 10^{-55}$).[9] In contrast, a meta-analysis of 6300 cases of CD and 15000 controls found a relatively modest level of association for CD within the HLA region, strongest with SNP rs1799964 ($P = 4.0 \times 10^{-11}$); 21 loci outside the HLA region had more robust significance.[15]

T-cell activation by HLA class II tetramers presenting peptide antigens involves costimulatory molecules and downstream signaling intermediates. A region on chromo-some 21q22, near *ICOSLG* (inducible T-cell costimulator ligand), which promotes T-cell proliferation and cytokine secretion, has been associated with CD and UC.[33] *PTPN22* encodes a lymphocyte-specific protein tyrosine phosphatase that down-regulates lymphocyte signaling; the variant Arg620Trp increases risk for several autoimmune diseases (eg, type I

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diabetes, rheumatoid arthritis, autoimmune thyroiditis, and systemic lupus erythematosus).[33,40,41] Arg620Trp increases the phosphatase activity of PTPN22, compared to Arg620, to inhibit B- and T-cell activation.[40] Interestingly, the wildtype arginine rather than threonine at codon 620 was associated with increased risk for CD.[33] The chromosome 6q25 region, which includes T-cell activation guanosine triphosphatase-activating protein (*TAGAP*) was recently associated with CD. This region has been associated with a number of autoimmune diseases; T-cell activation guanosine triphosphatase-activating protein has an expression pattern similar to that of IL-2.[15]

Cytokines and their receptors regulate T-cell survival and proliferation and have been associated with IBD. A region of chromosome 5p13 that contains *IL7R*[9], which encodes the α subunit of the functional IL-7 receptor, was associated with UC. IL-7 signaling controls survival of naïve and memory T cells, and the *IL7R* region has been associated with multiple sclerosis.[42] Multiple sclerosis[42] and IBD[15] are also both genetically associated with a region of chromosome 10p15 that contains *IL2RA* (IL-2 receptor, α subunit). IL-2 controls T-cell proliferation; its effects have complex mechanisms of regulation, based on low- and high-affinity binding to its receptor. Homodimers of IL2RA form a low-affinity receptor for IL-2, whereas the high-affinity receptor comprises α, β, and γ subunits. Finally, multiple sclerosis[43] and IBD are both associated with alterations in IL-23 signaling, although in multiple sclerosis (unlike IBD) genetic associations with IL-23 pathway genes have not been established.

IL-23

After variants in *NOD2*, the variant most significantly associated with CD encodes the amino acid change Arg381Gln in the IL-23 receptor (IL23R). Glutamine 381, present in approximately 14% of healthy individuals of European ancestry, reduces risk for CD by nearly 3-fold and for UC by slightly less, compared with Arg381 carriers. Other uncommon alleles that reduce risk have been reported recently.[44] Several more common polymorphisms in *IL23R* have independent contributions to IBD risk. IL23R is a component of the heterodimeric receptor for IL-23 (Figure 2). In addition to their association with IBD, polymorphisms in IL23R have been associated with psoriasis[45,46] and ankylosing spondylitis.[47] In preliminary studies, antibodies against the p40 subunit that is common to IL-23 and IL-12 were effective in treating patients with CD[48]; a similar antibody was recently approved for treatment of psoriasis.[49] Other genes whose products function in the IL-23 pathway have been associated with IBD (Figure 2). GWAS have therefore established a strong genetic signature for genes that regulate IL-23 signaling in the development of IBDs.[50,51]

Comparing CD and UC Associations Identified by GWAS

The approximately 100 genomic loci that have been significantly associated with IBD contain candidate genes whose products mediate a variety of cell functions, including microbial recognition, lymphocyte activation, cytokine signaling, metabolism (FUT2, fucosytransferase),[52] endoplasmic reticulum stress responses (eg, X box binding protein–1),[53] physicochemical defense (eg, MUC1 and MUC19, mucins), and epithelial barrier

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function.[33] Interestingly, a nonsense polymorphism in *FUT2* that determines susceptibility to norovirus infection was associated with CD.[15,54] Reflecting the clinical and epidemiologic overlap between the subtypes of IBD, it is not surprising that many of these loci demonstrate genome-wide significant associations for both CD and UC[55,56] (Table 1).

Many of the loci that have significant associations with CD and UC contain genes that encode transcription factors, especially those that regulate cytokine expression and function (Table 1 and Figure 2). Signal transducer and activator of transcription 3 (STAT3), gene located on chromosome 17q21, is activated in response to a variety of cytokines and growth factors, including IL-6, −10, −21, −22, −23, and −26. Similarly, SMAD family member 3 (SMAD3), gene located on chromosome 15q22, regulates transcription in response to signaling by transforming growth factor–β.[57] CD and UC are associated with the region on chromosome 10q21 that encodes zinc finger MIZ type 1 (ZMIZ1). ZMIZ1 increases SMAD signaling and is induced by retinoic acid,[58] which broadly mediates immune tolerance in the intestine. IBD is also associated with chromosome 2p16, which contains *REL*, which encodes c-Rel, a subunit of NF-κB. NF-κB is activated in response to signaling from pattern recognition receptors and tumor necrosis factor–α. The gene that encodes PR domain zinc finger protein 1 (PRDM1), on chromosome 6q21, represses expression of interferon-β and is associated with CD[9] and UC[15] as well as rheumatoid arthritis[59] and systemic lupus erythematosus.[60] Finally, both CD and UC demonstrate significant associations with a region on chromosome 10q24 that encodes the transcription factor NK2 transcription factor related, locus 3 (NKX2-3). Mice deficient in NKX2-3 have hyposplenia and defects in intestinal development.[61]

Although association studies indicate that CD and UC have similar mechanisms of pathogenesis[9,15] that involve some of the same transcription factors, comparative analyses of genes that regulate leukocyte mobility provide subtle evidence for different pathogenic mechanisms. For example, CD is significantly associated with the chromo-some 17q12 region that contains *chemokine C-C motif ligand (CCL2)* and *7 (CCL7)*, which encode small chemotactic proteins that promote migration of monocytes and macrophage.[15] In contrast, UC has a consistent but nominal association with this region.[9] Similarly, although CD is associated with a chromosome 6q27 region that contains *chemokine C-C motif receptor 6 (CCR6)*, UC is not.[9] CCR6 is specifically expressed by immature dendritic cells and memory T cells; it mediates leukocyte recruitment and migration under inflammatory conditions in which its ligand, chemokine C-C motif ligand 20 (CCL20), is expressed.[62] In contrast, the chromosome 11q15 region contains the gene *lymphocyte specific protein 1 (LSP1)* and is significantly associated with UC, but not CD.[9] Although LSP1 was initially thought to be expressed only in leukocytes, it was also found to be expressed in endothelial cells and to be essential for neutrophil extravasation in response to TNF–α and IL-1β.[63]

Many of the loci that have the strongest associations with UC do not have compelling candidate genes (eg, chr1p36 locus[64]; Table 1). A number of loci that contain UC-predominant signals include genes that regulate epithelial barrier function, including *GNA12* (encodes gua-nine nucleotide binding protein α12, which has a role in tight-junction assembly) on chromosome 7p22, *HNF4A* (encodes hepatocyte nuclear factor 4, α), *CDH* (encodes cadherin 1, epithelial, which mediates calcium-dependent glycoprotein binding) on

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chromosome 16q21, and *LAMB1* (laminin β1, which encodes a constituent of basement membranes) on chromosome 7q31.[9] Finally, one of the genetic variants that is predominantly associated with UC in patients of European ancestry and in Japanese is a polymorphism that encodes the amino acid change His131Arg in the Fcγ receptor FCGR2A. FCGR2A is found on the surface of a variety of immune cells, including neutrophils and macrophage, and is involved in phagocytosis and clearance of immune complexes.[65]

Associations Across Chronic Inflammatory Diseases

The overlap between CD- and UC-associated genetic loci reflects the significant epidemiologic and clinical overlap. Extraintestinal manifestations of IBD include primary sclerosing cholangitis (PSC), uveitis, and ankylosing spondylitis, with frequencies of at most 2.4%, 4.5%, and 4.1%, respectively, based on data from a population-based study of IBD.[66] Colitis is diagnosed in approximately 50% of patients with PSC, based on clinical evidence, and >80% on histopathology findings; it might be a disorder of overlapping phenotype, but of a distinct etiology, from UC. In a GWAS of PSC, a region that was just toward the centromere from HLA-B had the strongest association.[67]

Support for the concept that the colitis associated with PSC is pathophysiologically distinct comes from the observation that it is associated with distinct *HLA* genes, compared with UC (Table 2). Furthermore, PSC is not associated with non-HLA UC regions associated with UC, such as chromosome 1p36 (Table 1) or IL23R; however larger subsequent studies may yet demonstrate associations. In a recent GWAS, PSC was associated with a gene-rich region of 3p21 that was previously associated with IBD (Table 2), indicating some overlap in patho-physiology.[68] Primary biliary cirrhosis[69] and Behçet's disease[70,71] were associated with the intergenic region between *IL23R* and *IL12RB2,* although there were slightly different patterns of allelic association compared with IBD (see Figure 2). Gain-of-function mutations in *NOD2* are responsible for autosomal-dominant Blau syndrome, which can manifest with iritis and/or uveitis.[72] Uveitis occurs in patients with Behçet's disease, ankylosing spondylitis, sarcoidosis, and psoriatic arthritis; a GWAS of all these disorders might be useful in identification of uveitis-associated risk variants.

Like IBD and psoriasis, the Arg381Gln polymorphism in IL23R reduces risk for ankylosing spondylitis.[47] *IL23R* was 1 of the 2 most significant non-HLA genes in a GWAS of ankylosing spondylitis (the other is the 5q15 region that contains *endoplasmic reticulum aminopeptidase 1 (ERAP1)*, which was also associated with CD and with Psoriasis).[15,73,74] A recent study in Han Chinese found nominal evidence for an association of SNPs in *janus kinase 2 (JAK2)* and *STAT3* with ankylosing spondylitis; Arg 381Gln was not found in this population.[75] The other 2 loci that have shown significant associations with both ankylosing spondylitis and IBD are caspase recruitment domain family, member 9 (CARD9)[76,77] and the 21q22 region.[78,79]

Overall, there has been a striking overlap in loci associated with different chronic inflammatory diseases. Many genes that encode factors in the IL-23 pathway have been associated with both psoriasis and IBD (*IL23R, IL12B,* and *tyrosine kinase 2 [TYK2]*),[45,74] indicating the role of the IL-23 in mediating mucosal immunity (in the skin and intestine)

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(Figure 2). Numerous loci have been associated with both IBD and celiac disease, including those near *IL2* and *IL21* (chr4q21) and *IL18RAP* (*IL-18 receptor accessory protein,* 2q33).[9,15,80,81]

Future Directions—Uncommon Alleles, Population Differences, and Family Studies

The contributions of genetic factors to IBD are complex. Despite the success of GWAS in identifying significantly associated loci, they are estimated to account for <25% of predicted heritability.[15] GWAS find common, human genetic variants associated with disease, but it is possible that uncommon polymorphisms also contribute to IBD; these may be identified through whole-genome sequencing approaches. Thus far, with the exception of the region of *IRGM*,[35] large copy-number polymorphisms have not been associated with IBD.[82] Polymorphisms that have a stronger effect on disease development (Figure 1) might be maintained at a lower frequency in the population (uncommon alleles) through negative selection, because they reduce reproductive fitness.

If uncommon variants make significant contributions to complex disorders such as IBD, consideration of population differences will be particularly informative, as less common alleles are more likely to be population specific. African populations have the greatest genetic diversity and will undoubtedly provide important comparative insights. Studies in cohorts of Ashkenazi Jews might be particularly valuable because of a high prevalence of disease and greater allelic homogeneity from endogamy.

A main goal of human genetic studies is to better understand familial transmission of diseases and identify uncommon variants that make large contributions to pathogenesis. Uncommon alleles that are shared among affected individuals within a family are more likely to contribute to familial clustering of disease than common alleles carried within a population. In addition to uncommon, disease-associated alleles, families are more likely to share features of the intestinal microbiome; a functional integration of genetic and family-based microbiome analyses might help us better understand the complex causes of IBD.

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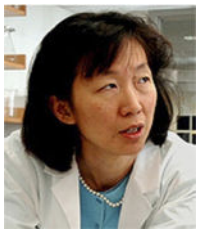
Biography



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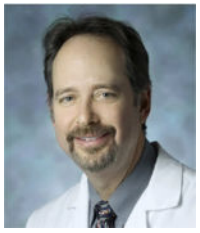

Steven R. Brant

Abbreviations used in this paper

CD	Crohn's disease
GWAS	genome-wide association studies
IBD	inflammatory bowel disease
IL	interleukin
IL23R	interleukin-23 receptor
IRGM	immunity-related guanosine triphosphatase M
NF-κB	nuclear factor–κB
PSC	primary sclerosing cholangitis
SNP	small nucleotide polymorphism
STAT	signal transducer and activator of transcription
UC	ulcerative colitis

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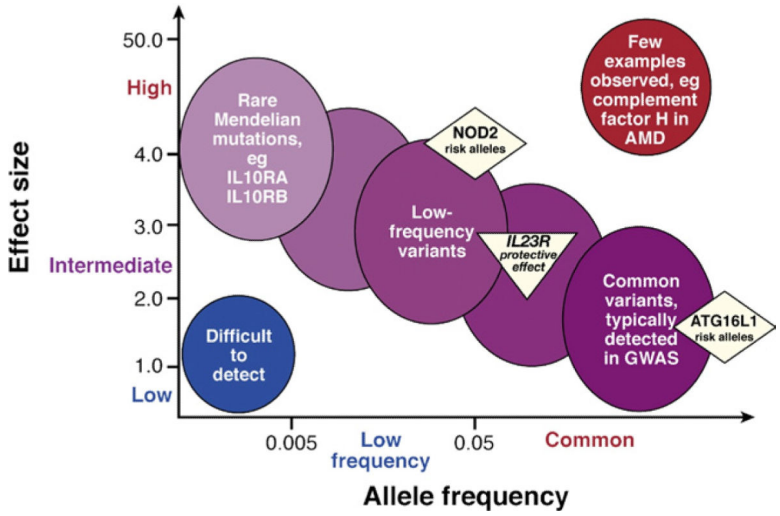

Figure 1.

Features of disease-associated genetic variation. Most cases of inflammatory bowel disease (IBD) are multifactorial in etiology, reflecting the effects of multiple genetic risk alleles and developmental and environmental factors. Rare cases of early-onset IBD, with extreme phenotypes, might be single-gene, Mendelian disorders (eg, autosomal recessive mutations in *IL10RA* or *ILRB*)—extremely rare mutations with strong effects. In contrast, most of the alleles identified by genome-wide association studies are relatively common (allele frequencies >5%), with modest or low effects and odds ratios <1.5. Greater effects (intermediate to high) include the relatively low-frequency risk alleles in *NOD2* and the variant that encodes Arg381Gln in *IL23R*. Among complex disorders, it is unusual to have common alleles that have strong effects; an exception is that some alleles of the gene that encodes complement factor H confer high-risk for age-related macular degeneration (AMD).

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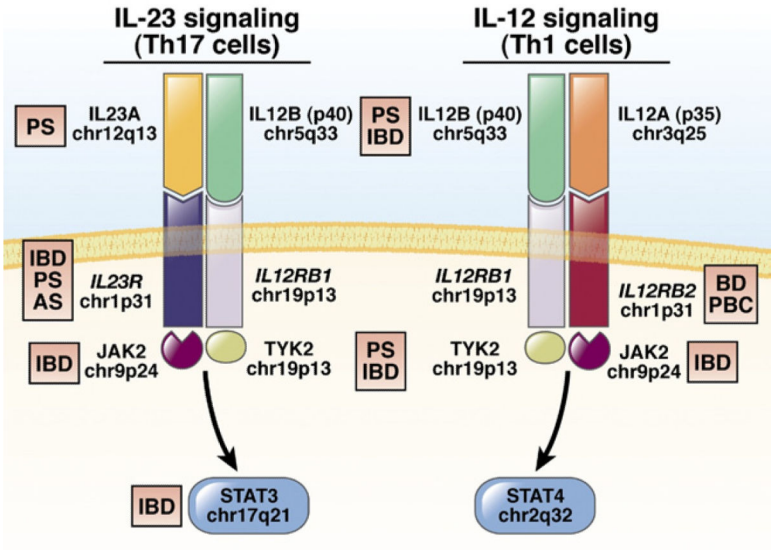

Figure 2.

Interleukin (IL)-23 vs IL-12 signaling. IL-23 and IL-12 signaling are mediated by binding of the cytokine heterodimer to a heterodimeric receptor. These pathways share components of the cytokine (IL12B, p40), receptor (IL12RB1), and downstream signaling components (JAK2 and TYK2). Activation and phosphorylation of downstream components result in the recruitment and activation of signal transducer and activator of transcription (STAT) proteins (STAT3 in IL-23 signaling, STAT4 in IL-12 signaling), which subsequently translocate to the nucleus to activate transcription. Inflammatory bowel disease (IBD) and psoriasis (PS) are each associated with variants in *IL23R*, *IL12B* (p40) and *TYK2*. IBD, PS, and ankylosing spondylitis (AS) are all associated with the chromosome 1p31 region that includes the C-terminal 7 exons of IL23R, and extends into the intergenic region between *IL23R* and *IL12RB2*. In contrast, Behçet's disease (BD) and primary biliary cirrhosis (PBC) are associated with the inter-genic region, between *IL23R* and *IL12RB2*.

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Table 1

Genomic Regions Significantly Associated with Inflammatory Bowel Disease in Genome-Wide Association Studies of Patients of European Ancestry

	Definition of association—signal or genes in region	Population differences	Other disease associations
Predominantly associated with CD			
NOD2 (16q12)	Multiple, uncommon, European-derived, loss-of-function alleles	Similar heterozygote risk in African Americans with CD[22]; mutations associated with patients of European ancestry not observed in Asians[23,24]	Graft-vs-host disease,[83] gain-of-function mutations associated with Blau syndrome[72][a]
5q31	Multiple	No association in Asian populations[84,85]	Psoriasis,[46] modest association with UC[a]
9q32	*ZNF365* (encodes zinc finger 365)	Not reported	Not reported
10q21	Multiple	Not reported	Not reported
18p11	*PTPN2*	Not reported	Type 1 diabetes mellitus,[86] celiac disease[87]
22q13	Multiple	Not reported	Not reported
Encode factors in the autophagy pathway			
ATG16L1 (2q37)	Common, loss-of-function variant Thr300Ala[29]	No association in Asian populations[88,89]	Not reported
IRGM (5q33.1)	Polymorphism in promoter that affects copy number[35]	No association with Japanese cases of CD[36]	Different allele found to protect against mycobacterium tuberculosis[90]
12q12	*LRRK2* and *MUC19*	Not reported	Parkinson's disease,[91][a] leprosy[24]
Predominantly associated with UC			
Major histocompatibility complex region (6p21)	Multiple, including class II genes	Predominant locus in European and Asian patients with UC	Distinct association patterns in multiple other diseases, including CD
FCGR2A (1q23, Fc fragment receptor)	Associated with histidine allele at His131Arg, which increases affinity for Fc fragment	Also associated with a Japanese cohort of patients with UC[92]	Arginine allele associated with systemic lupus erythematosus, type 1 diabetes)[93-95]
1p36	Multiple genes	Association with SNPs at 1p36 in Japanese patients with UC[92]	No reports in other chronic inflammatory diseases
12q14	*Interferon-γ, IL26, IL22*	Not reported	Not reported
Loci that affect epithelial defense			
7q22	Multiple, including *LAMB1* (encodes laminin *β*1)	Not reported	Not reported
20q13	Multiple, including *HNF4a* (encodes hepatocyte nuclear factor 4*α*)	Not reported	Not reported
Genome-wide significant associations with CD and UC			

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	Definition of association—signal or genes in region	Population differences	Other disease associations
Genes that encode factors in the IL-23 pathway	See Figure 2	Arg381Gln in IL23R (uncommon protective allele), absent in Asian populations[89]; common alleles associated with IBD in Asians	See Figure 2
1q32	Multiple, including *IL10*	Not reported	Type 1 diabetes,[86][a] systemic lupus erythematosus,[60] Behcet's disease[70,71]
5p13	Gene desert adjacent to *PTGER4* (encodes prostaglandin receptor 4)	Not reported	Multiple sclerosis[96][a]
9q32	*TNFSF8, TNFSF15*	Distinct alleles that confer higher risk (>2-fold) in Japanese and Korean subjects with CD[12,97] than Europeans with IBD	Leprosy[26]
9q34	Multiple, including *CARD9* (encodes caspase recruitment domain family, member 9)	Not reported	Ankylosing spondylitis[77]
Transcription factors			
10q22	*ZMIZ1* (encodes zinc finger, MIZ-type containing 1)	Not reported	Celiac disease,[87] multiple sclerosis,[96] vitiligo[98]
10q24	*NKX2-3* (encodes NK2 transcription factor)	Association replicated in Japanese CD[99]	No reports in other chronic inflammatory diseases
15q22	*SMAD3*	Not reported	Asthma[100]

NOTE. Loci with *P* values $<10^{-16}$ for Crohn's disease (CD) or ulcerative colitis (UC) are presented, excluding loci not containing genes. For a more comprehensive listing of inflammatory bowel disease (IBD) susceptibility loci, see IBD meta-analyses.[9,15]

[a] Association signals differ between disease and IBD.

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Table 2

Comparative Associations Between Inflammatory Bowel Disease and Related Chronic Inflammatory Diseases

Loci	IBD	Psoriasis	Celiac disease	Primary sclerosing cholangitis	Ankylosing spondylitis
Gene product in the IL-23 pathway	Yes	Yes	No	No	Yes
Major histocompatibility complex	Class II predominant	Class I predominant	Class II predominant	Class I predominant	Class I predominant
Loci of genome-wide significance shared with IBD	—	4	14	3p21(a gene-rich region that includes *MST1*)[68]	2: *ERAP1*[a] at chr5p15; *CARD9* at chr9q34

NOTE. The large number of loci shared between inflammatory bowel disease (IBD) and celiac disease might reflect the larger number of loci established for celiac disease, compared with psoriasis, ankylosing spondylitis, and primary sclerosing cholangitis.

IL-23, interleukin-23.

[a]The association with *ERAP1* is distinct from the association with Crohn's disease.