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From Genetics of Inflammatory Bowel Disease Towards Mechanistic Insights

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Summary

Advancements in human genetics now poise the field to illuminate the pathophysiology of complex genetic disease. In particular, genome-wide association studies have generated insights into the mechanisms driving inflammatory bowel disease (IBD) and implicated genes shared by multiple autoimmune and autoinflammatory diseases. Thus, emerging evidence suggests a central role for the mucosal immune system in mediating immune homeostasis and highlights the complexity of genetic and environmental interactions that collectively modulate risk of disease. Nevertheless, the challenge remains to determine how genetic variation can precipitate and sustain the inappropriate inflammatory response to commensals that is observed in IBD. Here, we highlight recent advancements in immunogenetics and provide a forward-looking view of the innovations that will deliver mechanistic insights from human genetics.

Keywords

Inflammatory Bowel Disease (IBD); Crohn's disease; ulcerative colitis; genome wide association study (GWAS); genomics; mucosal immunity; host defense

Genetics of IBD

Genetic predisposition to autoimmune and autoinflammatory diseases is well established, yet the interrelationship between multiple genetic components and environmental triggers remains to be elucidated. The observation that some individuals develop IBD at childhood and others during adulthood, suggests distinct environmental contributions to disease initiation versus disease progression. While the genetic elements predisposing to IBD are present from birth, disease onset occurs later in life, and there is further need to understand how host genetic and epigenetic factors interact with environmental triggers at disease onset and how genetics influence immune regulatory networks that sustain disease. The most recent advancement in the field came from a meta analysis of 15 prior GWA studies to aid in the design of the Immunochip [1]. This custom designed genotyping array contains high-density genomic coverage of SNPs implicated by GWAS to fine map disease loci and

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implicate new genes. In combination with imputed GWAS data, Immunochip validation studies on over 25,000 IBD cases identified 71 new loci for a total of 163 loci associated with IBD [1]. As a result, these studies substantially increase the estimated disease heritability for both Crohn's Disease (CD) and Ulcerative Colitis (UC). Furthermore, they highlight 110 shared loci for both disease subtypes, while 30 are classified as specific for CD and 23 for UC [1]. IBD shares the largest number of loci with type I diabetes and shows substantial enrichment of overlap with ankylosing spondylitis, psoriasis, and susceptibility to mycobacterial infection [1]. Such overlap in the genetics of autoimmune/autoinflammatory diseases points to several common immune processes, such as regulation of mucosal immunity, in mediating inflammatory pathology. Together, the immediate impact of implicating 163 loci in IBD resulted in identification of new candidate genes and pathways that may drive disease. However, taking human genetic studies a step further requires building new experimental systems to define the biological functions of these genes. For example, genetic studies in psoriasis patients implicated Act1 (*Traf3ip2*), an adaptor functioning downstream of the IL-17R [2–4]. Generation of a knockout mouse that modeled *TRAF3IP2* loss of function variants in humans revealed hyperactive TH17 responses driving IL-22-dependent inflammation [5]. Thus, GWAS led to the development of a novel mouse model that provided key insight into disease mechanisms. Here, we discuss how advancements in genomics and functional genetics have contributed to our current understanding of IBD, and how these approaches can be applied to provide new mechanistic insights and therapeutic opportunities (Figure 1).

Genetic Variation and Functional Repercussions

Many single nucleotide polymorphisms (SNPs) implicated by GWAS are not directly causal with respect to phenotype, rather they exist in linkage disequilibrium with yet to be discovered variants that are functional. This point highlights the fact that GWAS cover relatively common genetic variants including SNPs with >1% frequency within the population and fail to capture rare or undiscovered variants. Such germline encoded DNA variation can lead to nonsynonymous coding variants that change protein function and/or posttranslational regulation. However, the majority of the SNPs implicated by GWAS represent variation in noncoding regions of the genome. Thus, alterations in gene expression are likely to be important factors in immune dysregulation, and highlight the need to comprehensively characterize DNA and RNA regulatory elements.

Genetic variation impacts gene expression at the level of transcription, RNA stability, splicing, and epigenetic modification. Accordingly, new genomics tools have been developed to capture genetic regulation at multiple levels. Studies merging proteomics with genomics identified differential binding of transcription factors to SNPs in the *IL2RA* promoter that regulate gene expression [6]. As an additional mechanism of transcriptional regulation, long noncoding (lnc) RNAs within the genome have been shown to play key roles in modulating gene expression [7, 8]. Recent studies have identified a critical requirement for lncRNA in maintaining pluripotency and enforcing lineage specific gene expression profiles [9]. It is now clear that expression of lncRNAs is regulated in a cell type-specific manner. Thus, analysis of the human beta cell transcriptome identified tissue-specific lncRNAs that were transcriptionally dysregulated in type 2 diabetes (T2D) or that mapped to loci previously associated with T2D [10]. In the context of host defense, the lncRNA NeST has been identified as an epigenetic regulator of IFN- γ expression in CD8 T cells and determines susceptibility to viral and bacterial infection in mice [11]. However, the potential role for lncRNAs in regulating human inflammatory diseases remains largely unexplored.

Following transcription, mRNA splicing and stability are tightly regulated. In this context, inflammatory stimuli and microbial components induce a coordinated program of miRNA expression in monocytes that regulates inflammatory responses [12]. Consequently, variants in the gene encoding IL23R that associate with IBD are resistant to downmodulation by miRNA, which results in upregulation of IL23R expression [13]. Similarly, variants in the 3'UTR of genes encoding CTLA-4 and IL-10 alter recognition by miRNAs, resulting in dysregulated expression [14]. In addition to regulation at the level of mRNA stability, RNA splicing impacts gene function. SNPs in the 3' untranslated region of *Ctla4* associate with T1D and correlate with reduced expression of a soluble CTLA-4 splice variant [15]. Accordingly, transgenic mice with germline integration of a cassette encoding shRNA specifically targeting soluble CTLA-4 impaired Treg function and resulted in accelerated onset of diabetes in the NOD system and severe colitis in the CD45RB^{hi} transfer model [16].

Determining the impact of genetic variation on expression profiles has been a major focus in the field, as highlighted in studies of expression quantitative trait loci (eQTL) that aim to correlate SNPs with transcriptome data [17]. Recent studies have begun to identify SNPs that alter transcription of neighboring genes (cis eQTLs) and distant genes (trans eQTLs). Analysis of 92 strains of inbred mice identified several thousand eQTLs associated with macrophage responses to LPS [18]. Similarly, eQTL studies in human dendritic cells (DCs) identified 198 eQTLs associated with *Mycobacterium tuberculosis* infection [19]. These findings are notable given the genetic overlap between susceptibility to *Mycobacterium tuberculosis* infection and IBD and given the enrichment of IBD candidate genes in DCs [1]. In a direct example of eQTLs in IBD, SNPs associated with CD correlate with increased expression of Card9, which has been suggested to potentiate inflammatory signaling cascades [1]. Similarly, SNPs associated with T1D have been shown to act in trans on an antiviral inflammatory network driven by IRF7 in monocytes [20]. While many of the eQTLs highlighted above are cell type-specific and the mechanistic basis of this specificity is not entirely clear, it is likely to be regulated by differential pathway activity and epigenetic effects. In this context, the Encyclopedia of DNA Elements (ENCODE) project continues to deposit rich datasets of genome-wide epigenetic modifications across multiple cell types. Recent chromatin mapping studies highlight SNPs associated with autoimmunity that are enriched within enhancer elements containing epigenetic modifications in specific cell types [21, 22].

As the number of noncoding variants and SNPs associated with autoimmune disease has expanded, so has identification of coding variants. Exome sequencing at IBD loci has identified novel coding variants and helped pinpoint specific genes within these loci that are likely to impact disease [23]. For example, many IBD loci are gene-dense, and SNP signals are not able to precisely pinpoint the causative gene. A locus on chromosome 12 implicated by GWAS is comprised of the *LRRK2* gene and *MUC19*. While a great deal of attention has focused on study of the kinase LRRK2, the discovery of new coding variants in *MUC19* indicates the need for more detailed analysis of this gene in IBD pathogenesis [23]. *MUC19* is a gel-forming apomucin, thus genetic variants of *MUC19* may contribute to mucosal barrier dysfunction by causing quantitative changes in its production or structural changes in the glycoprotein core. The barrier function of the mucous layer acts in concert with its ability to retain antimicrobial effector molecules such as defensins and secreted IgA. Thus, B cell IgA production is a central pathway in mucosal immunity, which is consistent with a newly discovered role for the IBD candidate gene *BACH2* in class switch recombination [24]. In fact, exome sequencing recently defined coding variants in *BACH2* and identified a distinct profile in severe UC characterized by mutations in both *BACH2* and *IL10* [25]. Although B cell function was not directly tested in this study, *BACH2* and IL-10 can induce immunoglobulin class switching [24, 26], thus highlighting the potential of gene-gene interactions to impact cell type-specific phenotypes. Collectively, these studies demonstrate

the diverse mechanisms by which genetic variation impacts gene function and highlight the importance of genetic interactions.

Addressing Genetic Epistasis

The diversity of genetic backgrounds in human subjects complicates phenotyping endeavors, but highlights the notion that phenotypes derive from the aggregate effects of multiple genetic factors. Furthermore, IBD genes interact, as highlighted by the discovery of a MAST3-regulated transcriptional program that broadly controls expression of inflammatory genes associated with NF κ B activity, such as those induced by NOD2 and TLRs [27, 28]. It is now possible to discern the impact of genetic perturbation on transcriptional programs by employing RNAi-mediated knockdown of candidate genes followed by RNAseq.

Accordingly, this approach may provide a deeper understanding of how IBD genes interact with one another at the genetic level. Although genetic epistasis is thought to be an important component of disease, it is not captured well by GWAS [29]. Nevertheless, studies have shown that T1D risk alleles for HLA class II and *Ctla4* statistically interact and support a role for gene-gene interactions [30]. Epistasis is difficult to study systematically, because of the sheer number of possible genetic contributors. Furthermore, perturbing multiple genes simultaneously has practical limits, and addressing the issue of genetic epistasis in complex disease will ultimately require an unbiased discovery-based approach invoking GWAS on a much larger scale.

Exploring Gene-Environment Interactions

Following the logic that host genetic epistasis contributes to disease, emerging evidence indicates that host genetic interactions with microbes also shapes immunologic phenotypes. Twin studies suggest that infant and early childhood infections may be associated with IBD [31]. In addition, stable interactions of commensal communities with the host shape immune development, as demonstrated by the observation that segmented filamentous bacteria (SFB) promote development of Th17 cells in mice [32]. Similarly, innate lymphoid cell (ILC) development is shaped by the microbiome [33], and ILCs accumulate in inflamed mucosal tissues [34]. Dietary factors also promote ILC development, as aryl hydrocarbon receptor (AHR) ligands induce lymphoid follicle development in the intestine by acting on ILCs [35]. Conversely, ILCs shape the composition of the microbiome by limiting dissemination of lymphoid resident commensals [36]. These key observations begin to provide insight into the interactions between host immune system, microbiome, and dietary metabolites [37].

In addition to stable host-commensal interactions, transient interactions between host and pathogens irrevocably change the immune system. Prior pathogen exposure elicits more robust responses to subsequent infection. While memory within the adaptive immune system provides antigen-specific protection upon rechallenge, the innate immune system can be “trained” by prior infection and poised to respond more robustly to a variety of pathogens [38–41]. Thus, previous infection may condition the immune system to mount a pathologic response, which is not to suggest that IBD is caused by a particular pathogen. Rather, emerging evidence suggests a “multiple hit” model for conferring susceptibility to IBD [42]. Similar to IBD patients bearing *ATG16L1* risk alleles, *Atg16l1* hypomorphic mice exhibit paneth cell defects associated with abnormalities in granule packaging. Importantly, pathology associated with paneth cell function depended on prior exposure to virus [42]. Given the interconnection between host and microbes, the future challenge is to catalogue the metagenome and correlate host genotype to alterations in the microbiome. Still more challenging is the prospect of determining past history of pathogen infection in patients and identifying the immunologic consequences of prior infection. Notably, clues to prior pathogen exposure may be encoded in the specificity of gut IgA [43].

Extrapolating Pathways from Human Genetic Data

To date, GWAS studies have identified 163 loci associated with IBD [1]. Using pathway analysis tools to examine genes within these loci immediately reveals patterns related to immunity. For example, cytokines and their respective receptors are abundantly represented. Upon closer examination, additional immunoregulatory pathways can be distilled and implicate genetic programs associated with Treg function, Th17 development, negative regulation of TCR signaling, innate pathogen sensing pathways, antigen presentation, and apoptosis (Figure 2). While the function of caspases in eliciting apoptosis of T cells during activation-induced cell death is well characterized, caspases have additional functions in inflammasome signaling and processing of IL-1 family cytokines. Given that dysregulated caspase activity and inflammasome function have been associated with IBD, study of additional caspase-dependent pathways and caspase substrates may reveal novel insights into IBD pathophysiology [44].

Gene annotation and functional associations have also highlighted key pathways that surpass the traditional boundaries of immunology and would not have been easily predicted by previous studies (Box 1). Paramount among these are cellular processes related to autophagy, redox signaling and ER stress. Emerging evidence points to multiple pathway interactions; for example, ER stress and autophagy mutually regulate one another to maintain metabolic homeostasis during inflammation and to promote antimicrobial effector responses [45, 46]. In addition, macrophage exposure to bacterial lipopolysaccharide induces a metabolic switch to glycolysis resulting in accumulation of succinate that promotes IL-1p production by stabilizing HIF1- α (Tannahill et al. Nature, in press). Conversely, metabolism impinges upon the immune system by regulating tolerance. Tryptophan catabolism mediated by indoleamine 2,3-dioxygenase (IDO) generates kynurenine, which promotes IL-10 production by DCs and facilitates Treg differentiation, thus inhibiting Th17 responses [47]. Th17 differentiation is also regulated by environmental factors such as NaCl derived from dietary sources. In this context, elevated levels of salt stimulate expression of SGK1, which in turn induces expression of IL-23R to enhance Th17 differentiation [48]. Further work elucidating Th17 cytokine networks has uncovered previously unrecognized connections between IL-17 and maintenance of epithelial barrier function [49], thus indicating an important role for the immune system in maintaining epithelial homeostasis and restitution. In particular, neutrophil influx into inflamed tissues initially amplifies inflammation, and later promotes an anti-inflammatory healing response through macrophage-dependent clearance of apoptotic neutrophils [50]. In this context, mice deficient in the NADPH oxidase subunit P40phox exhibit an impairment in the healing response following acute colonic inflammation [51], thus revealing an additional role for reactive oxygen species (ROS) in epithelial restitution in addition to its known role as an antimicrobial agent. The importance of ROS in mucosal immunity is further supported by the discovery of rare variants of *NCF4* and *NCF2* that associate with IBD [52, 53]. These genetic studies implicating IBD genes in the ROS pathway suggest that neutrophils are key cell types in pathology, and further identify new functions for these cells that influence clinical manifestations of disease (Figure 3).

Pathway interactions identified by GWAS implicate several cell types in inflammatory pathology. By cross referencing candidate disease genes and pathways with gene expression patterns in immune cell subsets, DCs and memory T cells feature prominently as central cell types contributing to IBD [1]. Consistent with this notion, Ly6C^{hi} monocytes in the inflamed colon generate inflammatory DCs and antigen presenting DCs that drive autoinflammatory T cell responses [54]. Additional evidence implicates ILCs as key mediators of host defense and inflammatory pathology [33, 55]. Furthermore, expression of IBD genes identified by GWAS highlight the gut epithelium and innate immune

mechanisms including barrier function, goblet cell secretion of mucins, and paneth cell secretion of antimicrobial mediators [56]. With several functional pathways implicated in IBD, the next challenge will be to place unannotated genes in pathways that drive disease and to elucidate regulatory networks.

New Approaches in Assigning Function to Genes

Although many of the candidate IBD genes implicated by GWAS can be assembled into known pathways, a substantial fraction of these genes (> 40%) are poorly characterized at the functional level. A significant challenge is to identify functions for candidate IBD genes and to determine how signaling pathways work together to regulate mucosal immune effector mechanisms. One can posit that candidate IBD genes with unknown function may control key immune functions that drive disease, and that assigning function to these genes will expand our understanding of immunoregulatory mechanisms. To meet the challenge of assigning functions to candidate IBD genes in relevant immune responses, high throughput RNAi screening approaches have been developed. Implementing RNAi screens has shown initial signs of success, but has yet to be systematically applied to assign IBD candidate genes with immunologic function. As a recent example, RNAi screening was used to identify mediators of innate pathogen recognition through the NOD2 complex. Here, screening approaches identified NOD2-dependent regulators of NFkB and further demonstrated a novel mechanism for the spatial assembly of the NOD2 signaling complex [57]. In another recent study, genome wide RNAi screening approaches identified 190 cofactors required for mediating endosomal pathogen sensing pathways mediated by TLR7 and TLR9 [58].

Elucidating Mechanisms

Most functional genetic strategies aimed at assigning function to genes involve knockdown or overexpression of candidates. While this approach can establish the requirement, or define a regulatory role for a specific gene in a defined biological process, it does not effectively capture how genetic variation in human populations impacts immune regulation. For example, coding variants may result in gain of function, loss of function, or exist on a functional continuum somewhere in between. These are important distinctions when attempting to infer disease mechanisms or design new therapeutics. By the same token, determining how genetic variation in risk alleles versus protective alleles impacts a cellular response requires mechanistic insight. The next challenge will be to develop reliable approaches to demonstrate the causal effect of a genetic variant on disease progression and to determine the underlying mechanism of action.

With accessibility of exome sequencing technology on the rise, genetic diversity can be quantified and increasing numbers of coding variants have been identified [59, 60]. It has been estimated that human genomes typically harbor up to 100 loss of function variants and approximately 20 genes that are nonfunctional [60]. Due to limitations in the ability to predict which variants cause a given phenotype and which are benign, rigorous mechanistic studies must necessarily follow. IBD GWAS led to the identification of the autophagy gene *ATG16L1* and a putative loss of function coding variant thereof (T300A) [61, 62]. Knockdown of endogenous *ATG16L1* in epithelial cells and overexpression of RNAi-resistant *ATG16L1* T300A resulted in impaired antibacterial autophagy and formally demonstrated a role for this coding variant in a relevant biological readout [63]. While overexpression of coding variant cDNAs is ideally suited for high throughput analyses of many candidate mutations, overexpression can also mask subtle effects or exaggerate phenotypes. In gene replacement, or exon replacement approaches, a coding variant is introduced into the endogenous locus so as to retain regulation at the level of chromatin

remodeling, transcription, and splicing. Knockin mice have proven successful in this regard and can be crossed-bred to introduce mutations at multiple loci. More recent innovations in genome engineering now enable efficient generation of isogenic human cells. Approaches that employ transcription activator like effectors (TALEs) allow for targeting endogenous genes to introduce coding variants [64–68], and the CRISPR/Cas system has been recently adapted to target multiple genes simultaneously [69–71].

Assessing Disease Relevance

In progressing from identification of genetic loci by GWAS to defining functions for disease genes and variants, the next step towards determining the role for a candidate gene in disease pathology requires study *in vivo*. Here, multiple cell types and signaling pathways coordinately interact to mediate loss of immune tolerance and persistent inflammation. In this context, murine models have earned a prominent position as a mainstay for determining if a candidate gene is necessary or sufficient for disease. Mouse models have been used to demonstrate that the ubiquitin modifying enzyme A20 limits inflammatory responses, as conditional deletion in DCs resulted in spontaneous colitis and spondyloarthritis [72]. Furthermore, the role of DCs in maintaining tolerance is highlighted by the observation that regulatory DCs pulsed with bacterial antigen can mitigate experimental colitis in mice [73].

An emerging concept from mouse models and human genetic studies is that IBD cases are likely comprised of distinct subsets of mechanism-driven disorders [74]. In this context, systematic immunophenotyping of genotyped human cohorts will be required to define mechanism-based disease subsets. In disease free individuals bearing a T1D risk allele at the *IL2R* locus, IL-2R expression was reduced and Treg function was impaired [75]. Here, a rigorous approach with large sample sizes combined with rigorous quality control was implemented to address effects of different genetic backgrounds. In addition, inclusion of healthy controls with disease risk genotypes can help to exclude complicating effects of chronic disease that may alter immune phenotypes.

Concluding Remarks

Human genetics has provided key insights into complex disease. Significant overlap in genes implicated across several autoimmune/autoinflammatory diseases indicates common immunologic mechanisms as well as unique disease-specific pathways that must be tightly regulated to balance host defense against the risk for pathological inflammation. Only with a deeper understanding of the mechanisms driving disease and their underlying genetic components, will the goal of interpreting patient genotypes become feasible. Towards this end, the diagnostic power of genetics bears potential to stratify patient subsets based on disease mechanisms and treat them accordingly. Moreover, progress towards deciphering the genetic components of IBD pathophysiology will identify new points of entry for mechanism-based therapeutics. While it remains a challenge to mitigate pathological inflammation without compromising host defense, advancements in genetics offer the opportunity to treat the underlying mechanisms that incite IBD rather than broadly suppressing immune function.

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Box 1. Key Genes Implicated in IBD

Advancements in genomics have identified specific loci and rare coding variants associated with risk or protection from IBD. The genes identified by these studies highlight specific cellular pathways that may contribute to disease onset and/or progression (reviewed in [76]). Here, we highlight candidate IBD genes that implicate additional pathways that collectively suggest connections between cellular metabolism, inflammation, and mucosal microbial communities.

Select IBD Genes Identified by ImmunoChip [1]		
Gene	Locus	Putative Function
<i>RNF186</i>	1p36.13	Highly expressed in intestine and contains a RING-type zinc finger that may function as a ubiquitin ligase. Association with IBD has been validated in several populations [77, 78]. Evidence suggests genetic interaction with another IBD gene, <i>HNF4A</i> [79].
<i>SP110</i>	2q37.1	Associated with primary immunodeficiency. Expressed in hematopoietic cells and contains a bromodomain with potential involvement in epigenetic regulation. Loss of function mutations can decrease IL-10 production by B cells [80].
<i>SP140</i>	2q37.1	Expressed in hematopoietic cells and contains a bromodomain with potential involvement in epigenetic regulation.
<i>MST1</i>	3p21	Hepatocyte growth factor-like protein produced in the liver. Activates the receptor tyrosine kinase MST1R on epithelial cells (and some subsets of macrophages). Gain of function variants enhance macrophage motility [81].
<i>FUT2</i>	19q13.3	Golgi protein expressed in gastrointestinal tract. Enzymatic activity generates a secreted oligosaccharide that functions as a substrate for synthesis of A and B blood group antigens. Loss of function mutations (nonsecretor phenotype) lack expression of blood group antigens in mucosal surfaces. Secretor status correlates with alterations in the microbiome [82] and risk of IBD [83] and T1D [84].
<i>SLC22A4</i>	5q31.1	Ergothioneine transporter expressed in intestine and subsets of myeloid cells. May regulate cellular redox state, potentially linking metabolism with inflammatory responses [85].
<i>GSDMB</i>	17q12	May be involved in regulation of epithelial cell apoptosis [86]. It is also highly expressed in CD8 T cells.
<i>ORMDL3</i>	17q12	Regulates ER stress response associated with inflammation [87].
<i>TNFSF15</i>	9q32	Expressed on endothelial cells and activated APCs. One of its receptors (TNFRSF25) promotes Treg expansion in a ligand-dependent manner [88].
<i>TNFAIP3</i>	6q23	Ubiquitin modifying enzyme expressed in myeloid cells. Negatively regulates NFκB signaling and inflammatory cytokines [72].
<i>SLC6A7</i>	5q32	Proline transporter that may regulate cellular metabolic state and inflammation.
<i>IL10RA</i>	11q23	Receptor for IL-10 broadly expressed on hematopoietic cells. Transduces immunosuppressive signal through STAT3 and TYK2. Associated with early onset IBD [89].
Select IBD Genes with Coding Variants Identified by Exome Sequencing [23]		
Gene	Locus	Putative function
<i>IL23R</i>	1p31.3	Receptor for IL-23 expressed predominantly in T cells. Promotes differentiation of pathogenic Th17 cells [90].
<i>CARD9</i>	9q34.3	Expressed in myeloid cells where it promotes activation of NFκB and inflammatory cytokines downstream of pattern recognition receptors (PRRs) that are associated with immunoreceptor tyrosine-based activation motifs (ITAMs) or hemi-ITAMs [91]. Promotes cytokine environment conducive to Th17 differentiation.
<i>NOD2</i>	16q21	Intracellular PRR specific for bacterial peptidoglycans and is expressed in myeloid cells. Activates NFκB and promotes inflammatory cytokines. Can induce bacterial killing in an

Select IBD Genes Identified by ImmunoChip [1]		
Gene	Locus	Putative Function
		autophagy-dependent manner [92].
<i>IL18RAP</i>	2q12	Accessory protein for IL-18 receptor expressed on NK and T cells. Promotes stimulatory effect of IL-18 on T cell IFN- γ production [93].
<i>MUC19</i>	12q12	Gel-forming mucin expressed in epithelial tissues. Potential role in barrier function and interaction with microbial communities.
<i>CUL2</i>	10p11.21	Component of E3 ubiquitin-protein ligase complex potentially linking proteosomal system with autophagy.
<i>PTPN22</i>	1p13.2	Protein tyrosine phosphatase that regulates T and B cell responses at the level of antigen receptor signaling [94].
<i>C1orf106</i>	1q32.1	Expressed in epithelial cells of the gastrointestinal tract. May promote epithelial integrity and barrier function.

Highlights

- 163 loci have been identified that associate with IBD
- Genetic variation within IBD loci may dysregulate immune homeostasis in the gut
- Innovations in genomics pave the way to decipher genotype-phenotype relationships

Figure 1. From Genetics to Disease Mechanisms

Advancements in genomics technology have facilitated the discovery of 163 loci associated with IBD. Identifying causal mutations within coding and noncoding regions of these loci has begun to reveal gene function and shed new light on disease mechanisms. Progressing from genetics to mechanistic insight is accelerating as a result of new technology in the field of functional genetics.

Figure 2. IBD Pathways and Key Cell Types

Genetic studies have helped to identify critical biological processes and cell types that regulate intestinal inflammation. Genetic variation that perturbs any stage of immune homeostasis, inflammation, or resolution can result in the inappropriate inflammatory response to commensals that is observed in IBD. M cell (M), antibody-secreting cells (ASC), dendritic cell (DC), retinoic acid (RA), T cell (T), T regulatory cell (Treg), innate lymphoid cell (ILC), goblet cell (GC), Paneth cell (PC), antimicrobial proteins (AMPs), neutrophil (NΦ), inflammatory monocyte (Mo), macrophage (MΦ), reactive oxygen species (ROS), nitric oxide (NO), matrix metalloproteinase (MMP).

Figure 3. Molecular Pathogenesis of IBD: Assembling the Evidence

Identification of genes in the ROS pathway point to neutrophils as key cellular mediators of IBD, while functional studies implicated ROS in antibacterial defense, autophagy, and epithelial healing. Thus, genetics can be used to define a mechanism-based subset of IBD patients and guide treatment.

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<i>SPI40</i>	2q37.1	Expressed in hematopoietic cells and contains a bromodomain with potential involvement in epigenetic regulation.
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