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RAPID COMMUNICATION

Identification of Novel Therapeutic Molecular Targets in Inflammatory Bowel Disease by Using Genetic Databases

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Purpose: Utilization of genetic databases to identify genes involved in ulcerative colitis (UC), Crohn's disease (CD), and their extra-intestinal manifestations.

Methods: Protein coding genes involved in ulcerative colitis (3783 genes), Crohn's disease (3980 genes), uveitis (1043 genes), arthritis (5583 genes), primary sclerosing cholangitis (PSC) (1313 genes), and pyoderma gangrenosum (119 genes) were categorized using four genetic databases. These include Genecards: The Human Gene Database (www.genecards.org), DisGeNET (https://www.disgenet.org/), The Comparative Toxicogenomics Database (http://ctdbase.org/) and the Universal Protein Resource (https://www.uniprot.org/). NDex, Network Data Exchange (http://www.ndexbio.org/), was then utilized for mapping a unique signal pathway from the identified shared genes involved in the above disease processes.

Results: We have detected a unique array of 20 genes with the highest probability of overlay in UC, CD, uveitis, arthritis, pyoderma gangrenosum, and PSC. Figure 1 represents the interactome of these 20 protein coding genes. Of note, unique immune modulators in different disease processes are also noted. Interleukin-25 (IL-25) and monensin-resistant homolog 2 (MON-2) are only noted in UC, CD, pyoderma gangrenosum, and arthritis. Arachidonate 5-lipoxygenase (ALOX5) is involved in UC, CD, and arthritis. SLCO1B3 is exclusively involved with pyoderma gangrenosum, UC, and CD. As expected, TNF involvement is noted in CD, UC, PSC, and arthritis. Table 1 depicts the detailed result.

Conclusion: Our work has identified a distinctive set of genes involved in IBD and its associated extra-intestinal disease processes. These genes play crucial roles in mechanisms of immune response, inflammation, and apoptosis and further our understanding of this complex disease process. We postulate that these genes play a critical role at intersecting pathways involved in inflammatory bowel disease, and these novel molecules, their upstream and downstream effectors, are potential targets for future therapeutic agents.

Keywords: inflammatory bowel diseases, IBD, ulcerative colitis, UC, Crohn's disease, CD, arthritis, primary sclerosing cholangitis, PSC, uveitis, pyoderma gangrenosum

Plain Language Summary

In the era of translational and personalized medicine, Inflammatory Bowel disease (IBD) remains a complex disease. This complicated disease presents with a wide array of symptoms that arise from underlying pathophysiological alterations in the patient's mucosal immune system, the intestinal microbiome, the patient's genome, and environmental factors. While the predominant disease manifests with gastrointestinal symptoms, involvement of other organs, including but not limited to the skin, eyes, and bones that present as arthritis, uveitis, and pyoderma gangrenosum, is not uncommon. Though the last decade has identified

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possible genetic factors that confer susceptibility to IBD, the signaling pathways involved in these extra-intestinal manifestations still remain poorly understood. In this study, we use genetic databases to identify an exclusive set of genes that are involved in the extra-intestinal manifestations of IBD and propose these molecules as potential drug targets.

Introduction

Inflammatory Bowel Diseases, which primarily include Ulcerative Colitis and Crohn's disease, are now increasingly recognized as a complex, multi-factorial constellation of diseases whose incidence has been increasing globally.[1,2] While the disease is predominantly described as a gastrointestinal disease, symptoms involving other organ systems are increasingly recognized.[3,4] In the past decade, studies conducted in both animals and human models have suggested that several genetic factors are involved in the pathogenesis of IBD.[5–10] Animal studies have argued for an immune mediated role for IBD. These studies have utilized techniques like gene deletion, gene mutation, chemical induction, and genetic engineering, where manipulation of several genes, specifically distinct immune regulators increase the genetic susceptibility for IBD; possibly by alteration of host defense mechanisms and modulation of the individual's microbiome.[6,7,10] The human studies on the other hand posit that there is a multi-factorial basis, where genetic alterations in combination with environmental factors have been implicated. This data is derived from studies of inheritance patterns of Crohn's in monozygotic twins, where a higher incidenceof Crohn's has been noted.[7,8,11] Further, association studies of genomewide databases have postulated that more than 230 IBD loci are implicated in the pathogenesis of IBD.[12–14] However, understanding of the mechanistic basis of extra-intestinal manifestations of IBD still remains limited. Few of the signaling pathways known have been proposed to be shared with host response to various bacteria and other immune mediated disorders which comprise extra-intestinal manifestations. This study aims to identify genes involved in IBD and its' extra-intestinal manifestations, ie, PSC, pyoderma gangrenosum, arthritis, and uveitis. We hypothesize a network of signaling cascades exist that form the etiological backbone of these diseases, their diverse manifestations, and can offer potential pharmaceutical targets.

Methods

We utilized four genetic databases, including the Genecards: The Human Gene Database (www.genecards.org), DisGeNET (https://www.disgenet.org/), The Comparative Toxicogenomics Database (http://ctdbase.org/) and the Universal Protein Resource (https://www.uniprot.org/), to identify genes implicated in UC, CD, uveitis, arthritis, PSC, and pyoderma gangrenosum. Subsequently, using these genes as possible nodes (aka the common genes involved), and the underlying common signaling cascade in these disease processes, we queried NDex, Network Data Exchange (http://www.ndexbio.org/), an open source bioinformatic platform to predict signaling networks.[15,16] Of note, these databases provide unique scores to each gene, based on information of curated databases and the likelihood of protein–protein interactions.

Results

Our initial analysis from the Genecards: The Human Gene Database, DisGeNET, The Comparative Toxicogenomics Database and the Universal Protein Resource, identified 3783 genes in UC, 3980 genes in CD, 1043 genes in uveitis, 5583 genes in arthritis, 1313 genes in PSC, and 119 genes in pyoderma gangrenosum. Of note, genes identified from these databases do not directly implicate casualty, but are a summation of altered genes in the respective disease state, from studies of animal models, tissue culture, and human databases. We then identified a unique array of 20 genes, that had the highest probability of involvement in UC, CD, uveitis, arthritis, pyoderma gangrenosum, and PSC. A signaling network or interactome (Figure 1) was then formulated using the NDex, Network Data Exchange.[15,16] Of note, this genetic array had a strong emphasis on immune modulators, further arguing for an immune basis in the extra-intestinal presentations of IBD (Table 1 and Figure 1). As expected, we noted Tumor necrosis factor (TNF) involvement in CD, UC, PSC, and arthritis. Further, C-C motif chemokine ligand 2 (CCL2), a chemokine essential for recruitment of monocytes, memory T-cells, and dendritic cells, and an important agent in Protein kinase B (AKT) signaling and Pigment epithelium derived factor (PEDF) pathways, was also involved in CD, UC, arthritis and uveitis.[17] Interestingly, unique modulators were also identified as common nodes in distinctive disease processes. We noted that two immune modulators (a) Interleukin-17A (IL-17A), a proinflammatory cytokine, and (b) Interleukin-21 (IL-21), a regulator of Natural Killer (NK) cells and cytotoxic T cells, are both implicated in CD, UC, uveitis, PSC, and arthritis.[18,19] Arachidonate 5-lipoxygenase (ALOX5), an important member of the lipoxygenase gene family, was exclusively involved in UC, CD, and arthritis.[20] Fas

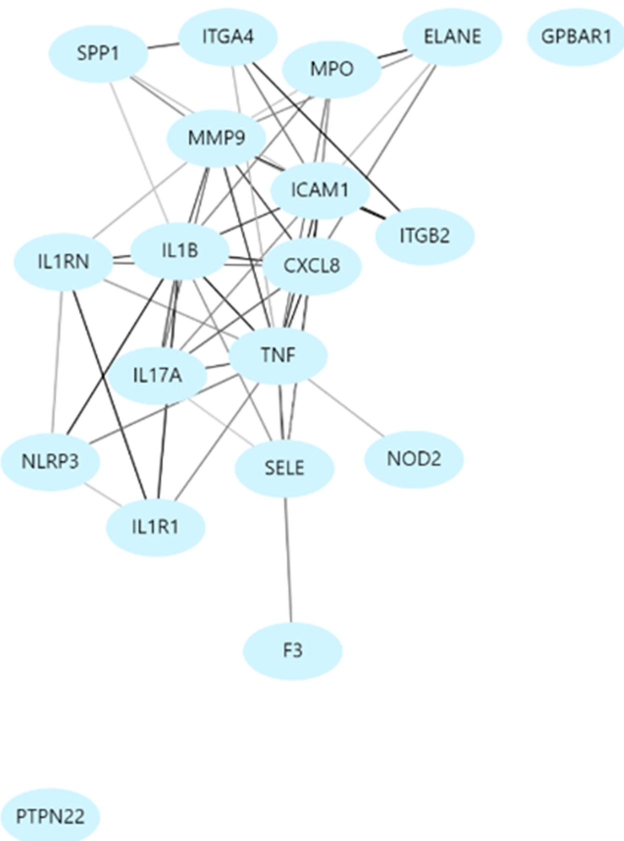

Figure 1 Signaling map of genes (interactome) overlapping in inflammatory bowel disease (UC and CD) and its extra-intestinal manifestations.

Ligand (FASLG), an important player in apoptosis and death receptor, and CCR5, a known HIV receptor, were detected in UC, CD, PSC, uveitis, and arthritis, but not in pyoderma gangrenosum.[21,22] MON2, a regulator of endosome to golgi trafficking and IL-25, a mediator in IL-17 and PEDF signaling, were only noted in CD, UC, pyoderma gangrenosum, and arthritis.[23,24] In contrast, SLCO1B3, which encodes for organic anion transporter, was exclusively involved in Pyoderma gangrenosum, UC and CD.[25] (Table 1)

Discussion

IBD is a complex group of heterogeneous disorders, with an underlying multifactorial pathophysiological basis. A dysregulation between environmental, underlying human microbiome, and genetic susceptibility factors, is hypothesized to play a crucial role in varying manifestation of IBD.[1,–2,–5–13] In our study, we have used genetic data sets to look for overlapping genes involved in IBD and its' extra-intestinal disease forms (like arthritis, uveitis, and pyoderma gangrenosum). Our study supports the theory that immune modulators are critical mediators in extra-intestinal manifestations of IBD. These genes allude towards cross-sectional nodes, that could further implicate to involvement of different signal transduction molecule cascades in different manifestations of IBD.

We hypothesize that these overlapping molecules act as focal points of intersecting signal transduction pathways and are involved in distinctive clinical presentations of IBD and hence are potential therapeutic targets. While our in silico analysis is limited by a lack of wet-lab experiments, it highlights interesting candidate molecules and possible network pathways, which can be utilized in future more focused experimental designs. We believe our analysis consolidates existing information and lays the groundwork for future in vitro and in vivo studies, dedicated towards understanding the pathophysiology of this complex disease. In vitro tissue culture experiments looking at overexpression, underexpression, and protein–protein interactions are key in elucidating the specific function of these molecules; which in turn would offer more insights towards in vivo studies, either in animal models or towards clinical trials in patients with IBD.

Of particular interest in this regard, and noteworthy here is IL-17A, which was identified as a potential target in our analysis.[29,30] Secukinumab, an anti-IL-17A monoclonal antibody, was found to be safe and efficacious in psoriasis and rheumatoid arthritis.[29,30] However, higher adverse events were noted in patients with moderate-to-severe CD.[30] This highlights an inherent limitation of in silico database analyses and in vitro studies, where there is an inability to re-create the unique human intestinal immunological environment and the complex interactions of the host immune system with the gut microbes, which is perhaps critical in the pathophysiology of IBD. This could, in turn, be a limitation in direct translation of data retrieved from in silico analyses to animal model studies and then in therapeutic clinical trials.

Lastly, databases are ever changing, and comprise information from both animal and human tissues. Thus, we anticipate advancement in cell–cell networking, genomewide association studies to keep evolving over time. Though these ever-growing database repositories do offer the advantage of high throughput screening, we acknowledge that this information still has to be used in conjunction with wet lab data to advance our understanding of IBD.[31–33]

Conclusion

Our work identifies a unique set of 20 genes involved in IBD and associated extra-intestinal diseases. These

Table 1 Genes Overlapping in IBD (UC and CD) and Its Extra-Intestinal Manifestations (Uveitis, Arthritis, Primary Sclerosing Cholangitis and Skin Manifestations – Pyoderma Gangrenosum); with the Individual Gene, Specific Disease Processes, and Gene Function Listed

SN #	Genes	Conditions	Pathways*
1	*IL17A*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	Mucin expression in CF via IL6, IL17, IL27 mediated pathway, PDGF signaling, Th17 differentiation, RA pathway
2	*NOD2*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	Activated TLR4 signaling, NF-kappaB Pathway, NOD Pathway, Deubiquitination
3	*TNF*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	TNFR1 pathway, IL6 pathway, STAT 3 pathway, Death Receptor signaling, Toll Like Receptor signaling
4	*CCR6*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	Akt Signaling, Defensins, GPCR Signaling
5	*CXCL8*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	PEDF induced signaling, Toll-like receptor signaling pathway, TGF-Beta Pathway, GPCR ligand binding
6	*ILIB*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	PEDF induced signaling, Toll-like receptor signaling pathway, TGF-Beta Pathway, GPCR ligand binding, ERK Signaling
7	*NLRP3*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	NLR signaling pathway, Innate immune system, metabolism of proteins, Toll-like receptor signaling pathway
8	*MPO*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	Innate immune system, Folate Metabolism, NF-kappaB Pathway, Cytochrome P450
9	*IL1RN*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	NF-kappaB Pathway, IL1 Signaling, PEDF induced signaling, Toll-like receptor signaling pathway
10	*ITGB2*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	MAPK Erk Pathway, PPAR Pathway, Rho Family GTPases, FAK1 signaling, Actin nucleation, and Branching
11	*PTPN22*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	PAK pathway, CTLA4 signaling, NF-kappaB Pathway
12	*MMP9*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	Matrix Metalloproteinase's, Integrin pathway, Degradation of extracellular matrix, Innate immune system
13	*ICAM1*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	VCAM-1/CD106 signaling, Folate metabolism, Interferon gamma signaling
14	*GPBAR1*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	GPCR signaling
15	*ITGA4*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	GPCR signaling, PPAR pathway, FAK1 signaling, Focal adhesion, Actin Nucleation, and branching
16	*F3*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	Formation of fibrin clot, AGE-RAGE signaling pathway, complement, and coagulation cascades
17	*SELE*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	AGE-RAGE signaling pathway, Cell adhesion molecules, VEGF Signaling
18	*SPP1*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	FAK1 signaling, ERK signaling, Toll-like receptor signaling pathway, ECM receptor interaction, Focal adhesion
19	*ILIRI*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	PEDF Signaling, Toll-like receptor signaling pathway, TGF-Beta Pathway
20	*ELANE*	UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum	Degradation of extracellular matrix, Innate immune system, Transcriptional misregulation in cancer
21	*IL20*	UC,CD, Arthritis, Uveitis, and PSC	PEDF, TGF beta, AKT signaling, Rho family Gtpase, PAK pathway
22	*IL21*	UC, CD, Arthritis, Uveitis, and PSC	PEDF, Rho Gtpase, PAK, AKT, Th17
23	*IL2RA*	UC, CD, Arthritis, Uveitis, and PSC	Apoptosis, IL-receptor SHC signaling, PEDF pathway, TGF Beta, AKT
24	*SAG*	UC, CD, Arthritis, Uveitis, and PSC	Rhodopsin mediated signal pathway
25	*IFNG*	UC, CD, Arthritis, Uveitis, and PSC	Allograft rejection, Immune response INF γ signaling pathway, Toll Pathway
26	*CXCR3*	UC,CD, Arthritis, Uveitis, and PSC	Class A/1, GPCR, Neuropeptide signaling, AKT
27	*CXCL10*	UC, CD, Arthritis, Uveitis, and PSC	PEDF, Class A/1 receptor, Rho family GTPase, Toll like receptor
28	*CTLA4*	UC, CD, Arthritis, Uveitis, and PSC	PKC-theta, CD28, Cell adhesion molecules

(*Continued*)

Table 1 (Continued).

SN #	Genes	Conditions	Pathways*
29	*CCL2*	UC, CD, Arthritis, Uveitis, and PSC	PEDF, TGF beta, AKT, and Rho
30	*LTA*	UC, CD, Arthritis, Uveitis, and PSC	PEDF, Rho, TRAF, NF-Kb
31	*IL10*	UC, CD, Arthritis, Uveitis, and PSC	PEDF, TGF, Rho, AKT
32	*CCR5*	UC, CD, Arthritis, Uveitis, and PSC	HIV Receptor-Class A1, Akt, GPCR, Neuropeptide, and Chemokine
33	*RBP3*	UC, CD, Arthritis, Uveitis, and PSC	Visual cycle, metabolism of fat-soluble vitamins, GPCR signaling
34	*CXCR1*	UC, CD, Arthritis, Uveitis, and PSC	IL8-R pathway-Class A/1, GPCR, Neuropeptide signaling, Cell Adhesion ECM modeling, Inhibitory actions of lipoxins on SOD
35	*FASLG*	UC, CD, Arthritis, Uveitis, and PSC	Apoptosis and Death receptor
36	*TNFRSF1A*	UC, CD, Arthritis, Uveitis, and PSC	TWEAK, Apoptosis, TGF, PEDF
37	*TLR4*	UC, CD, Arthritis, Uveitis, and PSC	TRAF, Toll like receptor pathway
38	*IL2RB*	UC, CD, Arthritis, Uveitis, and PSC	PEDF, AKT, TGF-beta, IL22 pathway
39	*NLRC4*	UC, CD, Uveitis, and Arthritis	Gene Expression, innate immune system, Legionellosis, and NLR signaling
40	*SLC22A4*	UC, CD, Arthritis, and PSC	Phospholipase D signaling pathway, Transport of metal ions, glucose, bile salt, and organic acids
41	*AREG*	UC, CD, Arthritis, and PSC	TGF Beta, Rho Gtpases, Nanpg on mammalian ESC pluriopotency
42	*IL25*	UC,CD, Arthritis, and Pyoderma Gangrenosum	IL17 signaling pathway, PEDF induced signaling, TH2 differentiation
43	*MON2*	UC,CD, Arthritis, and Pyoderma Gangrenosum	Regulates endosome to golgi trafficking
44	*FASN*	UC, CD, and Arthritis	AMPK signaling pathway, Fatty acid biosynthesis, Fatty acid metabolism, Insulin signaling pathway, Metabolic pathways
45	*LZTR1*	UC, CD, and Arthritis	Protein modification and ubiquitination
46	*LAMP2*	UC, CD, and Arthritis	Autophagy, Platelet, and Neutrophil degranulation
47	*ALOX5*	UC, CD, and Arthritis	arachidonic acid, LT, Selenium pathway
48	*SLCO1B3*	UC, CD, and Pyoderma Gangrenosum	Bile acid, bile salt metabolism

Notes: *Source – Kegg pathway database (https://www.genome.jp/kegg/pathway.html); UniProt (https://www.uniprot.org/) and Genecards – the human genome database (https://www.genecards.org/).[26–28]

Abbreviations: UC, ulcerative colitis; CD, Crohn's disease; PSC, primary sclerosing cholangitis; IL-17A, interleukin 17A; NOD2, nucleotide binding oligomerization domain containing 2; TNF, tumor necrosis factor; CCR6, C-C motif chemokine receptor 6; CXCL8, C-X-C motif chemokine ligand 8; IL1B, interleukin 1 beta; NLRP3, NLR family pyrin domain containing 3; MPO, myeloperoxidase; IL1RN, interleukin 1 receptor antagonist; ITGB2, integrin subunit beta 2; PTPN22, protein tyrosine phosphatase non-receptor type 22; MMP9, matrix metallopeptidase 9; ICAM1, intercellular adhesion molecule 1; GPBAR1, G protein-coupled bile acid receptor 1; ITGA4, integrin subunit alpha 4; F3, coagulation factor III, tissue factor; SELE, selectin E; SPP1, secreted phosphoprotein 1; IL-1R1, interleukin 1 receptor type 1; ELANE, elastase, neutrophil expressed; IL-20, interleukin 20; IL-21, interleukin 21; IL-2RA, interleukin 2 receptor subunit alpha; SAG, S-antigen visual arrestin; IFNG, interferon gamma; CXCR3, C-X-C motif chemokine receptor 3; CXCL10, C-X-C motif chemokine ligand 10; CTLA4, cytotoxic T-lymphocyte associated protein 4; CCL2, C-C motif chemokine ligand 2; LTA, lymphotoxin alpha; IL10, interleukin 10; CCR5, C-C motif chemokine receptor 5; RBP3, retinol binding protein 3; CXCR1, C-X-C motif chemokine receptor 1; FASLG, Fas ligand; TNFRSF1A, TNF receptor superfamily member 1A; TLR4, toll like receptor 4; IL2RB, interleukin 2 receptor subunit beta; NLRC4, NLR family CARD domain containing 4; SLC22A4, solute carrier family 22 member 4; AREG, amphiregulin; IL25, interleukin 25; MON2, MON2 homolog, regulator of endosome-to-golgi trafficking; FASN, fatty acid synthase; LZTR1, leucine zipper like transcription regulator 1; LAMP2, lysosomal associated membrane protein 2; ALOX5, arachidonate 5-lipoxygenase; SLCO1B3, solute carrier organic anion transporter family member 1B3; CF, cystic fibrosis; IL-6, interleukin 6; IL-17, interleukin 17; IL-27, interleukin 27; PDGF, platelet derived growth factor; RA pathway, retinoic acid pathway; NF-kappaB, nuclear factor kappa light chain enhancer of activated B cells; NOD, nucleotide binding oligomerization domain; STAT 3, signal transducer and activator of transcription 3; AKT, protein kinase B; GPCR, G protein coupled receptor; PEDF, pigment epithelium derived factor; TGF–Beta, transforming growth factor beta; ERK, extracellular signal regulated kinase; NLR, nod like receptor; MAPK, mitogen activated protein kinase; PPAR, peroxisome proliferator-activated receptors; FAK1, focal adhesion kinase 1; PAK, P21 activated protein kinase; VCAM-1, vascular cell adhesion molecule 1; AGE, advanced glycation end products; RAGE, receptor for advanced glycation end products; Rho family, Ras homolog family; Class A/1, rhodopsin like receptors; PKC, protein kinase C; HIV, human immunodeficiency virus; IL-8, interleukin 8; ECM, extracellular matrix; SOD, superoxide dismutase; TWEAK, TNF related weak inducer of apoptosis; TRAF, tumor necrosis factor receptor associated factor; ESC, embryonic stem cells; AMPK, AMP activated protein kinase; LT, leukotriene.

genes are involved in various aspects of cellular processes and signal transduction like processes of apoptosis, inflammation, and immune response. We propose that bioinformatics and system immunology is a potent tool to dissect the complex signaling networks in IBD, and further exploration of upstream and downstream effectors of these candidate genes may help in greater understanding of IBD and its extra-intestinal manifestations.

Disclosure

The authors declare that they have no personal nor financial or non-financial conflicts of interest for this work.

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