Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47

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Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47

Carl A. Anderson[1], **Gabrielle Boucher**[2,3,79], **Charlie W. Lees**[4,79], **Andre Franke**[5,79], **Mauro D'Amato**[6,79], **Kent D. Taylor**[7], **James C. Lee**[8], **Philippe Goyette**[2,3], **Marcin Imielinski**[9], **Anna Latiano**[10], **Caroline Lagacé**[2,3], **Regan Scott**[11], **Leila Amininejad**[12], **Suzannah Bumpstead**[1], **Leonard Baidoo**[11], **Robert N. Baldassano**[13], **Murray Barclay**[14], **Theodore M. Bayless**[15], **Stephan Brand**[16], **Carsten Büning**[17], **Jean-Frédéric Colombel**[18], **Lee A. Denson**[19], **Martine De Vos**[20], **Marla Dubinsky**[21], **Cathryn Edwards**[22], **David Ellinghaus**[5], **Rudolf S.N. Fehrmann**[23], **James A.B. Floyd**[1], **Tim Florin**[24], **Denis Franchimont**[25], **Lude Franke**[23], **Michel Georges**[26], **Jürgen Glas**[16], **Nicole L. Glazer**[27], **Stephen L. Guthery**[28], **Talin Haritunians**[29], **Nicholas K. Hayward**[30], **Jean-Pierre Hugot**[31], **Gilles Jobin**[2,32], **Debby Laukens**[20], **Ian Lawrance**[33], **Marc Lémann**[34], **Arie Levine**[35], **Cecile Libioulle**[36], **Edouard Louis**[36], **Dermot P. McGovern**[7,29], **Monica Milla**[37], **Grant W. Montgomery**[30], **Katherine I. Morley**[1], **Craig Mowat**[38], **Aylwin Ng**[39,40], **William Newman**[41], **Roel A Ophoff**[42], **Laura Papi**[43], **Orazio Palmieri**[10], **Laurent Peyrin-Biroulet**[44], **Julián Panés**[45], **Anne Phillips**[38], **Natalie J. Prescott**[46], **Deborah D. Proctor**[47], **Rebecca Roberts**[14], **Richard Russell**[48], **Paul Rutgeerts**[49], **Jeremy Sanderson**[50], **Miquel Sans**[51], **Philip Schumm**[52], **Frank Seibold**[53], **Yashoda Sharma**[47], **Lisa Simms**[30], **Mark Seielstad**[54,55], **A. Hillary Steinhart**[56], **Stephan R. Targan**[7], **Leonard H. van den Berg**[57], **Morten Vatn**[58], **Hein Verspaget**[59], **Thomas Walters**[60], **Cisca Wijmenga**[23], **David C. Wilson**[48,61], **Harm-Jan Westra**[23], **Ramnik J. Xavier**[39,40], **Zhen Z. Zhao**[30], **Cyriel Y. Ponsioen**[62], **Vibeke Andersen**[63], **Leif Torkvist**[64], **Maria Gazouli**[65], **Nicholas P. Anagnou**[65], **Tom H. Karlsen**[58], **Limas Kupcinskas**[66], **Jurgita Sventoraityte**[66], **John C. Mansfield**[67], **Subra Kugathasan**[68], **Mark S. Silverberg**[56], **Jonas Halfvarson**[69], **Jerome I. Rotter**[29], **Christopher G. Mathew**[46], **Anne M. Griffiths**[60], **Richard Gearry**[14], **Tariq Ahmad**[70], **Steven R. Brant**[15], **Mathias Chamaillard**[71], **Jack Satsangi**[4], **Judy H. Cho**[47,72], **Stefan Schreiber**[5,73], **Mark J. Daly**[74], **Jeffrey C. Barrett**[1], **Miles Parkes**[8], **Vito Annese**[10,37], **Hakon Hakonarson**[13,75,80], **Graham Radford-Smith**[76,80], **Richard H. Duerr**[11,77,80], **Séverine Vermeire**[49,80], **Rinse K. Weersma**[78,80], and **John D. Rioux**[2,3]

[1]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK [2]Université de Montréal, Medicine, Montréal, Québec, Canada [3]Montreal Heart Institute, Research Center, Montréal, Québec, Canada [4]University of Edinburgh, Western General Hospital, Gastrointestinal Unit, Molecular Medicine Centre, Edinburgh, UK [5]Christian-Albrechts-University Kiel, Institute of Clinical Molecular Biology, Kiel, Germany [6]Karolinska Institute,

Correspondence should be addressed to C.A.A. (carl.anderson@sanger.ac.uk)or J.D.R. (john.david.rioux@umontreal.ca).
[79]These authors contributed equally to this work.
[80]These authors contributed equally to this work.

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Department of Biosciences and Nutrition, Stockholm, Sweden [7]Cedars-Sinai Medical Center, Inflammatory Bowel and Immunobiology Research Institute, Los Angeles, California, USA [8]Addenbrooke's Hospital, University of Cambridge, Gastroenterology Research Unit, Cambridge, UK [9]The Children's Hospital of Philadelphia, Center for Applied Genomics, Philadelphia, Pennsylvania, USA [10]IRCCS-CSS Hospital, Unit of Gastroenterology, San Giovanni Rotondo, Italy [11]University of Pittsburgh School of Medicine, Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, Pittsburgh, Pennsylvania, USA [12]Erasmus Hospital, Free University of Brussels, Department of Gastroenterology, Brussels, Belgium [13]The Children's Hospital of Philadelphia, Department of Pediatrics, Center for Pediatric Inflammatory Bowel Disease, Philadelphia, Pennsylvania, USA [14]University of Otago, Department of Medicine, Christchurch, New Zealand [15]Johns Hopkins University School of Medicine, Meyeroff Inflammatory Bowel Disease Center, Dept. of Medicine, Baltimore, Maryland, USA [16]University Hospital Munich, Department of Medicine II, Munich, Germany [17]Universitätsmedizin Berlin, Department of Gastroenterology, Charité, Campus Mitte, Berlin, Germany [18]Université de Lille Department of Hepato-Gastroenterology, Lille, France [19]Cincinnati Children's Hospital Medical Center, Pediatric Gastroenterology, Cincinnati, Ohio, USA [20]Ghent University Hospital, Department of Hepatology and Gastroenterology, Ghent, Belgium [21]Cedars-Sinai Medical Center, Department of Pediatrics, Los Angeles, California, USA [22]Torbay Hospital, Department of Gastroenterology, Torbay, Devon, UK [23]University Medical Center Groningen, Department of Genetics, Groningen, the Netherlands [24]Mater Health Services, Department of Gastroenterology, Brisbane, Australia [25]Erasmus Hospital, Free University of Brussels, Department of Gastroenterology, Brussels, Belgium [26]University of Liège, Department of Genetics, Faculty of Veterinary Medicine, Liège, Belgium [27]University of Washington, Cardiovascular Health Research Unit, Department of Internal Medicine, Seattle, Washington, USA [28]University of Utah School of Medicine, Department of Pediatrics, Salt Lake City, Utah, USA [29]Cedars-Sinai Medical Center, Medical Genetics Institute, Los Angeles, California, USA [30]Queensland Institute of Medical Research, Genetic Epidemiology, Brisbane, Australia [31]Université Paris Diderot & INSERM & Hopital Robert Debre APHP, Gastroenterology, Paris, France [32]Hôpital Maisonneuve-Rosemont, Dept of Gastroenterology, Montréal, Québec, Canada [33]The University of Western Australia, School of Medicine and Pharmacology, Fremantle, Australia [34]Université Paris Diderot, GETAID group, Paris, France [35]Tel Aviv University, Pediatric Gastroenterology Unit, Wolfson Medical Center and Sackler School of Medicine, Tel Aviv, Israel [36]Centre Hospitalier Universitaire Université de Liège, Division of Gastroenterology, Liège, Belgium [37]AOU Careggi, Unit of Gastroenterology SOD2, Florence, Italy [38]Ninewells Hospital and Medical School, Dept of Medicine, Dundee, UK [39]Massachusetts General Hospital, Harvard Medical School, Gastroenterology Unit Boston, Massachusetts, USA [40]Center for Computational and Integrative Biology, Massachusetts General Hospital, Boston, Massachusetts, USA [41]University of Manchester Department of Medical Genetics, Manchester, UK [42]University Medical Center Utrecht, Department of Medical Genetics, Utrecht, Netherlands [43]University of Florence, Institute of Human Genetics, Florence, Italy [44]University Hospital of Nancy, Department of Hepato-Gastroenterology, Vandoeuvre-lès-Nancy, France [45]Hospital Clínic de Barcelona, IDIBAPS, CIBERehd, Department of Gastroenterology, Barcelona, Spain [46]King's College London School of Medicine, Guy's Hospital, Department of Medical and Molecular Genetics, London, UK [47]Yale University, Section of Digestive Diseases, Department of Medicine, New Haven, Connecticut, USA [48]Royal Hospital for Sick Children, Paediatric Gastroenterology and Nutrition, Glasgow, UK [49]University Hospital Gasthuisberg, Division of Gastroenterology, Leuven, Belgium [50]Guy's & St Thomas' NHS Foundation Trust, St Thomas' Hospital, Dept Gastroenterology, London, UK [51]Hospital Clínic de Barcelona, IDIBAPS, CIBERehd, Department of Gastroenterology, Barcelona, Spain [52]University of Chicago, Department of Health Studies, Chicago, Illinois, USA [53]University of Bern, Division of Gastroenterology, Inselspital, Bern, Switzerland [54]Genome Institute of Singapore, Human Genetics, Singapore [55]Institute for Human Genetics, University of

California San Fransisco, San Francisco, California, USA [56]University of Toronto, Mount Sinai Hospital Inflammatory Bowel Disease Centre, Toronto, Ontario, Canada [57]Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Department of Neurology, Utrecht, the Netherlands [58]Rikshospitalet University Hospital, Medical Department, Oslo, Norway [59]Leiden University Medical Center, Experimental Gastroenterology, Leiden, the Netherlands [60]The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada [61]Child Life and Health, University of Edinburgh, Scotland [62]Academic Medical Center, Department of Gastroenterology, Amsterdam, the Netherlands [63]Viborg Regional Hospital, Medical Department, Viborg, Denmark [64]Karolinska Institutet, Department of Clinical Science Intervention and Technology, Stockholm, Sweden [65]University of Athens, Department of Biology, School of Medicine, Athens, Greece [66]Kaunas University of medicine, Department of Gastroenterology, Kaunas, Lithuania [67]Newcastle University, Institute of Human Genetics, Newcastle upon Tyne, UK [68]Emory School of Medicine, Department of Genetics and Department of Pediatrics, Atlanta, Georgia, USA [69]Örebro University Hospital, Department of Medicine, Örebro, Sweden [70]Peninsula College of Medicine and Dentistry, Barrack Road, Exeter, UK [71]Inserm, U1019, Lille, France [72]Yale University, Department of Genetics, Yale School of Medicine, New Haven CT [73]Department for General Internal Medicine, Christian-Albrechts-University, Kiel, Germany [74]Massachusetts General Hospital, Harvard Medical School, Center for Human Genetic Research, Boston, Massachusetts, USA [75]Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA [76]Queensland Institute of Medical Research, IBD Research Group, Brisbane, Australia [77]University of Pittsburgh Graduate School of Public Health, 130 Desoto Street, Pittsburgh, PA, USA [78]University Medical Center Groningen, Department of Gastroenterology, Groningen, the Netherlands

Abstract

Genome-wide association studies (GWAS) and candidate gene studies in ulcerative colitis (UC) have identified 18 susceptibility loci. We conducted a meta-analysis of 6 UC GWAS, comprising 6,687 cases and 19,718 controls, and followed-up the top association signals in 9,628 cases and 12,917 controls. We identified 29 additional risk loci ($P<5\times10^{-8}$), increasing the number of UC associated loci to 47. After annotating associated regions using GRAIL, eQTL data and correlations with non-synonymous SNPs, we identified many candidate genes providing potentially important insights into disease pathogenesis, including *IL1R2, IL8RA/B, IL7R, IL12B, DAP, PRDM1, JAK2, IRF5, GNA12* and *LSP1*. The total number of confirmed inflammatory bowel disease (IBD) risk loci is now 99, including a minimum of 28 shared association signals between Crohn's disease (CD) and UC.

UC and CD represent the two major forms of inflammatory bowel disease (IBD: OMIM #266600), which together affect approximately 1:250 people in Europe, North America and Australasia. Clinical features, epidemiological data and genetic evidence suggest that UC and CD are related polygenic diseases. In contrast to CD, bowel inflammation in UC is limited to the colonic mucosa. While disease-related mortality is low, morbidity remains high and 10-20% of affected individuals will undergo colectomy. Though the precise etiology is unknown, the current hypothesis is a dysregulated mucosal immune response to commensal gut flora in genetically susceptible individuals[1]. Recent genome-wide and candidate-gene association studies have identified 18 UC susceptibility loci, including 7 that overlap with CD (e.g. *IL23* pathway genes, *NKX2-3* and *IL10*). Known UC specific loci (*HNF4A, CDH1* and *LAMB1*) have highlighted the role of defective barrier function in disease pathogenesis[2].

The 18 confirmed UC loci explain approximately 11% of UC heritability (see Online Methods). To identify additional UC susceptibility loci and further elucidate disease pathogenesis, we combined data from six GWAS using genotype imputation and meta-analysis methodology (see Online Methods). The discovery panel consisted of 6,687 cases and 19,718 controls of European descent with data available for at least 1.1 million SNPs (Supplementary Table 1). A quantile-quantile plot of the meta-analysis test statistics showed a marked excess of significant associations in the tail of the distribution (Supplementary Figure 1). Although the majority (16/18) of previously confirmed UC loci are at a genome-wide significant level ($P<5\times10^{-8}$), two just failed to meet this threshold in the meta-analysis – 4q27[3], and 22q13[4] (Table 1), though we still consider these to be true risk loci given the strength of association in the initial studies ($P=1.35\times10^{-10}$ and $P=4.21\times10^{-8}$ respectively). Fifty loci with $P< 1\times10^{-5}$ and not previously associated with UC were followed up by genotyping the most associated SNP from each locus in an independent panel of 9,628 UC cases and 12,917 population controls (see Online Methods and Supplementary Table 2). Of these, 28 loci had evidence of association ($P<0.05$) in the follow-up panel and attained genome-wide significance ($P<5\times10^{-8}$) in the combined analysis of meta-analysis and follow-up cohorts (Table 2 and Supplementary Table 3). In addition, although the locus on 1q32 failed follow-up genotyping (rs7554511) it had been previously tested for association to UC in an independent cohort (rs11584383: $P = 1.2\times10^{-5}$)[5]. This alternative tag SNP achieves genome-wide significancein our current meta-analysis ($P=3.7\times10^{-11}$) and therefore we consider this a confirmed UC locus, bringing the total number of new UC loci to 29. It should be noted that 12 of the 29 loci had documented nominal evidence of association ($5\times10^{-8}<P<0.05$) to UC in previous reports (1p36[2], 1q32[6], 5q33[6], 6p21[5], 7q32[7], 9p24[5,8], 9q34[5,9], 10p11[6], 11q23[5], 13q12[8], 13q13[2] and 20q13[10]). We also tested the 28 loci with follow-up genotype data for association with two clinically relevant disease sub-phenotypes (maximum disease extent and need for colectomy for medically refractory disease) but no significant associations were seen following correction for multiple testing ($P<5.2\times10^{-4}$) (Supplementary Table 4). In summary, there are 47 confirmed UC susceptibility loci, 18 from previous studies and 29 from the current study.

As a first step towards obtaining biological insight from the identification of these 47 loci, we examined the gene content of the associated regions (Supplementary Figure 2). Although three regions contained a single gene (5p15:*DAP*, 6q21:*PRDM1*, 10q24:*NKX2-3*), most (35/47) contain multiple genes and nine are not believed to contain any gene (Table 1). We attempted to identify plausible candidate genes by (a) using a literature-mining tool (GRAIL) to identify non-random, evidence-based links between genes, (b) searching an existing eQTL database[11] for correlations with our most associated SNPs (Supplementary Table 5), (c) using 1000 genomes data to identify non-synonymous SNPs in linkage disequilibrium (LD) ($r^2>0.5$) with the most associated SNP in the locus (Supplementary Table 6), and (d) determining the gene in closest physical proximity to the most associated SNP (see Online Methods). These approaches (results summarized in Table 1, Table 2 and Supplementary Table 7) consistently identified a single candidate gene in six of the associated regions (2q11:*IL1R2*, 5p15:*IL7R*, 7p22:*GNA12*, 10p11:*CCNY*, 1p31:*IL23R*, 16q22:*ZFP90*), potentially prioritizing which genes to follow up in future genetic and functional studies. Noteworthy candidate genes are described in Box 1. Follow-up genotyping in even larger independent panels of cases and controls from a range of ethnicities may be needed to identify the genes containing causal variants.

BOX 1 – Candidate genes within associated loci

***TNFRSF14 / MMEL1* (1p36)**. *TNFRSF14* encodes a member of the TNF receptor superfamily. In a T cell transfer model of colitis, *TNFRSF14* expression by innate immune cells has an important role in preventing intestinal inflammation[22]. *MMEL1*

encodes membrane metalloendopeptidase-like 1. This locus is associated with susceptibility to celiac disease and primary biliary cirrhosis; a nsSNP in MMEL1 was nominally associated with multiple sclerosis.

***TNFRSF9* (1p36)**: Tumour necrosis factor receptor superfamily member 9 is involved as a co-stimulator in the regulation of peripheral T cell activation, with enhanced proliferation and IL2 secretion. It is expressed by dendritic cells, granulocytes and endothelial cells at sites of inflammation. SCID mice transferred with naive CD4+ T cells from TNFRFSF9-deficient mice develop colitis of equal intensity as SCID mice transferred with wild type naïve T cells, but with amodified cytokine response[23].

***IL1R2* (2q11)**: Interleukin 1 receptor, type II binds IL1a, IL1b and IL1R1, inhibiting the activity of these ligands. Two alternative splice transcripts of *IL1R2* have been reported. This protein serves to antagonise the action of IL1a and IL1b, pleiotropic cytokines with various roles in inflammatory processes. IL1b production by lamina propria macrophages is increased in patients with UC[24].

This locus is immediately adjacent to a CD-associated locus containing *IL18RAP, ILR1* and other genes. It is unclear at present whether the CD-associated and UC-associated SNPs in these regions tag two separate loci or one locus. The lead CD SNP has a P=0.001 in our UC meta-analysis. There is a large recombination hotspot between *IL1R2* (UC) and *IL1R1* (CD).

***IL8RA / IL8RB* (2q35)**: *IL8RA* and *IL8RB* encode two receptors for interleukin-8, a powerful neutrophil chemotactic factor. *IL8RA* expression, limited to a subpopulation of lamina propria macrophages and germinal centre lymphocytes in the healthy colon, is increased in macrophages, lymphocytes and epithelium in UC[25]. *IL8RB* expression is more limited and not upregulated in UC. *IL8* expression is profoundly increased in colonic tissue from UC patients compared with controls; this increase is driven by inflammation[26].

***DAP* (5p15)** encodes death-associated protein. The DAPs are a heterogenous group of polypeptides isolated in a screen for elements involved in the IFNγ – induced apoptosis of HeLa cells. *DAP* negatively regulates autophagy and is a substrate of mTOR[13].

***IL7R* (5p13)** encodes the receptor for interleukin-7. IL7 is a key regulator of naïve and memory T cell survival, specifically the transition from effector to memory T cells[27]. T cells expressing high levels of IL7R are seen in human and murine colitis; selective depletion of these cells ameliorates established colitis [28]. *IL7R* is a confirmed multiple sclerosis susceptibility gene[29]. The gene may have undergone extensive evolutionary selective pressure by intestinal helminths[30].

***PRDM1* (6q21)** encodes PR domain containing 1, with ZNF domain (synonym BLIMP1), the master transcriptional regulator of plasma cells and a transcriptional repressor of the IFN-β promoter. It plays important roles in the proliferation, survival and differentiation of B and T lymphocytes.

***GNA12* (7p22)** encodes guanine nucleotide binding protein (G protein) alpha 12, a membrane bound GTPase that plays an important role in tight junction assembly in epithelial cells, through interactions with ZO-1 and Src[20].

IRF5 (7q32) encoding interferon regulatory factor 5, is a confirmed susceptibility gene for rheumatoid arthritis, SLE and primary biliary cirrhosis. This transcription factor regulates activity of type I interferons and induces cytokines including IL-6, IL-12 and TNFα, via TLR signaling. In response to mycobacterium tuberculosis infection of macrophages, Type I interferon expression is dependent on a pathway including *IRF5, NOD2* and *RIP2*[31].

***LSP1* (11q15)**: Lymphocyte-specific protein-1 is expressed by lymphocytes and macrophages, and also in endothelium wherein it is critical for normal neutrophil transmigration[32].

Additional bioinformatic analyses were also performed on the entire set of genes in the associated regions to search for functional commonalities across this large number of loci (see Online Methods). Specifically, using a gene set enrichment approach the UC loci are seen to have more genes associated with cytokines and cytokine receptors (including IFNγ, several interleukins, five TNF and TNFR superfamily members), key regulators of cytokine-mediated signaling pathways, innate and adaptive immune response, macrophage activation and regulation of apoptosis than would be expected by chance (Supplementary Table 8 and Supplementary Figure 3). Enrichment analysis of the subset of candidate loci with no known association to other inflammatory diseases showed significant over-representation of gene sets associated with MAP kinase signaling, actin binding, calcium-dependent processes, fatty acid and lipid metabolism (Supplementary Table 8 and Supplementary Figure 3).

The 5p15 locus contains a single gene, *DAP* (death-associated protein), with the most associated SNP in this region having a strong eQTL effect on *DAP* expression ($P=2.59\times10^{-12}$)[11]. DAP kinase expression has been shown to increase with inflammation in UC[12], and DAP itself has recently been identified as a novel substrate of mTOR (mammalian target of rapamycin)[13] and as a negative regulator of autophagy. While autophagic processes have previously been implicated in CD due to associations with *ATG16L1* and *IRGM*[14], this association with *DAP* suggests a possible link between autophagy and UC.

Association to loci containing *PRDM1, IRF5* and *NKX2-3* suggests an important role for transcriptional regulation in UC pathogenesis. A key example is BLIMP-1, encoded by the *PRDM1* gene, whose most important function is in B cells, as the master transcriptional regulator of plasma cells[15]. It also functions in T cells to attenuate IL-2 production upon antigen stimulation[16], and topromote the development of short-lived effector cells and regulate clonal exhaustion in both CD4 and CD8 cells[17]. It is noteworthy that the 11q24 celiac disease susceptibility locus containing ETS1, a transcription factor essential for T-bet induced production of *IFNγ* and the development of colitis in animal models, just fails to reach genome-wide significance in our study ($P=1.22\times10^{-7}$, Supplementary Table 3b)[18,19].

Identification of *GNA12* as the most likely candidate at the 7p22 locus suggests a role for intestinal barrier function as this gene is implicated in tight junction assembly in epithelial cells[20]. Barrier integrity appears to be a key pathway in UC pathogenesis given previous associations to loci containing *HNF4A, CDH1* and *LAMB1*[2,5].

Given the phenotypic overlap between UC and CD, we examined the evidence for association at all 47 UC loci in our recently completed CD GWAS meta-analysis comprising 6,333 cases and 15,056 controls[14] and, conversely, for evidence of association at all confirmed CD loci in our UC meta-analysis (Table 3 and Supplementary Table 9). We find that, among the 99 confirmed IBD loci meeting genome-wide significance ($P<5\times10^{-8}$) either in UC and/or CD, 28 independent index SNPs have $P<1\times10^{-4}$ in both scans. Interestingly, all index SNPs meeting these criteria showed the same direction of effect in both diseases, thus pointing to a minimum of 28 shared association signals between UC and CD. Multiple genes involved in the IL23 signaling pathway are included in this overlapping SNP list, specifically *IL23R, JAK2, STAT3, IL12B (p40)*, and *PTPN2*. The significance of these findings is underlined by the central role played by *IL23* in the induction of *IL17* by Th17 lymphocytes, its established role in other autoimmune disorders, and the intense interest in

therapeutic manipulation of the *IL23-IL23R* interaction through blockade of the p40 or p19 IL23 subunits.

Loci not meeting these inclusion criteria cannot be formally discounted as shared loci, indeed many of the confirmed UC/CD loci with nominal association ($1\times10^{-4}<P<0.05$) to the other disease may be shared. Among the confirmed UC loci with no evidence ($P>0.05$) of association to CD are the three containing candidate genes that play a role in intestinal barrier function (*GNA12, HNF4A*, and *LAMB1*).

In addition to loci shared with CD, 19 of the 47 UC risk loci are also associated with other immune-mediated diseases (Table 1 and Table 2). In particular, these "shared loci" are enriched for genes involved in T-cell differentiation, specifically in the differentiation of T_H1 and T_H17 cells (e.g. loci encoding *IL23R, IL21, IL10, IL7R, IFNG*). Dysregulated auto-antigen specific T_H1 responses are believed to be involved in organ-specific autoimmune diseases, and T_H17 cells are increasingly recognized to contribute to host defense and induction of autoimmunity and tissue inflammation[21]. Another shared pathway between UC and other immune mediated diseases involves TNF-signaling (*TNFRSF9, TNFRSF14, TNFSF15*) with widespread immunological effects including NF-κB activation, a known key component of the inflammatory response in IBD.

The current study has more than doubled the number of confirmed UC susceptibility loci and we estimate that 16% of UC heritability is explained by these loci (see Online Methods). We have identified potentially causal genes at several loci but confirmation of causality awaits detailed fine-mapping, expression and functional studies. Dense fine-mapping and large-scale re-sequencing studies are underway with the goal of identifying the causal variation within many of these loci.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Association results and *in silico* analyses for the 18 previously confirmed ($P<5\times10^{-8}$) ulcerative colitis (UC) loci

Left-right association boundaries are given for each index SNP (see Online Methods). RAF = risk allele frequency. OR is estimated using the meta-analysis cohort only. Known associations represent phenotypes previously associated with the locus at $P<5\times10^{-8}$). AS = ankylosing spondylitis, Ast = Asthma, BD = Behçet's disease, CD = Crohn's disease, CeD = celiac disease, Graves' disease = GD, HL = Hodgkin's lymphoma, MS = multiple sclerosis, PBC = primary biliary sclerosis, Ps = psoriasis, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, T1D = type 1 diabetes and WBC = white blood cell count. Candidate genes of interest are listed. Those in bold were highlighted by *in silico* analyses (GRAIL connectivity and/or presence of an eQTL or nonsynonymous SNP. See Online Methods and Supplementary Table 7 for more details).

dbSNP ID	Chr.	Left-right(Mb)	Risk Allele	Allele frequency in controls	P-value (meta)	OR (95% CI)	Association reported with other phenotypes	Positional candidate genes of interest
rs6426833	1p36	19.93-20.18	A	0.541	3.93×10^{-35}	1.30 (1.25-1.35)		
rs11209026	1p31	67.30-67.54	G	0.935	5.12×10^{-28}	1.74 (1.57-1.92)	CD, AS, BD, Ps	***IL23R***
rs1801274	1q23	159.54-159.91	A	0.505	2.16×10^{-20}	1.21 (1.16-1.26)	SLE	***FCGR2A, FCGR2B, HSPA6***
rs3024505	1q32	204.85-205.11	A	0.159	5.76×10^{-17}	1.25 (1.19-1.32)	CD, BD, SLE, T1D	***IL10, IL19***
rs7608910	2p16	60.76-61.87	G	0.390	1.70×10^{-14}	1.19 (1.14-1.24)	CD, CeD, RA	*PUS10*
rs4676406	2q37	241.20-241.32	T	0.516	8.32×10^{-11}	1.14 (1.09-1.18)		***GPR35***
rs9822268	3p21	48.14-51.77	A	0.302	1.60×10^{-17}	1.21 (1.16-1.26)	CD	**MST1, *UBA7, APEH, AMIGO3, GMPPB, BSN***
rs17388568	4q27	123.20-123.78	A	0.273	9.49×10^{-7}	1.12 (1.07-1.17)	CeD, T1D	***IL21, IL2****, ADAD1*
rs11739663	5p15	0.48-0.80	T	0.767	2.80×10^{-8}	1.15 (1.09-1.21)		***EXOC3***
rs9268853	6p21	31.49-33.01	T	0.661	1.35×10^{-55}	1.40 (1.34-1.47)	CD, CeD, GrD, MS, PBC, RA, T1D	***HLA-DRB5, HLA-DQA1, HLA-DRB1, HLA-DRA, BTNL2***
rs4510766	7q22	107.20-107.39	A	0.559	2.00×10^{-16}	1.20 (1.15-1.26)		
rs6584283	10q24	101.25-101.33	T	0.472	8.46×10^{-21}	1.21 (1.16-1.26)	CD	
rs7134599	12q14	66.72-66.92	A	0.385	1.06×10^{-16}	1.19 (1.14-1.24)		***IFNG, IL26***
rs6499188	16q22	66.98-67.40	A	0.749	3.97×10^{-8}	1.14 (1.09-1.20)		***ZFP90***
rs2872507	17q12	34.62-35.51	A	0.463	5.44×10^{-11}	1.15 (1.10-1.19)	CD, Ast, PBC, T1D, WBC	***IKZF3, ORMDL3, IKZF3, PNMT*****, ZPBP2, GSDML**
rs6017342	20q13	42.49-42.70	C	0.538	1.09×10^{-20}	1.20 (1.15-1.26)	HDL	***SERINC3***
rs2836878	21q22	39.34-39.41	G	0.738	1.86×10^{-22}	1.25 (1.20-1.32)	AS	
rs5771069	22q13	48.70-48.83	G	0.515	1.87×10^{-7}	1.11 (1.07-1.16)		***PIM3, IL17REL***

Table 2

Association results and *in silico* analyses for the 29 newly confirmed ulcerative colitis (UC) loci

UC loci that meet genome-wide significance $P<5\times10^{-8}$ in the combined analysis and $P<0.05$ in the replication study. Left-right association boundaries are given for each index SNP (see Online Methods). RAF = risk allele frequency. OR is estimated using the replication cohort only. Known associations represent phenotypes previously associated with the locus at $P<5\times10^{-8}$. AtD = atopic dermatitis, BMD = bone mineral density, CD = Crohn's disease, CeD = celiac disease, Gli = glioma, Lep = leprosy, MS = multiple sclerosis, MyN = myeloproliferative neoplasms, PBC = primary biliary sclerosis, Ps = psoriasis, RA = rheumatoid arthritis and SLE = systemic lupus erythematosus. Candidate genes of interest are listed. Those in bold were highlighted by *in silico* analyses (GRAIL connectivity and/or presence of an eQTL or nonsynonymous SNP. See Online Methods and Supplementary Table 7 for more details).

dbSNP ID	Chr.	Left-right(Mb)	Risk Allele	Allele frequency in controls	P-value (meta)	P-value (follow-up)	P-value (comb)	OR (95% CI)	Association reported with other phenotypes	Positional candidate genes of interest
rs734999	1p36	2.39-2.80	C	0.524	1.21×10^{-9}	1.51×10^{-2}	3.34×10^{-9}	1.05 (1.01-1.09)	CeD, PBC	***TNFRSF14, MMEL1, PLCH2, C1orf93***
rs35675666	1p36	7.83-8.13	G	0.829	1.09×10^{-8}	1.13×10^{-2}	4.84×10^{-9}	1.08 (1.02-1.15)	CD	***TNFRSF9, ERFF11,UTS2****,PARK7*
rs7524102	1p36	22.54-22.61	A	0.828	1.04×10^{-11}	2.06×10^{-4}	1.65×10^{-13}	1.10 (1.05-1.16)	BMD	
rs7554511	1q32	199.06-199.33	C	0.721	2.04×10^{-13}	NA	NA	1.19 (1.14-1.25)	CD, CeD	*C1orf106*
rs2310173	2q11	101.66-102.13	T	0.461	8.44×10^{-8}	5.94×10^{-6}	3.17×10^{-12}	1.09 (1.05-1.14)		***IL1R2***
rs11676348	2q35	218.58-218.97	T	0.486	8.78×10^{-9}	6.18×10^{-4}	1.25×10^{-10}	1.07 (1.03-1.11)		***IL8RA, SLC11A1, IL8RB, AAMP, ARPC***
rs267939	5p15	10.72-10.90	C	0.368	9.67×10^{-7}	1.27×10^{-6}	6.01×10^{-12}	1.10 (1.06-1.15)		***DAP***
rs3194051	5p13	35.83-36.07	G	0.269	2.19×10^{-6}	2.06×10^{-3}	4.22×10^{-8}	1.07 (1.02-1.12)	MS	***IL7R***
rs6451493*	5p13	40.32-40.85	T	0.610	1.78×10^{-6}	2.09×10^{-4}	2.80×10^{-9}	1.08 (1.04-1.12)	CD, MS	***PTGER4***
rs254560	5q31	134.41-134.53	A	0.397	3.06×10^{-7}	4.19×10^{-4}	1.25×10^{-9}	1.07 (1.03-1.12)		
rs6871626	5q33	158.46-158.86	A	0.334	1.02×10^{-8}	1.40×10^{-14}	1.11×10^{-21}	1.17 (1.12-1.22)	CD, Ps, SLE	***IL12B***
rs943072	6p21	43.88-43.92	G	0.092	1.05×10^{-6}	3.71×10^{-5}	2.37×10^{-10}	1.15 (1.08-1.23)		
rs6911490	6q21	106.51-106.67	T	0.210	3.51×10^{-7}	1.70×10^{-3}	1.01×10^{-8}	1.08 (1.03-1.13)	CD, RA, SLE	***PDRM1***
rs6920220	6q23	137.88-138.17	A	0.207	6.38×10^{-10}	1.94×10^{-8}	8.05×10^{-17}	1.14 (1.09-1.20)	CeD, Ps, RA, SLE	
rs798502	7p22	2.70-2.90	A	0.711	1.21×10^{-8}	3.82×10^{-8}	2.61×10^{-15}	1.13 (1.08-1.18)		***GNA12***
rs4728142	7q32	128.33-128.56	A	0.444	1.68×10^{-6}	1.25×10^{-3}	1.74×10^{-8}	1.07 (1.03-1.11)	SLE, RA, PBC	***IRF5, TNPO3***
rs10758669	9p24	4.93-5.28	C	0.350	8.52×10^{-13}	3.78×10^{-14}	2.22×10^{-25}	1.17 (1.12-1.21)	CD, MyN	***JAK2***
rs4246905	9q32	116.48-116.74	C	0.713	4.77×10^{-8}	1.44×10^{-5}	5.65×10^{-12}	1.10 (1.05-1.15)	CD, Lep	***TNFSF8, TNFSF15***

dbSNP ID	Chr.	Left-right(Mb)	Risk Allele	Allele frequency in controls	P-value (meta)	P-value (follow-up)	P-value (comb)	OR (95% CI)	Association reported with other phenotypes	Positional candidate genes of interest
rs10781499	9q34	138.27-138.55	A	0.411	6.95×10^{-13}	2.50×10^{-8}	2.62×10^{-19}	1.12 (1.08-1.17)	CD	***CARD9, INPP5E, SDCCAG3, SEC16A, SNAPC4***
rs12261843	10p11	35.22-35.94	G	0.286	2.35×10^{-8}	1.22×10^{-3}	7.09×10^{-10}	1.07 (1.03-1.12)	CD	***CCNY***
rs907611	11q15	1.82-1.93	A	0.317	2.49×10^{-8}	3.58×10^{-4}	1.38×10^{-10}	1.08 (1.03-1.13)		***LSP1***
rs2155219	11q13	75.72-76.02	T	0.500	6.33×10^{-8}	1.61×10^{-9}	5.39×10^{-16}	1.13 (1.08-1.17)	CD, AtD	
rs678170	11q23	113.76-114.08	A	0.661	6.88×10^{-11}	2.50×10^{-5}	4.65×10^{-14}	1.09 (1.05-1.14)		
rs17085007	13q12	26.39-26.46	C	0.178	3.30×10^{-9}	4.66×10^{-9}	9.65×10^{-17}	1.16 (1.10-1.21)		
rs941823	13q13	39.90-39.95	C	0.756	3.93×10^{-7}	1.93×10^{-6}	3.82×10^{-12}	1.12 (1.07-1.17)		
rs16940202	16q24	84.53-84.58	C	0.180	1.27×10^{-12}	1.42×10^{-8}	5.96×10^{-19}	1.15 (1.10-1.21)	MS	
rs2297441	20q13	61.66-61.98	A	0.766	5.78×10^{-8}	2.68×10^{-4}	1.70×10^{-10}	1.09 (1.04-1.15)	CD, Gli	***SLC2A4RG, STMN3, ZBTB46, ZGPAT, RTEL1, TNFRSF6B***
rs1297265	21q21	15.62-15.77	A	0.564	1.73×10^{-7}	5.02×10^{-7}	6.99×10^{-13}	1.11 (1.06-1.15)	CD	
rs2838519	21q22	44.41-44.52	G	0.390	2.26×10^{-8}	7.10×10^{-4}	6.41×10^{-11}	1.14 (1.05-1.22)	CD	***ICOSLG***

Table 3

Shared association signals between UC and CD

A shared association is defined as a confirmed association ($P_{combined} < 5\times10^{-8}$) in either UC or CD and $P_{meta} < 1\times10\text{-}4$ in the other form of IBD. For more details and comparative results across all 99 reported IBD risk loci see Supplementary table 9.

LOCUS		GENE	INDEX SNP			CD-META (6333/15056)		UC-META (6687/19718)	
Chr.	**Left-Right (Mb)**	**Candidate**	**SNP**	**Risk Allele**	**Allele frequency in controls**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**
1p31	67.30-67.54	*IL23R*	rs11209026	G	0.94	1.00×10^{-64}	2.67 (2.37-3.01)	5.12×10^{-28}	1.74 (1.57-1.92)
1q32	199.0 -199.33	*KIF21B*	rs7554511	C	0.72	1.58×10^{-7}	1.14 (1.08-1.19)	2.04×10^{-13}	1.19 (1.14-1.25)
1q32	204.85-205.11	*IL10*	rs3024505	A	0.16	8.32×10^{-9}	1.18 (1.12-1.25)	5.76×10^{-17}	1.25 (1.19-1.32)
2p16	60.76-61.87	*REL*	rs7608910	G	0.39	3.11×10^{-7}	1.14 (1.09-1.21)	1.70×10^{-14}	1.19 (1.14-1.24)
2q11	101.66-102.13	*IL1R2*	rs2310173	T	0.46	8.31×10^{-5}	1.09 (1.04-1.14)	8.44×10^{-8}	1.12 (1.07-1.16)
3p21	48.14-51.77	*MST1*	rs3197999	A	0.30	6.17×10^{-17}	1.22 (1.16-1.27)	1.86×10^{-17}	1.21 (1.16-1.26)
5p13	40.32-40.85	*PTGER4*	rs6451493	T	0.61	1.61×10^{-27}	1.35 (1.28-1.43)	1.78×10^{-6}	1.12 (1.07-1.17)
		IL12B	rs6871626	A	0.33	6.08×10^{-12}	1.15 (1.10-1.20)	1.02×10^{-8}	1.12 (1.08-1.17)
5q33	158.46-158.86	*IL12B*	rs6556412 (r^2=0.03)	A	0.34	5.37×10^{-14}	1.18 (1.13-1.23)	1.69×10^{-5}	1.09 (1.05-1.14)
6p22	20.60-21.25	*CDKAL1*	rs6908425	C	0.78	1.41×10^{-8}	1.17 (1.11-1.23)	7.75×10^{-5}	1.11 (1.05-1.16)
6q21	106.51-106.67	*PRDM1*	rs6911490	T	0.21	4.28×10^{-7}	1.12 (1.07-1.18)	3.51×10^{-7}	1.13 (1.07-1.18)
9p24	4.93-5.29	*JAK2*	rs10758669	C	0.35	1.00×10^{-13}	1.18 (1.13-1.23)	8.52×10^{-13}	1.16 (1.11-1.21)
9q32	116.48-116.74	*TNFSF15*	rs4246905	C	0.71	1.33×10^{-15}	1.21 (1.15-1.28)	4.77×10^{-8}	1.13 (1.08-1.18)
9q34	138.27-138.55	*CARD9*	rs10781499	A	0.40	3.49×10^{-18}	1.20 (1.15-1.26)	6.95×10^{-13}	1.16 (1.11-1.21)
10p11	35.22-35.94	*CREM/CCNY*	rs12261843	G	0.29	1.87×10^{-9}	1.15 (1.10-1.20)	2.35×10^{-8}	1.13 (1.08-1.18)
10q21	63.97-64.43	*ZNF365*	rs10761659	G	0.54	4.37×10^{-22}	1.23 (1.18-1.28)	7.39×10^{-6}	1.10 (1.05-1.14)
10q24	101.25-101.33	*NKX2.3*	rs6584283	T	0.47	7.18×10^{-20}	1.21 (1.16-1.27)	8.46×10^{-21}	1.21 (1.16-1.26)

LOCUS		GENE	INDEX SNP			CD-META (6333/15056)		UC-META (6687/19718)	
Chr.	Left-Right (Mb)	Candidate	SNP	Risk Allele	Allele frequency in controls	p-value	OR (95% CI)	p-value	OR (95% CI)
11q13	75.72-76.02	*C11Orf30*	rs2155219	T	0.50	1.58×10^{-12}	1.16 (1.11-1.21)	6.33×10^{-8}	1.12 (1.07-1.16)
15q22	65.2-65.27	*SMAD3*	rs17293632	T	0.24	1.41×10^{-13}	1.19 (1.14-1.25)	9.52×10^{-6}	1.11 (1.06-1.16)
17q12	34.62-35.51	*ORMDL3*	rs2872507	A	0.46	1.51×10^{-9}	1.14 (1.09-1.19)	5.44×10^{-11}	1.15 (1.10-1.19)
18p11	12.73-12.92	*PTPN2*	rs1893217	G	0.16	1.29×10^{-14}	1.25 (1.18-1.32)	4.78×10^{-5}	1.12 (1.06-1.18)
19p13	10.26-10.5	*TYK2*	rs12720356	C	0.08	9.20×10^{-10}	1.22 (1.14-1.31)	3.90×10^{-6}	1.17 (1.09-1.26)
19q13	38.42-38.47	-	rs736289	T	0.61	2.69×10^{-7}	1.11 (1.06-1.16)	1.89×10^{-5}	1.08 (1.03-1.12)
20q13	61.66-61.98	*RTEL1/SLC2A4RG*	rs2297441	A	0.76	1.83×10^{-11}	1.19 (1.13-1.25)	5.78×10^{-8}	1.14 (1.09-1.20)
21q21	15.62-15.77	-	rs1297265	A	0.57	1.41×10^{-8}	1.16 (1.10-1.22)	1.73×10^{-7}	1.11 (1.06-1.16)
21q22	39.34-39.41	-	rs2836878	G	0.74	3.22×10^{-6}	1.12 (1.06-1.17)	1.86×10^{-22}	1.25 (1.20-1.32)
21q22	44.41-44.52	*ICOSLG*	rs2838519	G	0.39	2.09×10^{-14}	1.18 (1.13-1.23)	2.26×10^{-8}	1.12 (1.08-1.17)
22q11	20.14-20.39	*YDJC*	rs181359	A	0.19	6.31×10^{-13}	1.21 (1.15-1.28)	2.73×10^{-5}	1.11 (1.06-1.17)