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

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Genome-wide association studies and candidate gene studies in ulcerative colitis have identified 18 susceptibility loci. We conducted a meta-analysis of six ulcerative colitis genome-wide association study datasets, 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 ($P < 5 \times 10^{-8}$), increasing the number of ulcerative colitis–associated loci to 47. After annotating associated regions using GRAIL, expression quantitative trait loci data and correlations with non-synonymous SNPs, we identified many candidate genes that provide potentially important insights into disease pathogenesis, including *IL1R2*, *IL8RA-IL8RB*, *IL7R*, *IL12B*, *DAP*, *PRDM1*, *JAK2*, *IRF5*, *GNA12* and *LSP1*. The total number of confirmed inflammatory bowel disease risk loci is now 99, including a minimum of 28 shared association signals between Crohn's disease and ulcerative colitis.

Ulcerative colitis and Crohn's disease represent the two major forms of inflammatory bowel disease (IBD, MIM#266600), which together affect approximately 1 in 250 people in Europe, North America and Australasia. Clinical features, epidemiological data and genetic evidence suggest that ulcerative colitis and Crohn's disease are related polygenic diseases. In contrast to Crohn's disease, bowel inflammation in ulcerative colitis is limited to the colonic mucosa. Although 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 susceptibility loci for ulcerative colitis, including seven that overlap with Crohn's disease (for example, *IL23* pathway genes, *NKX2-3* and *IL10*). Established risk loci specific for ulcerative colitis (*HNF4A*, *CDH1* and *LAMB1*) have highlighted the role of defective barrier function in disease pathogenesis[2].

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The 18 confirmed ulcerative colitis risk loci explain approximately 11% of the heritability for this disease (Online Methods). To identify additional ulcerative colitis susceptibility loci and further elucidate disease pathogenesis, we combined data from six genome-wide association studies (GWAS) using genotype imputation and meta-analysis methodology (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 Fig. 1**). Although the majority (16 out of 18) of the previously confirmed ulcerative colitis risk loci were at a genome-wide significant level ($P < 5 \times 10^{-8}$), two just failed to meet this threshold in the meta-analysis (4q27 and 22q13; **Table 1**), though we still consider these to be true risk loci given the strength of associations in the initial studies[3,4] ($P = 1.35 \times 10^{-10}$ and $P = 4.21 \times 10^{-8}$, respectively). We followed up fifty loci with $P < 1 \times 10^{-5}$ which were not previously associated with ulcerative colitis by genotyping the most-associated SNP from each locus in an independent panel of 9,628 ulcerative colitis cases and 12,917 population controls (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 ($P < 5 \times 10^{-8}$) in the combined analysis of the meta-analysis and follow-up cohorts (**Table 2** and **Supplementary Table 3**). In addition, although the locus on 1q32 (rs7554511) failed follow-up genotyping, it had been previously tested for association to ulcerative colitis in an independent cohort (rs11584383, $P = 1.2 \times 10^{-5}$)[5]. This alternative tag SNP achieved genome-wide significance in our current meta-analysis ($P = 3.7 \times 10^{-11}$) and therefore we consider the locus on 1q32 to be a confirmed ulcerative colitis risk locus, bringing the total number of new ulcerative colitis risk loci to 29. It should be noted that 12 of the 29 loci had documented nominal evidence of association ($5 \times 10^{-8} < P < 0.05$) to ulcerative colitis in previous reports[2,5–10] (1p36, 1q32, 5q33, 6p21, 7q32, 9p24, 9q34, 10p11, 11q23, 13q12, 13q13 and 20q13). We also tested the 28 loci with follow-up genotype data for association with two clinically relevant disease subphenotypes (maximum disease extent and need for colectomy for medically refractory disease), but we saw no significant associations following correction for multiple testing ($P < 5.2 \times 10^{-4}$) (**Supplementary Table 4**). In summary, there are now 47 confirmed ulcerative colitis susceptibility loci, 18 from previous studies and 29 from the current study.

As a first step toward obtaining biological insight from the identification of these 47 loci, we examined the gene content of the associated regions (**Supplementary Fig. 2**). Although three regions each contain a single gene (5p15, *DAP*; 6q21, *PRDM1*; and 10q24, *NKX2-3*), most (35 out of 47) contain multiple genes and nine are not believed to contain any gene (**Table 1**). We attempted to identify plausible candidate genes by: (i) using a literature-mining tool (GRAIL) to identify non-random, evidence-based links between genes, (ii) searching an existing expression quantitative trait loci (eQTL) database[11] for correlations with our most-associated SNPs (**Supplementary Table 5**), (iii) using 1000 Genomes Project 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 (iv) determining the gene in closest physical proximity to the most-associated SNP (Online Methods). These approaches (with the results summarized in **Tables 1** and **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*; and 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.

Table 1 Association results and *in silico* analyses for 18 previously confirmed ulcerative colitis risk loci

dbSNP ID	Chr.	Left–right (Mb)	Risk allele	Allele frequency in controls	P_{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***

Loci previously associated at genome-wide significance ($P < 5 \times 10^{-8}$). Left–right association boundaries are given for each index SNP (Online Methods). The odds ratio was estimated using the meta-analysis cohort data only. Known associations represent phenotypes previously associated with the locus at $P < 5 \times 10^{-8}$. Chr., chromosome; OR, odds ratio; 95% CI, 95% confidence interval; AS, ankylosing spondylitis; Ast, asthma; BD, Behçet's disease; CD, Crohn's disease; CeD, celiac disease; GD, Graves' disease; HL, Hodgkin's lymphoma; MS, multiple sclerosis; PBC, primary biliary sclerosis; Ps, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; 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 non-synonymous SNP; see Online Methods and **Supplementary Table 7** for more details).

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Table 2 Association results and *in silico* analyses for 29 newly confirmed ulcerative colitis risk loci

dbSNP ID	Chr.	Left–right (Mb)	Risk allele	Allele frequency in controls	P_{meta}	$P_{follow\text{-}up}$	$P_{combined}$	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*, *ERFFI1*, *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***
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***

Ulcerative colitis risk loci that met genome-wide significance ($P < 5 \times 10^{-8}$) in the combined analysis and $P < 0.05$ in the replication study. Left–right association boundaries are given for each index SNP (Online Methods). The odds ratio was estimated using the replication cohort only. Known associations represent phenotypes previously associated with the locus at $P < 5 \times 10^{-8}$. Chr., chromosome; OR, odds ratio; 95% CI, 95% confidence interval; 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; 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).

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We also performed additional bioinformatic analyses on the entire set of genes in the associated regions to search for functional commonalities across this large number of loci (Online Methods). Specifically, using a gene set enrichment approach, the ulcerative colitis loci were seen to have more genes associated with cytokines and cytokine receptors (including IFNγ, several interleukins and 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 Fig. 3**). Enrichment analysis of the subset of candidate loci with no known association to other inflammatory diseases showed significant ($P < 0.05$) overrepresentation of gene sets associated with MAP kinase signaling, actin binding, calcium-dependent processes, fatty acid and lipid metabolism (**Supplementary Table 8** and **Supplementary Fig. 3**).

The 5p15 locus contains a single gene, *DAP* (encoding the death-associated protein), with the most-associated SNP in this region having a strong eQTL effect on *DAP* expression ($P = 2.59 \times 10^{-12}$)[11]. DAP kinase expression has been shown to increase with inflammation in ulcerative colitis[12], and DAP itself has recently been identified as a new substrate of mTOR (mammalian target of rapamycin)[13] and as a negative regulator of autophagy. Although autophagic processes have previously been implicated in Crohn's disease due to associations with *ATG16L1* and *IRGM*[14], this association with *DAP* suggests a possible link between autophagy and ulcerative colitis.

Association to loci containing *PRDM1*, *IRF5* and *NKX2-3* suggests an important role for transcriptional regulation in ulcerative colitis pathogenesis. A key example is BLIMP-1, encoded by *PRDM1*, 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 to promote 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*, encoding a transcription factor essential for T-bet–induced production of IFNγ and the development of colitis in animal models, just failed to reach genome-wide significance in our study ($P = 1.22 \times 10^{-7}$; **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

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 non-synonymous SNP in *MMEL1* was previously nominally associated with multiple sclerosis.
***TNFRSF9* (1p36).** Tumor necrosis factor receptor superfamily member 9 is involved as a co-stimulator in the regulation of peripheral T-cell activation, with enhanced proliferation and IL-2 secretion. It is expressed by dendritic cells, granulocytes and endothelial cells at sites of inflammation. Severe combined immunodeficient (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 have a modified cytokine response[23].
***IL1R2* (2q11).** Interleukin 1 receptor, type II binds IL-1α, IL-1β and IL1R1, inhibiting the activity of these ligands. Two alternative splice transcripts of *IL1R2* have been reported. This protein serves to antagonize the action of IL-1α and IL-1β, pleiotropic cytokines with various roles in inflammatory processes. IL-1β production by lamina propria macrophages is increased in patients with ulcerative colitis[24]. This locus is immediately adjacent to a Crohn's disease–associated locus containing *IL18RAP*, *ILR1* and other genes. It is unclear at present whether the Crohn's disease–associated and ulcerative colitis–associated SNPs in these regions tag two separate loci or just one locus. The lead Crohn's disease SNP had $P = 0.001$ in our ulcerative colitis meta-analysis. There is a large recombination hotspot between *IL1R2* (ulcerative colitis) and *IL1R1* (Crohn's disease).
***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 center lymphocytes in the healthy colon, is increased in macrophages, lymphocytes and epithelium in ulcerative colitis[25]. *IL8RB* expression is more limited and is not upregulated in ulcerative colitis. *IL8* expression is profoundly increased in colonic tissue from ulcerative colitis cases compared with controls; this increase is driven by inflammation[26].
***DAP* (5p15).** *DAP* 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).** *IL7R* encodes the receptor for interleukin-7. IL-7 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).** *PRDM1* encodes PR domain containing 1, with ZNF domain (also known as 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).** *GNA12* 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).** *IRF5*, encoding interferon regulatory factor 5, is a confirmed susceptibility gene for rheumatoid arthritis, systemic lupus erythematosus 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 that includes IRF5, NOD2 and RIP2 (ref. 31).
***LSP1* (11q15)**. Lymphocyte-specific protein-1 is expressed by lymphocytes and macrophages and also in endothelium, where it is critical for normal neutrophil transmigration[32].

to be a key pathway in ulcerative colitis pathogenesis given previous associations[2,5] to loci containing *HNF4A*, *CDH1* and *LAMB1*.

Given the phenotypic overlap between ulcerative colitis and Crohn's disease, we examined the evidence for association at all 47 ulcerative colitis loci in our recently completed Crohn's disease GWAS meta-analysis comprising 6,333 cases and 15,056 controls[14] and, conversely, for evidence of association at all confirmed Crohn's disease loci in our ulcerative colitis meta-analysis (**Table 3** and **Supplementary Table 9**). We found that, among the 99 confirmed IBD loci meeting genome-wide significance ($P < 5 \times 10^{-8}$) in ulcerative colitis and/or Crohn's disease, 28 independent index SNPs also have $P < 1 \times 10^{-4}$ in both scans. Notably, 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 ulcerative colitis and Crohn's disease. Multiple genes involved in the IL23 signaling pathway are included in this overlapping SNP list, specifically *IL23R*, *JAK2*, *STAT3*, *IL12B* (encoding p40) and *PTPN2*. The significance of these findings is underlined by the central role played by IL-23 in the induction of IL-17 by Th17 lymphocytes, its established role in other autoimmune disorders and the intense interest in therapeutic manipulation of the IL-23–IL23R interaction through blockade of the p40 or p19 IL-23 subunits.

Loci not meeting these inclusion criteria cannot be formally discounted as shared loci; indeed, many of the confirmed ulcerative colitis and/or Crohn's disease loci with nominal association ($1 \times 10^{-4} < P < 0.05$) to the other disease may be shared. Among the confirmed ulcerative colitis loci with no evidence ($P > 0.05$) of association to Crohn's disease are the three loci containing candidate genes that play a role in intestinal barrier function (*GNA12*, *HNF4A* and *LAMB1*).

In addition to loci shared with Crohn's disease, 19 of the 47 ulcerative colitis risk loci are also associated with other immune-mediated diseases (**Tables 1** and **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 (for example, *IL23R*, *IL21*, *IL10*, *IL7R* and *IFNG*). Dysregulated auto-antigen–specific T_H1 responses are believed to be involved in organ-specific autoimmune diseases, and T_H17 cells have been increasingly recognized to contribute to host defense and induction of autoimmunity and tissue inflammation[21]. Another shared pathway between ulcerative colitis and other immune-mediated diseases involves TNF signaling (*TNFRSF9*, *TNFRSF14* and *TNFSF15*) with widespread immunological effects including NF-κB activation, a known key component of the inflammatory response in IBD.

This current study has more than doubled the number of confirmed ulcerative colitis susceptibility loci, and we estimate that 16% of ulcerative colitis heritability is explained by these loci (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 resequencing studies are currently underway with the goal of identifying the causal variation within many of these loci.

URLs. MACH, http://www.sph.umich.edu/csg/abecasis/MACH/; GRAIL, http://www.broadinstitute.org/mpg/grail/; IMPUTE,

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Table 3 Association signals shared between ulcerative colitis and Crohn's disease

Locus		Gene	Index SNP			CD-META (6,333/15,056)		UC-META (6,687/19,718)	
Chr.	Left–right (Mb)	Candidate	SNP	Risk allele	Allele frequency in controls	*P*	OR (95% CI)	*P*	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)
5q33	158.46–158.86	*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)
		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)
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)

A shared association is defined as a confirmed association ($P_{combined} < 5 \times 10^{-8}$) in either ulcerative colitis or Crohn's disease and $P_{meta} < 1 \times 10^{-4}$ in the other form of IBD. For more details and comparative results across all 99 reported IBD risk loci, see **Supplementary Table 9**. For CD and UC meta-analyses, the numbers in parentheses represent the number of cases and controls, respectively. CD, Crohn's disease; UC, ulcerative colitis; OR, odds ratio; 95% CI, 95% confidence interval.

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https://mathgen.stats.ox.ac.uk/impute/impute.html; 1000 Genomes Project March 2010 release, ftp://ftp.sanger.ac.uk/pub/1000genomes/PILOT/REL-1005/QCALL/.

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Note: Supplementary information is available on the Nature Genetics website.

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The authors declare no competing financial interests.

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ONLINE METHODS

Study samples. For the meta-analysis, all study subjects were of European origin. The meta-analysis was based on data from 6,687 ulcerative colitis cases and 19,718 population controls derived from six index genome-wide scans from Cedars-Sinai[5], Germany[4,33], Sweden[5], the Early onset IBD consortium[10,34], the NIDDK IBD Genetics Consortium[35] and the Wellcome Trust Case Control Consortium 2 (WTCCC2)[2]. All cases were ascertained using standard clinical, endoscopic and histopathological criteria for diagnosis of ulcerative colitis. Details of the genotyping platform and the number of cases and controls in each study are given in **Supplementary Table 1**. Sample ascertainment and quality control procedures are fully described in the index publications. Controls for the Cedars-Sinai study were obtained from the Cardiovascular Health Study (CHS)[36], a population-based longitudinal study of risk factors for cardiovascular disease and stroke in adults 65 years of age or older recruited at four field centers. Five thousand two hundred and one individuals, predominantly of European descent, were recruited in 1989–1990 from random samples of Medicare eligibility lists, followed by an additional 687 African-Americans recruited in 1992–1993 (total n = 5,888).

For the follow-up study, all samples were of European origin. Details of the follow-up panel of 9,628 cases and 12,917 controls are provided in **Supplementary Table 2**. Each center supplying cases also supplied its own panel of population controls. All participating centers received approval from their local and national institutional review boards, and informed consent was obtained from all participants in the study.

Statistical methods. Genome-wide SNP imputation was carried out using BEAGLE[37] and the HapMap3 reference samples from the CEU, TSI, MEX and GJT cohorts, with the exception of the CHOPSTICKS samples, which were imputed using the MACH program (see URLs) and the HapMap2 CEU reference samples. In total, 1,428,850 autosomal markers (HapMap3 X chromosome data were not available) were available for association analysis in at least one GWAS dataset.

To carry out the meta-analysis, we employed the methodology used in both our previous Crohn's disease meta-analyses[14,38]. For each individual and SNP, post-imputation genotype class probabilities were converted to allelic dosages. For example, the allelic dosage for the A allele at a given SNP with post-imputation genotype probabilities of AA = 0.8, Aa = 0.1 and aa = 0.1 in a given individual is $2 \times 0.8 + 1 \times 0.1 + 0 \times 0.1 = 1.7$ (and the allelic dosage for allele a is 0.3). Per SNP, the dosage at each allele is summated separately across cases and controls within each of the GWAS datasets. An empirical variance is calculated on a per-SNP per-study basis to correctly weight the association analysis according to GWAS sample size. The empirical variance (σ^2) is given by:

$$\frac{1}{N}\sum_{i=1}^{N}(x_i - \mu)^2$$

where x_i is the allelic dosage for individual i at the reference allele, μ is the mean dosage across all individuals in the study, and N is the total number of individuals in the study. z scores were calculated using the empirical variance (rather than the binomial variance) and summated across studies to yield a meta-analysis z score and P value.

Linkage disequilibrium regions around focal SNPs were calculated by extending in both directions a distance of 0.1 centimorgans (cM). If another SNP within this region had $P < 10^{-5}$, the addition of 0.1 cM was repeated from this SNP[2,38]. A gene was considered a positional candidate if the index SNP was located within the gene.

Follow up. Loci previously associated with ulcerative colitis at $P < 5 \times 10^{-8}$ were not taken forward for follow up. The most-associated SNP from remaining loci with $P < 1 \times 10^{-5}$ was selected for follow up if it was associated at $P < 0.05$ in at least two GWAS datasets (or three studies if only a single SNP in the locus reached $P < 1 \times 10^{-5}$). This reduces the possibility that SNPs are followed up due to bias in any one study. In total, 50 SNPs were taken forward for follow up. SNPs were selected for follow up based on the results of a pre-final version of the meta-analysis. As a result, the lead SNP in the final version of the meta-analysis was not selected for follow up for three loci: 5p13, rs348594; 16q12, rs1894942; and 17q21, rs744166. Genotyping was carried out according to standard protocols associated with the various genotyping platforms (**Supplementary Table 2**). Individuals with more than 10% missing data were removed, in addition to SNPs with more than 10% missing data or a Hardy-Weinberg equilibrium $P < 0.0001$. Duplicate samples across studies were identified (identity by state = 2) and the sample with the lowest call rate was removed. Follow-up and joint P values were calculated using the weighted z score method described above, using binomial variance for genotype data. Odds ratios and corresponding 95% confidence intervals were also calculated. A genome-wide significance threshold of $P < 5 \times 10^{-8}$ for the combined analysis was adopted. Study-specific results for all SNPs listed in **Tables 1** and **2** are given in **Supplementary Table 3**; region-wide association plots (created using SNAP[39]) are given in **Supplementary Fig. 2**.

Using genotype data from the follow-up cohort, we tested all newly confirmed loci for association to three disease subphenotypes. Disease location was defined using the Montreal classification system and we compared: (i) proctitis (E1) to left-sided disease (E2) and pancolitis (E3), and (ii) proctitis (E1) and left-sided disease (E2) to pancolitis (E3). We also compared cases requiring surgical intervention for acute severe or medically refractory disease to those with no recorded surgical intervention. Individuals receiving colectomy for dysplasia or malignancy were excluded. Cochran-Mantel-Haenszel tests were conducted, stratifying by cohort, and the Bonferroni significance threshold (calculated as 0.05/87; $P < 5.75 \times 10^{-4}$) was adopted.

GRAIL analysis. To obtain insight into the functional relatedness of all ulcerative colitis risk loci, we performed a Gene Relationship Across Implicated Loci (GRAIL) pathway analysis (see URLs). GRAIL is a statistical tool that uses text mining of PubMed abstracts to annotate candidate genes from loci associated with disease risk[40]. We used HG17 and December 2006 PubMed datasets, default settings for SNP rsNumber submission and all 47 ulcerative colitis loci as query and seed. Seven of 47 SNPs were not in HapMap r21 so the second, third or fourth most strongly associated SNP from the GWAS meta-analysis was used.

eQTL analysis. We used eQTL data from 1,469 peripheral blood DNA and RNA (PAXgene) samples from Dutch and UK individuals, as described in detail elsewhere[11]. All samples had been genotyped using either an Illumina Hap370 or 610-Quad platform. SNPs that had a minor allele frequency ≥5%, call rate ≥95% and exact Hardy-Weinberg equilibrium $P > 0.001$ were included. Imputation for ungenotyped SNPs was performed using IMPUTE software (see URLs). We applied a window of 500 kb around each SNP (250 kb on each side). *cis* eQTLs were considered statistically significant, with a Spearman $P < 0.0055$ corresponding to a 5% false discovery rate (FDR). Forty-two of 47 genome-wide significant ulcerative colitis loci were included for analysis (**Supplementary Table 4**).

nsSNP analysis. Data from the 1000 Genomes Project March 2010 release (see URLs) were used to find non-synonymous, splice or stop-encoding SNPs in high linkage disequilibrium ($r^2 \geq 0.5$) with our most-associated SNP within the locus. Results are shown in **Supplementary Table 5**.

Shared association signals between ulcerative colitis and Crohn's disease. We selected the most-associated SNP for each of the 99 reported ulcerative colitis and/or Crohn's disease loci from the current study and our recent Crohn's disease meta-analysis[14]. From those loci, 71 were reported in Crohn's disease and 47 were reported in ulcerative colitis, including an overlap of 19 loci reported in both studies. When for a given locus these SNPs differed between the two studies, we included both SNPs in downstream analyses and calculated the correlation between them (in terms of r^2 and D'). Loci were defined by physical position, which means that, for some loci, more than one independent signal may be present. The overlapping loci are those with overlapping physical intervals. For all 112 index SNPs meeting our criteria, we extracted association results from both ulcerative colitis and Crohn's disease scans and aligned them to the same reference allele. For a signal of association to be considered shared, the index SNP from one disease needed to achieve $P < 1 \times 10^{-4}$ in the other and show the same direction of effect. This threshold was

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selected because of the number of loci tested, similarity of sample size between studies and the known biological and clinical similarities between ulcerative colitis and Crohn's disease. Due to the inclusion of some shared controls between the Crohn's disease and ulcerative colitis meta-analyses, we expect some small correlation between their *z* scores. This could explain some excess of shared directionality for non-significant associations but is not enough to explain a shared association signal achieving $P < 1 \times 10^{-4}$ in both scans.

Functional enrichment analysis. To assess the statistical enrichment of functional gene sets from molecular function, biological process categories and pathways for candidate genes, *P* values were computed using the hypergeometric test[41] and implemented in the R programming language as described[42]. The gene sets were compiled from multiple sources: molecular function and biological process categories from Gene Ontology (GO)[43] and Panther[44,45]; and canonical pathways from MSigDB[46] and Panther. A weighted Jaccard coefficient was used to compute gene overlap[47,48]. Strongly connected components in the network were identified using Tarjan's algorithm[49]. It should be noted that gene length was not taken into account in this enrichment analysis, which can potentially bias enrichment of pathways containing long genes; however, the genes that contributed to the strong immune enrichment featured in the network (**Supplementary Fig. 3** and **Supplementary Table 8**) are considered relatively short (mean, 32.3 kb; median, 18.9 kb) as compared to the average length of all GO annotated genes (106.5 kb as per Staley *et al.*[50]).

Variance explained. The proportion of variance explained is based on the liability threshold model and formula outlined by Risch and Merikangas[51] and assuming a population prevalence of 0.0024[52], an MZ/DZ concordance of 10%/3%[53], an MZ/DZ correlation of 0.196/0.055 and thus a heritability of 28%. Odds ratios and allele frequency estimates were taken from the follow-up cohort where available and the meta-analysis cohort otherwise.

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

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