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Blood and Intestine eQTLs from an Anti-TNF-Resistant Crohn's Disease Cohort Inform IBD Genetic Association Loci

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OBJECTIVES: Genome-wide association studies (GWAS) have identified loci reproducibly associated with inflammatory bowel disease (IBD) and other immune-mediated diseases; however, the molecular mechanisms underlying most of genetic susceptibility remain undefined. Expressional quantitative trait loci (eQTL) of disease-relevant tissue can be employed in order to elucidate the genes and pathways affected by disease-specific genetic variance.

METHODS: In this study, we derived eQTLs for human whole blood and intestine tissues of anti-tumor necrosis factor-resistant Crohn's disease (CD) patients. We interpreted these eQTLs in the context of published IBD GWAS hits to inform on the disease process.

RESULTS: At 10% false discovery rate, we discovered that 5,174 genes in blood and 2,063 genes in the intestine were controlled by a nearby single-nucleotide polymorphism (SNP) (i.e., cis-eQTL), among which 1,360 were shared between the two tissues. A large fraction of the identified eQTLs were supported by the regulomeDB database, showing that the eQTLs reside in regulatory elements (odds ratio; OR = 3.44 and 3.24 for blood and intestine eQTLs, respectively) as opposed to protein-coding regions. Published IBD GWAS hits as a whole were enriched for blood and intestine eQTLs (OR = 2.88 and 2.05; and *P* value = 2.51E-9 and 0.013, respectively), thereby linking genetic susceptibility to control of gene expression in these tissues. Through a systematic search, we used eQTL data to inform 109 out of 372 IBD GWAS SNPs documented in National Human Genome Research Institute catalog, and we categorized the genes influenced by eQTLs according to their functions. Many of these genes have experimentally validated roles in specific cell types contributing to intestinal inflammation.

CONCLUSIONS: The blood and intestine eQTLs described in this study represent a powerful tool to link GWAS loci to a regulatory function and thus elucidate the mechanisms underlying the genetic loci associated with IBD and related conditions. Overall, our eQTL discovery approach empirically identifies the disease-associated variants including their impact on the direction and extent of expression changes in the context of disease-relevant cellular pathways in order to infer the functional outcome of this aspect of genetic susceptibility.

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INTRODUCTION

Translational impact. The majority of IBD genetic loci identified by GWAS resides in the non-coding region and is thought to have regulatory roles. Discovering the functional outcome of these regulatory variations is integral to understanding IBD susceptibility. In this report, we identify shared and unique eQTLs in the two key tissues of IBD the blood and intestine, which were assessed in the same set of CD patients. These eQTLs pinpoint the association between IBD genetic loci and the downstream genes under influence, as well as their magnitude and direction of genetic effect (ie., does the disease risk allele up- or downregulate downstream genes). Alongside the deeper understanding of the context of IBD susceptibility, eQTLs also provide guidance in designing new therapeutic treatments. In this way, eQTLs, either as protective or pathogenic variants, directly or indirectly could be candidates for further consideration as drug targets. EQTLs may also be predictive of drug response, as reported in other disease studies,[1–3] and might inform on mechanistic insight in drug response. For example, the disease allele of rs4728142 upregulates certain transcripts of IRF5 gene in both the blood and the intestine among CD patients. IRF5 has also been described as leading to late phase TNFα secretion in human dendritic cells.[4] Therefore, this genetic polymorphism (rs4728142) may have a role in affecting anti-TNF response. These types of data aid future precision medicine efforts that will ultimately include optimized models based on scoring an

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individual's cumulative genetic risk to predict downstream molecular level changes, disease progression and drug response.

Inflammatory bowel disease (IBD) is comprised of two different disease sub-types, Crohn's disease (CD) and ulcerative colitis, which are distinguished by specific clinical and pathological features. Inflammation in Crohn's is patchy, affecting the distal ileum and/or colon with peri anal involvement; whereas in ulcerative colitis, inflammation manifests in a continuous manner from the rectum toward the proximal region of the colon. Crohn's disease is characterized by transmural inflammation, whereas the inflammation in ulcerative colitis is confined to the mucosa. IBD can be initiated by an environmental trigger in a genetically susceptible individual altering immune homeostasis in the intestinal mucosa, often resulting in compromised intestinal function.[5] Lack of resolution of inflammation in response to an infectious or inflammatory trigger can lead to chronic intestinal inflammation and tissue damage further compromising barrier function.

Understanding the genetic and environmental interaction in the intestine is critical in uncovering the basis for IBD onset, progression, and remission.[5] Many of the most significant genome-wide association study (GWAS) hits are at loci with unknown function and extensive linkage disequilibrium within many of these associated loci make it difficult to identify the causal susceptibility variant, let alone which genes they influence. Integrative genomics is a promising new approach to identify true causal genes and variants, with improved statistical power. The known associated polymorphisms can only explain a relatively small proportion of the variability of the IBD risk in human populations.[6] A component of this so-called missing heritability could be due to the limited power of GWAS as these studies may miss disease susceptibility single-nucleotide polymorphisms (SNPs) that are of small-to-moderate effect size. Interestingly, most of these SNPs are not in protein-coding regions, meaning they are less likely to impact protein function *per se*. In fact, the majority of this genetic contribution to disease is thought to come from expression quantitative trait loci (eQTL) or in other words, genomic loci that contribute to variation in the expression levels of mRNAs. An eQTL is the genetic polymorphism whose genotype is significantly associated with an mRNA's expression level, and that genetic polymorphism that in most cases is a SNP is in turn called an expression SNP or eSNP. An important distinction is made as to the location of the eQTL relative to the physical location of the gene whose expression level it is associated to. If the eQTL is close to the gene (which codes the mRNA), it is defined as a cis-eQTL. In contrast, if the eQTL is distant (typically >500 kb away or on another chromosome altogether) from the gene, it is defined as a trans-eQTL. In the current paper, we also applied this definition. A cis-eQTL is usually stronger (of larger genetic effect size) than trans-eQTLs. Also, the number of tests performed in discovering cis-eQTLs is much less than for trans-eQTLs because given the nature of the definition we only search the chromosome region approximate to a gene to discover cis-eQTLs but search the entire genome for trans-eQTLs. The heavier multiple testing burden means studies inherently have lower statistical power in detecting trans-eQTL, and in fact, eQTL studies routinely define significantly more cis-eQTLs than trans-eQTLs.[7–9]

The outcome of any GWA study of a case and control design is a statistical association between a region of the genome (of a certain size) and the disease of interest. This means, GWAS do not reveal the tissue, organ or cell type where the associated SNPs are functional or how they may modify disease risk. One way to capture this information is via integration with eQTL analysis. EQTL is a powerful approach that empirically links the GWAS SNPs to pathologically relevant genes expressed in a tissue of interest. In this study the blood and intestine were studied given the importance of these tissues in IBD disease biology. By using gene expression as a phenotype and examining how DNA polymorphisms contribute to both gene expression and disease phenotype, true causal relationships can be dissected.[10–12] Although many eQTLs are conserved across tissues the impact of the polymorphism on the extent and direction of change in expression may be tissue specific. Thus, by capturing the direction of modulation specific to intestine and blood eQTLs and then linking this to variants with associated IBD disease risk, one can infer in a disease tissue context the impact of the genetic variation. Given this rationale, we systematically profiled the transcriptome of intestine and blood tissue collected from a previously described cohort of anti-tumor necrosis factor (TNF) refractory Crohn's patients,[13] and identified eQTLs both conserved and specific to blood and intestine. Importantly, these eQTLs were mined alongside other disease GWAS hits including more general IBD as well as canonical biological pathway databases, enabling us to provide a framework to understand the nature of the IBD-associated eQTLs from the blood and intestine of this anti-TNF refractory IBD patient cohort.[9,12,14]

METHODS

Dataset. Blood and biopsy data were collected at baseline from anti-TNF resistant Crohn's disease (CD) patients enrolled in the Ustekinumab trial previously described.[15] All patients met the criteria of a primary nonresponse, a secondary nonresponse, or unacceptable side-effects after receiving a TNF antagonist at an approved dose. Patients were permitted to continue receiving stable doses of drugs for the treatment of CD, including oral prednisolone ($\leq$40 mg/day) or budesonide ($\leq$9 mg/day), immunomodulators (e.g., azathioprine, mercaptopurine, or methotrexate), mesalamine, and antibiotics, if they had been taking the drugs for at least the pre-specified period before study entry of 3 weeks, 4 weeks, 3 weeks, and 3 weeks, respectively. Patients had not received previous therapies specifically targeting interleukin-12 or interleukin-23. Previous treatment with intravenous glucocorticoids, TNF antagonists, or natalizumab was not permitted for the pre-specified washout periods of 3 weeks, 8 weeks, and 12 months, respectively.[15] Two 2.5 ml blood samples were collected at the trial baseline using PAXgene tubes from all subjects (1,528 blood samples in total). All blood samples were stored at -80 °C until RNA isolation was performed. A subset of 150 blood samples was hybridized by microarray for genome-wide mRNA expression profiling. Ileal, rectal, and colonic biopsies were collected at the screening visits from a sub-group of subjects who consented to this

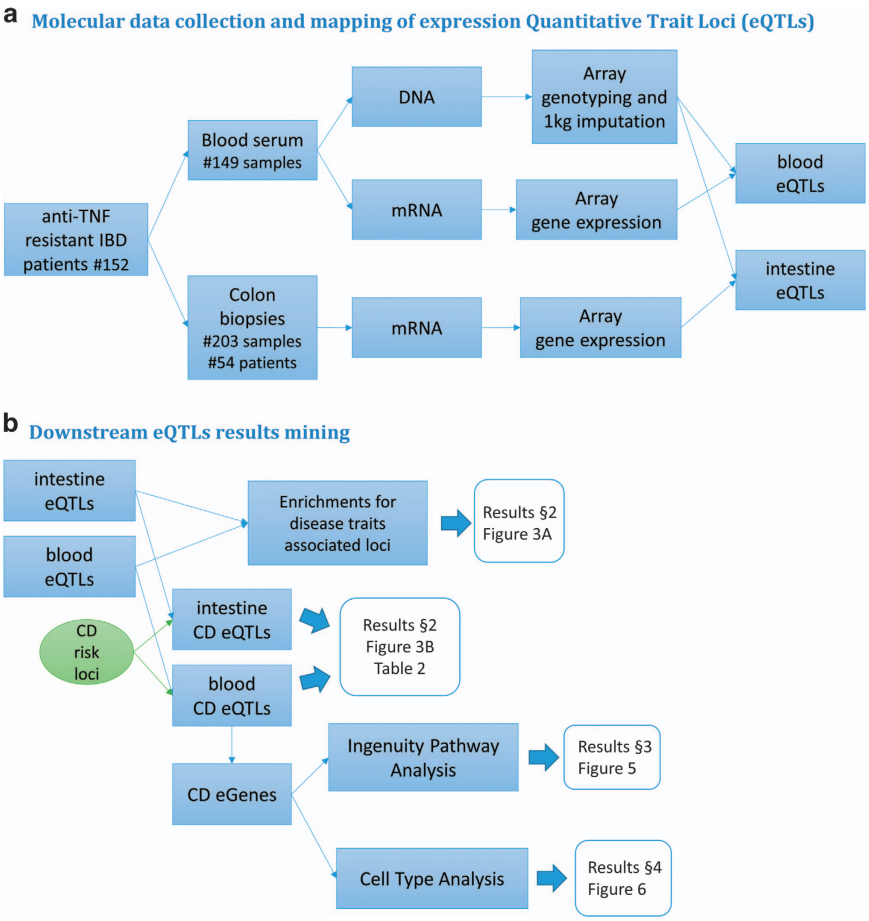

Figure 1 Data analysis workflow. (**a**) Molecular data collection and mapping of expression Quantitative Trait Loci (eQTLs). (**b**) Downstream eQTLs results mining.

procedure. Biopsies were obtained from selected colonic sections, including the ascending, transverse, and descending colonic regions, and from both inflamed and non-involved areas. The inflamed regions were defined as the colonic segments with the most severe disease activity. Additional biopsies were collected from the terminal ileum and from the rectum (i.e., the distal 10 cm of the colon).

Total RNA including micro ribonucleic acids was isolated with PAXgene Blood RNA MDx Kit plus customized reagent BM3 (Qiagen Inc., Valencia, CA, USA). RNA quantity and quality were determined with a LabChip GX (Caliper Life Sciences, Hopkinton, MA, USA). Gene expression were carried out using Affymetrix GeneChip HTHGU133+ (Affymetrix, Santa Clara, CA, USA Cat# 901262) according to the manufacturer's protocol with the exception that dimethyl sulphoxide replaced the Tetramethylammonium Chloride Solution in the hybridization buffer. Arrays were washed and stained on the Affymetrix GeneChip Array Station then scanned on an HTAPS scanner. Genotyping was performed at the Medical Genetics Institute as Cedars-Sinai Medical Center using Illumina OmniExpress chips (Human610-Quadv1 Chips; Illumina, San Diego, CA, USA). Genotypes were determined based on clustering of the raw intensity data for the two dyes using Illumina BeadStudio software. Six samples performed in duplicate yielded >99% concordance. In total, 733,120 SNPs were successfully genotyped.

Data analysis workflow. In Figure 1a and Figure 1b we report a schematic of the data analysis workflow and subsequent eQTL results mining, respectively. In brief, after quality control filtering of the data, we collected blood and intestine biopsies from 152 anti-TNF-resistant IBD patients. Gene expression was quantified by microarray on all samples, whereas blood samples were used for genotyping. Genotype and gene expression data, separately for blood and intestine, were then used for eQTL mapping. One the two eQTL sets were computed, we applied several data mining techniques to facilitate interpretation of the results in the context of disease including: testing for whether eQTLs (blood and intestine) were enriched for disease GWAS loci, overlap with known CD and IBD risk loci, Ingenuity Pathway Analysis and cell type enrichment analysis. Details about data QC, eQTL mapping and downstream mining of results are reported in the Supplementary Methods section.

RESULTS

Discovery of new eQTLs in blood and intestine. Discovery of eQTLs were based on genetic and microarray gene expression profiles collected from a cohort of anti-TNF-resistant CD patients.[15] In all, 149 blood samples (all from unique subjects) and 203 intestine specimens from 54 unique

Table 1 Summary of 10% false discovery rate expressional quantitative trait loci statistics

Tissue	Unique subjects	Samples	Unique gene symbols	Unique dbSNP rsIDs	Odds ratio of overlap with regulomeDB
Blood	149	149			
Cis			5,174	352,736	3.44
Trans			1,238	78,434	3.24
Intestine	54	203			
Cis			2,063	95,827	3.35
Trans			76	7,030	4.66

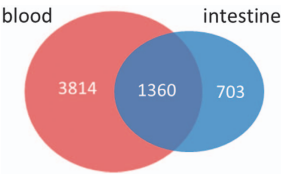

Figure 2 Overlap between SNP-controlled genes in blood and intestine. A large degree of overlap was observed between discovered SNP-controlled genes from blood and intestine tissues.

subjects were employed. The demographic statistics were summarized in Supplementary Table S1. Given that the 203 intestine samples were not all from unique subjects, we applied a mixed effect model to address the inherent correlation structure arising from testing multiple biopsies of the same subject. At 10% false discovery rate, we mapped 10 706 unique cis-eQTLs (eQTLs located within 50 Kb of the expression probe) and 1924 unique trans-eQTLs (eQTLs farther than 50Kb from the expression probe) from the blood (Supplementary Table S2A and Supplementary Table S3A) and 2,974 unique cis-eQTLs and 87 unique trans-eQTLs from the intestine (Supplementary Table S2B and Supplementary Table S3B). At the gene level, based on the official microarray annotation, we discovered 5,174 cis- and 1,238 trans-eQTLs from the blood, respectively; and 2,063 cis- and 76 trans-eQTLs from the intestine, respectively (Table 1).

Results from the two tissues showed a high degree of overlap, with $>60\%$ of the intestine genes also reaching significance in whole blood (Figure 2). The lower number of eQTLs discovered in intestine as compared with the blood was mainly due to the smaller sample size of unique individuals in the intestine dataset (Table 1). The newly mapped gene expression controlling loci (eSNPs henceforth) are enriched in the regulomeDB database[16] (odds ratio; OR = 3.44 and 3.35 for blood and intestine cis-eQTLs, respectively) with similar results observed for trans-eQTLs (Table 1), indicating their concentration in regulatory regions and further supporting their putative functional relevance.

Within the 149 analyzed blood samples, we quantified the eQTLs effects sizes as quantified the fraction of gene expression variability explained by the eSNP genotype (termed as R^2). For the 203 intestine biopsy samples it was not obvious how to quantify R^2 owing to repeated measures from only 54 independent individuals, and we thus omitted them from this specific analysis. Several eQTLs showed a large R^2. For example, ERAP2 expression (Endoplasmic Reticulum Aminopeptidase 2, which has been previously reported in multiple studies[6,17]) was influenced by the cis eSNP rs2927608 in both blood and intestine, with the IBD risk allele associated with higher gene expression in both tissues. The genotype of this locus alone accounted for 74.5% of the total variability of ERAP2 expression in blood. Overall, R^2 was distributed between 8.5 and 74.5% within blood cis-eQTLs, and between 37.6 and 69.7% within blood trans-eQTLs, indicating the powerful effect of these eSNPs on gene expression.

One of the primary utilities of eQTLs is to assign functional relevance to findings from GWAS. We employed different data mining strategies to embed our eQTL results in the context of human diseases and traits in general, and of CD in particular (see Figure 1b): enrichment for disease-associated loci; remapping of eQTLs within known CD risk loci; Ingenuity Pathway Analysis for biological pathway insights; and finally cell type enrichment analysis of remapped genes controlled by CD risk SNPs. The results of these analyses are reported in the following sections.

Blood and intestine eQTLs are enriched in disease risk loci. To embed our eQTL results in the context of human disease we first surveyed the SNPs in the National Human Genome Research Institute (NHGRI) GWAS catalog[18–20] as a whole. The NHGRI public catalog maintains a list of GWAS hits (of various diseases including CD) using stringent *P* value thresholds based on the strict guidelines of replication. We detected significant enrichment for the eQTLs discovered in this study (*P* value = 6.2e-203; OR = 3.25), indicating that GWAS hits (as a whole regardless of the disease/trait) were more likely to be eQTLs than non-risk associated loci: 8.8% of the NHGRI catalog loci were significant eQTLs in either blood or intestine in our dataset, compared with 2.9% for the rest of the tested genome.

Second, we focused on diseases/traits with at least 90 GWAS association loci documented in NHGRI GWAS catalog (Figure 3a and Supplementary Table S4). The rationale of limiting the analysis within diseases/traits with many GWAS hits (i.e., ≥ 90) is to ensure sufficient statistical power in enrichment test. The tests showed that IBD GWAS hits were highly enriched for both intestine and blood (Figure 3a). In other words, a significant fraction of IBD risk loci were influencing gene expression (i.e., as eQTLs) in blood and intestine tissue. In total, 57 out of 201 IBD risk loci were supported by eQTLs in at least one tissue. As already observed for the entire set of mapped eQTLs, many of these (14 loci) were shared between blood and intestine. In all, 40 IBD risk loci were supported by blood-specific eQTLs, and three loci (rs11741861, associated with ZNF300P1 gene expression; rs12677663, associated with SBSPON gene expression; and rs1728918, associated with 240330_at probeset expression level) were intestine-only eQTLs (Figure 3 and Supplementary Table S4). Furthermore, there was a high ranking of eQTL enrichment in IBD-associated disease traits indicating that blood and intestine are highly relevant tissues for this disease. Some of these eQTL enriched trait categories included growth and development (e.g., metabolite levels, bone mineral density, and height) and inflammatory diseases (e.g.

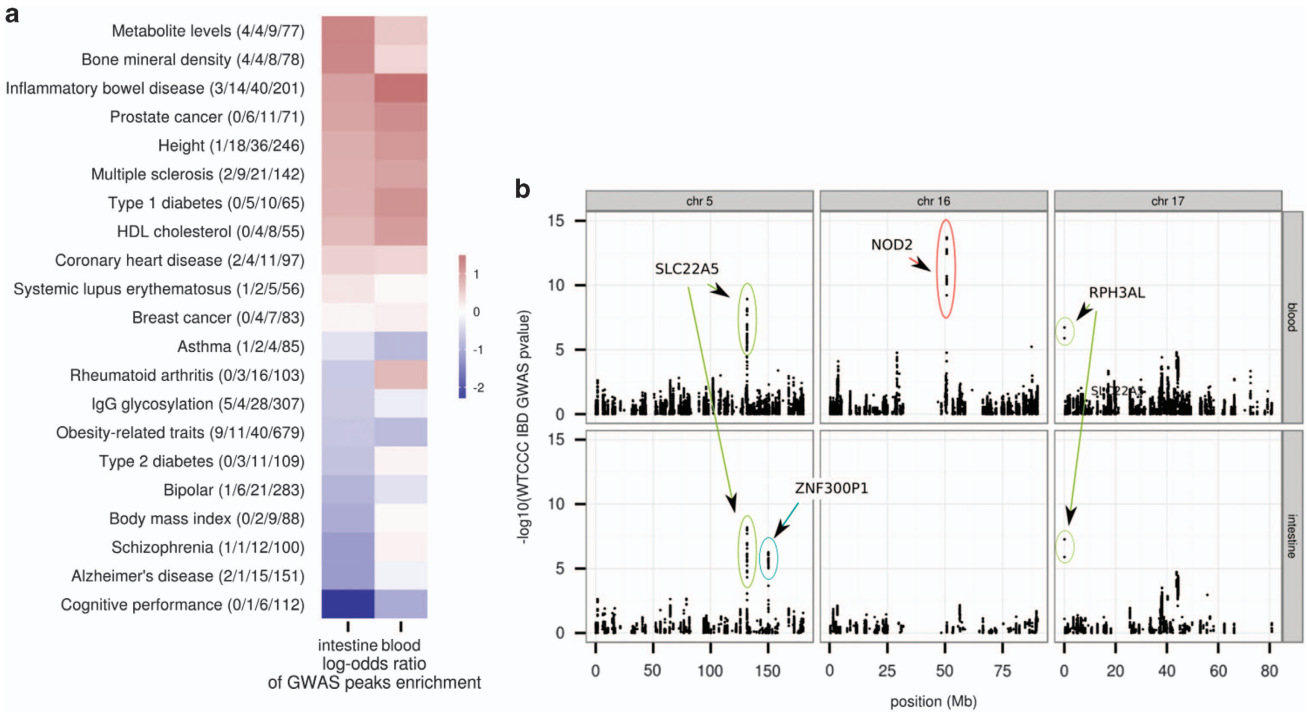

Figure 3 eQTLs enrichments for disease-associated loci. (**a**) We tested the overlap between known and validated disease/trait-associated loci (from the NHGRI GWAS catalog) and expression Quantitative Trait loci discovered from the blood and intestine of anti-TNF-resistant patients. Disease traits were sorted according to odds ratio of enrichment for disease/trait-associated loci within intestine eQTLs. In parentheses, we present the number of overlaps in the following order: number of disease/trait loci overlapping with intestine-specific eQTLs; number of disease/trait loci overlapping with eQTLs shared by blood and intestine; number of disease/trait loci overlapping with blood-specific eQTLs; total number of loci for the considered disease/trait. The heatmap color indicates the overlap log-odds ratio, with red, white, and blue indicating overlap above, in line with, and below what would be expected by random chance. (**b**) Intersection between IBD-associated loci (from a genome-wide analysis of the WTCCC dataset) and blood/intestine eQTLs. Highlighted some shared (green circles), blood-specific (red circle), and intestine-specific (blue circle) eQTL peaks.

IBD and type-1-diabetes), indicating the role of these two tissue types in these diseases. In contrast, psychiatric and neurological disease GWAS loci were under-present among blood and intestine eQTLs, indicating that these tissues are less relevant to these conditions. It should be noted that the background of enrichment test for each disease/trait (Figure 3a) was the NHGRI catalog SNPs as a whole. As GWAS hits are enriched among eQTLs (regardless of disease type), the individual disease/trait enrichment test and point estimations (i.e., OR) tend to be conservative (Figure 3a and Supplementary Table S4). But the ranking of the disease traits, which is the main purpose of the analysis, was not affected.

Importantly, known IBD GWAS loci were shown as tissue-specific or shared eQTLs (Figure 3b). For example, SLC22A5 (Solute Carrier Family 22 Member 5) loci act as eQTLs in both blood and intestine, and the genetic control of gene expression follow similar pattern in blood and various sections of intestine (Supplementary Table S4 and Figure 3a). NOD2 locus was a blood-specific eQTL, where the rs17221417-G allele was associated with lower expression level in blood (Figure 3b), whereas the rs17221417-NOD2 association was inconsistent among the intestine sections. ZNF300P1 locus was an intestine-specific eQTL, and the eQTL pattern was highly consistent in intestine sections (Figure 3c), but not in blood.

Supplementary Table S2 presents the genome-wide eQTLs discovery, which is subject to heavy multiple testing penalty and consequently relatively low statistical power. We conducted a secondary eQTL discovery only focus on the known IBD risk loci. By these means, we limited the number of tests and therefore achieved higher statistical power (than genome-wide search). In total, we found that 110 unique genes were influenced by IBD risk loci (Table 2), and provided empirical evidence of directionality and magnitude of modulation through which IBD risk loci modify disease susceptibility. The GWA studies typically propose genes affected by association loci based on physical location and proximity on the genome. In many cases, several genes are close to the association peak and it is difficult to identify the gene(s) that mediate genetic effect. For example, the Chr17q12 locus showed strong association with IBD (lead SNP rs12946510, *P* value = 4.00E-38), and several genes (IKZF3, ZPBP2, GSDMB, ORMDL3, GSDMA, etc.) were proposed as genes affected by this variant in this locus.[6] In blood of our CD subjects, we now show that rs12946510 profoundly influences GSDMB (Gasdermin B) gene expression in this locus (Table 2). In total, 10.5% of the GSDMB gene expression variance was explained by this single eSNP. Furthermore GSDMB was linked to other inflammatory diseases (e.g. asthma) by GWAS,[21] and its expression levels were under eQTL control in lung[9] and epithelium.[22] In another unrelated loci we also found evidence for a single eSNP controlling multiple genes. For example, rs1363907 was reported in association with IBD (*P* value = 6E-13) in GWAS,[6] as upregulating both ERAP2 (eQTL *P* value = 2.95E-38 in blood

Table 2 Intersection of blood and intestine eQTLs with GWAS hits

SNP position (hg19)	rsID	Alleles	GWAS			Reported gene(s)	eQTL		Effect of eff./risk allele on gene expression		eQTL *P* value	
			Risk All.	OR	*P* value		ProbeID	Gene(s)	Blood	Intestine	Blood	Intestine
Intersection of blood and intestine eQTLs with inflammatory bowel disease GWAS hits[a]												
chr2:219151218	rs2382817	A/C	A	1.07	4.00E-12	SLC11A1, CXCR2, CXCR1, PNKD, ARPC2, TMBIM1, CTDSP1	239064_at	(Intergenic)	↓	↓	1.40E-16	1.40E-05
chr6:167373547	rs1819333	T/G	T	1.08	7.00E-21	CCR6, RPS6KA2, RNASET2	240720_at	(Intergenic)	↓	NS	9.40E-05	NS
chr6:167373547	rs1819333	T/G	T	1.08	7.00E-21	CCR6, RPS6KA2, RNASET2	239388_at	(Intergenic)	↓	NS	2.70E-20	NS
chr6:167373547	rs1819333	T/G	T	1.08	7.00E-21	CCR6, RPS6KA2, RNASET2	241838_at	(Intergenic)	↓	NS	1.50E-04	NS
chr2:25118885	rs6545800	T/C	T	1.11	6.00E-16	ADCY3	209321_s_at	ADCY3	↑	↑	7.30E-08	7.40E-07
chr2:25118885	rs6545800	T/C	T	1.11	6.00E-16	ADCY3	209320_at	ADCY3	↑	↑	1.40E-07	7.30E-07
chr11:118754353	rs630923	C/A	C	1.07	7.00E-09	CXCR5	227616_at	**BCL9L**	↓	NS	2.10E-03	NS
chr11:76299194	rs2155219	T/G	T	1.15	4.00E-36	Intergenic	222806_s_at	**C11orf30**	↓	NS	2.00E-03	NS
chr9:139266405	rs10781499	A/G	A	1.19	4.00E-56	CARD9, PMPCA, SDCCAG3, INPP5E	220162_s_at	**CARD9**	↑	NS	2.70E-08	NS
chr16:28517709	rs26528	C/T	C	1.10	1.00E-21	RABEP2, IL27, EIF3C, SULT1A1, SULT1A2, NUPR1	221822_at	**CCDC101**	↓	NS	1.50E-11	NS
chr1:160856964	rs4656958	G/A	G	1.06	7.00E-09	CD48, SLAMF1, ITLN1, CD244, F11R, USF1, SLAMF7, ARHGAP30	220307_at	**CD244**	↓	NS	5.40E-04	NS
chr20:44742064	rs1569723	C/A	C	1.09	1.00E-13	CD40, MMP9, PLTP	35150_at	**CD40**	↓	NS	1.40E-03	NS
chr20:44742064	rs1569723	C/A	C	1.09	1.00E-13	CD40, MMP9, PLTP	205153_s_at	**CD40**	↓	NS	2.10E-03	NS
chr11:60776209	rs11230563	C/T	C	1.09	9.00E-13	CD6, CD5, PTGDR2	208602_x_at	**CD6**	↑	NS	6.20E-04	NS
chr11:60776209	rs11230563	C/T	C	1.09	9.00E-13	CD6, CD5, PTGDR2	211900_x_at	**CD6**	↑	NS	9.70E-04	NS
chr11:60776209	rs11230563	C/T	C	1.09	9.00E-13	CD6, CD5, PTGDR2	211893_x_at	**CD6**	↑	NS	4.20E-04	NS
chr10:59997926	rs2790216	G/A	G	1.07	8.00E-09	CISD1, IPMK	218597_s_at	**CISD1**	↑	NS	4.30E-18	NS
chr1:1247494	rs12103	T/C	T	1.10	8.00E-13	TNFRSF18, TNFRSF4	217994_x_at	**CPSF3L**	↑	NS	7.60E-05	NS
chr1:1247494	rs12103	T/C	T	1.10	8.00E-13	TNFRSF18, TNFRSF4	233625_x_at	**CPSF3L**	↑	NS	2.40E-07	NS
chr5:96252803	rs1363907	A/G	A	1.07	6.00E-13	ERAP2, ERAP1, LNPEP	1569521_s_at	**CTD-2260A17.2**	↓	NS	1.60E-03	NS
chr11:65656564	rs2231884	T/C	T	1.08	3.00E-10	RELA, FOSL1, CTSW, SNX32	214450_at	CTSW	↓	NS	4.20E-05	NS
chr10:35295431	rs11010067	G/C	G	1.12	2.00E-25	CREM	203078_at	**CUL2**	↓	NS	2.60E-06	NS
chr4:74857708	rs2472649	G/A	G	1.10	3.00E-08	CXCL5, CXCL1, CXCL3, IL8, CXCL6, PF4, CXCL2, PF4V1	215101_s_at	**CXCL5**	↓	NS	2.20E-04	NS
chr4:74857708	rs2472649	G/A	G	1.10	3.00E-08	CXCL5, CXCL1, CXCL3, IL8, CXCL6, PF4, CXCL2, PF4V1	214974_x_at	**CXCL5**	↓	NS	3.60E-05	NS
chr5:10695526	rs2930047	C/T	C	1.07	1.00E-08	DAP	201095_at	DAP	↓	NS	7.40E-04	NS
chr20:31376282	rs4911259	G/T	G	1.08	1.00E-09	DNMT3B	220668_s_at	**DNMT3B**	↓	NS	1.50E-04	NS
chr12:12657513	rs11612508	G/A	G	1.06	1.00E-08	LOH12CR1	224832_at	DUSP16	↓	NS	3.20E-03	NS
chr12:12657513	rs11612508	G/A	G	1.06	1.00E-08	LOH12CR1	236511_at	DUSP16	↓	NS	1.30E-04	NS
chr5:96252803	rs1363907	A/G	A	1.07	6.00E-13	ERAP2, ERAP1, LNPEP	219759_at	ERAP2	↑	↑	3.00E-38	1.50E-13
chr5:96252803	rs1363907	A/G	A	1.07	6.00E-13	ERAP2, ERAP1, LNPEP	235104_at	ERAP2	↑	↑	5.00E-35	5.40E-10
chr5:96252803	rs1363907	A/G	A	1.07	6.00E-13	ERAP2, ERAP1, LNPEP	227462_at	ERAP2	↑	↑	1.50E-36	2.40E-12
chr5:96252803	rs1363907	A/G	A	1.07	6.00E-13	ERAP2, ERAP1, LNPEP	1554273_a_at	ERAP2	↑	NS	8.00E-13	NS
chr11:61564299	rs4246215	T/G	T	1.08	2.00E-15	C11orf9, FADS1, FADS2	208962_s_at	**FADS1, MIR1908**	↑	NS	2.10E-03	NS
chr11:61564299	rs4246215	T/G	T	1.08	2.00E-15	C11orf9, FADS1, FADS2	202218_s_at	FADS2	↑	NS	2.60E-06	NS
chr11:65656564	rs2231884	T/C	T	1.08	3.00E-10	RELA, FOSL1, CTSW, SNX32	202041_s_at	**FIBP**	↑	NS	1.60E-03	NS
chr2:28614794	rs925255	C/T	C	1.09	3.00E-15	FOSL2, BRE	225262_at	**FOSL2**	NS	↑	NS	1.70E-06
chr2:28614794	rs925255	C/T	C	1.09	3.00E-15	FOSL2, BRE	205409_at	**FOSL2**	↓	NS	2.20E-05	NS
chr2:28614794	rs925255	C/T	C	1.09	3.00E-15	FOSL2, BRE	228188_at	**FOSL2**	↓	NS	4.90E-03	NS
chr2:28614794	rs925255	C/T	C	1.09	3.00E-15	FOSL2, BRE	218880_at	**FOSL2**	↓	NS	1.90E-04	NS
chr17:37912377	rs12946510	T/C	T	1.16	4.00E-38	IKZF3, ZPBP2, GSDMB, ORMDL3, GSDMA	215659_at	GSDMB	↓	NS	5.70E-05	NS
chr12:48208368	rs11168249	C/T	C	1.05	8.00E-09	VDR	244263_at	**HDAC7**	↑	NS	2.50E-03	NS
chr10:59997926	rs2790216	G/A	G	1.07	8.00E-09	CISD1, IPMK	239878_at	**IPMK**	↑	NS	2.90E-03	NS
chr10:59997926	rs2790216	G/A	G	1.07	8.00E-09	CISD1, IPMK	238739_at	**IPMK**	↑	NS	9.20E-04	NS
chr5:131770805	rs2188962	T/C	T	1.16	1.00E-52	IRF1, IL13, CSF2, SLC22A4, IL4, IL3, IL5, PDLIM4, SLC22A5, ACSL6	238725_at	**IRF1**	↑	NS	3.00E-03	NS
chr1:160856964	rs4656958	G/A	G	1.06	7.00E-09	CD48, SLAMF1, ITLN1, CD244, F11R, USF1, SLAMF7, ARHGAP30	223597_at	**ITLN1**	NS	↓	NS	1.90E-04
chr10:94436851	rs7911264	C/T	C	1.07	3.00E-08	Intergenic	204444_at	**KIF11**	↑	NS	4.70E-03	NS
chr5:96252803	rs1363907	A/G	A	1.07	6.00E-13	ERAP2, ERAP1, LNPEP	207904_s_at	**LNPEP**	↑	NS	7.40E-05	NS
chr5:96252803	rs1363907	A/G	A	1.07	6.00E-13	ERAP2, ERAP1, LNPEP	236728_at	**LNPEP**	↑	NS	3.20E-16	NS
chr20:31376282	rs4911259	G/T	G	1.08	1.00E-09	DNMT3B	200712_s_at	MAPRE1	↑	NS	5.50E-03	NS
chr5:141513204	rs6863411	T/A	T	1.09	4.00E-14	SPRY4, NDFIP1	222423_at	**NDFIP1**	↓	NS	2.40E-03	NS
chr16:50756881	rs2076756	A/G	NA	NA	5.00E-10	CARD15	220066_at	**NOD2**	↑	NS	4.40E-05	NS
chr10:75673101	rs2227564	C/T	C	1.08	7.00E-10	Intergenic	205479_s_at	**PLAU**	↓	NS	2.10E-03	NS
chr2:219151218	rs2382817	A/C	A	1.07	4.00E-12	SLC11A1, CXCR2, CXCR1, PNKD, ARPC2, TMBIM1, CTDSP1	233177_s_at	PNKD	↓	NS	7.50E-05	NS

Table 2 *(Continued)*

SNP position (hg19)	rsID	Alleles	GWAS			Reported gene(s)	eQTL		Effect of eff./risk allele on gene expression		eQTL *P* value	
			Risk All.	OR	*P* value		ProbeID	Gene(s)	Blood	Intestine	Blood	Intestine
chr16:23864590	rs7404095	C/T	C	1.06	1.00E-09	PRKCB	207957_s_at	**PRKCB**	↑	NS	1.60E-07	NS
chr16:23864590	rs7404095	C/T	C	1.06	1.00E-09	PRKCB	209685_s_at	**PRKCB**	↑	NS	3.90E-09	NS
chr18:12809340	rs1893217	G/A	G	1.17	3.00E-26	Intergenic	240843_at	**PTPN2**	↑	NS	8.40E-04	NS
chr1:155878732	rs670523	A/G	A	1.06	6.00E-11	UBQLN4, RIT1, MSTO1	239843_at	**RIT1**	↓	NS	1.40E-04	NS
chr6:167373547	rs1819333	T/G	T	1.08	7.00E-21	CCR6, RPS6KA2, RNASET2	1556201_at	RNASET2	↓	NS	3.50E-08	NS
chr6:167373547	rs1819333	T/G	T	1.08	7.00E-21	CCR6, RPS6KA2, RNASET2	1568977_at	RNASET2	↓	NS	2.10E-06	NS
chr6:167373547	rs1819333	T/G	T	1.08	7.00E-21	CCR6, RPS6KA2, RNASET2	232722_at	RNASET2	↓	NS	1.20E-17	NS
chr6:167373547	rs1819333	T/G	T	1.08	7.00E-21	CCR6, RPS6KA2, RNASET2	217984_at	RNASET2	↓	NS	5.30E-20	NS
chr6:167373547	rs1819333	T/G	T	1.08	7.00E-21	CCR6, RPS6KA2, RNASET2	217983_s_at	RNASET2	↓	NS	5.90E-26	NS
chr5:131770805	rs2188962	T/C	T	1.16	1.00E-52	IRF1, IL13, CSF2, SLC22A4, IL4, IL3, IL5, PDLIM4, SLC22A5, ACSL6	205074_at	SLC22A5	↓	↓	2.50E-10	4.60E-06
chr1:160856964	rs4656958	G/A	G	1.06	7.00E-09	CD48, SLAMF1, ITLN1, CD244, F11R, USF1, SLAMF7, ARHGAP30	202043_s_at	**SMS**	↓	NS	1.60E-04	NS
chr11:65656564	rs2231884	T/C	T	1.08	3.00E-10	RELA, FOSL1, CTSW, SNX32	231194_at	SNX32	NS	↑	NS	1.10E-04
chr11:65656564	rs2231884	T/C	T	1.08	3.00E-10	RELA, FOSL1, CTSW, SNX32	1554181_at	SNX32	NS	↑	NS	2.80E-04
chr2:43806918	rs10495903	T/C	T	1.09	8.00E-12	Intergenic	1566888_at	**THADA**	↑	NS	3.00E-10	NS
chr2:43806918	rs10495903	T/C	T	1.09	8.00E-12	Intergenic	1566889_at	**THADA**	↑	↑	6.00E-10	8.40E-08
chr20:30725648	rs6142618	G/A	G	1.07	6.00E-10	HCK	212194_s_at	**TM9SF4**	↑	NS	7.40E-10	NS
chr9:117553249	rs4246905	C/T	C	1.14	3.00E-32	TNFSF8, TNFSF15, TNC	229242_at	**TNFSF15**	↓	NS	2.70E-05	NS
chr9:117568766	rs6478109	G/A	NA	1.36	3.00E-08	TNFSF15	221085_at	**TNFSF15**	↓	NS	2.20E-03	NS
chr9:117568766	rs6478109	G/A	NA	1.36	3.00E-08	TNFSF15	229242_at	**TNFSF15**	↓	NS	1.60E-05	NS
chr10:82254047	rs6586030	G/A	G	1.12	9.00E-16	TSPAN14, C10orf58	221002_s_at	TSPAN14	↓	↓	1.70E-12	4.90E-07
chr13:99956622	rs9557195	T/C	T	1.11	2.00E-14	GPR183, GPR18	224298_s_at	**UBAC2**	↑	NS	4.40E-05	NS
chr13:99956622	rs9557195	T/C	T	1.11	2.00E-14	GPR183, GPR18	233554_at	**UBAC2**	↑	↑	1.80E-07	1.80E-06
chr22:21922904	rs2266959	T/G	T	1.11	1.00E-16	MAPK1, YDJC, UBE2L3, RIMBP3, CCDC116	200682_s_at	UBE2L3	↓	NS	9.00E-08	NS
chr22:21922904	rs2266959	T/G	T	1.11	1.00E-16	MAPK1, YDJC, UBE2L3, RIMBP3, CCDC116	200684_s_at	UBE2L3	↑	NS	2.40E-04	NS
chr22:21922904	rs2266959	T/G	T	1.11	1.00E-16	MAPK1, YDJC, UBE2L3, RIMBP3, CCDC116	200683_s_at	UBE2L3	↑	NS	5.70E-03	NS
chr22:21922904	rs2266959	T/G	T	1.11	1.00E-16	MAPK1, YDJC, UBE2L3, RIMBP3, CCDC116	200676_s_at	UBE2L3	↑	NS	2.70E-09	NS
chr14:69273905	rs194749	C/T	C	1.08	3.00E-10	ZFP36L1	211965_at	**ZFP36L1**	↓	↓	6.80E-07	3.60E-04
chr20:62343956	rs2315008	G/T	G	1.36	9.00E-15	TNFRSF6B	221848_at	**ZGPAT**	↑	NS	2.60E-03	NS
chr20:62348907	rs6062504	G/A	G	1.10	1.00E-23	TNFRSF6B, LIME1, SLC2A4RG, ZGPAT	221848_at	**ZGPAT**	↑	NS	2.80E-03	NS
chr5:150277909	rs11741861	G/A	G	1.25	3.00E-37	TNIP1, IRGM, ZNF300P1	244289_at	ZNF300P1	NS	↑	NS	5.40E-15
chr20:57824309	rs259964	A/G	A	1.09	1.00E-12	ZNF831, CTSZ	1558826_at	**ZNF831**	↓	NS	5.30E-03	NS
chr20:57824309	rs259964	A/G	A	1.09	1.00E-12	ZNF831, CTSZ	1558827_a_at	**ZNF831**	↓	NS	3.90E-04	NS
chr10:81060317	rs1250550	C/A	NA	1.16	6.00E-09	ZMIZ1	201490_s_at	**PPIF**	↑	NS	8.70E-04	NS
chr16:28837515	rs8049439	C/T	C	1.14	2.00E-09	IL27, CCDC101, CLN3, EIF3C, NUPR1, SULT1A1, SULT1A2	201113_at	TUFM	↑	NS	5.40E-32	NS
chr16:28837515	rs8049439	C/T	C	1.14	2.00E-09	IL27, CCDC101, CLN3, EIF3C, NUPR1, SULT1A1, SULT1A2	238190_at	TUFM	↑	NS	1.20E-04	NS
Intersection of blood and intestine eQTLs with ulcerative colitis GWAS hits[a]												
chr7:2789880	rs798502	A/C	A	1.13	3.00E-15	GNA12	231296_at	(Intergenic)	↓	NS	2.00E-03	NS
chr7:2789880	rs798502	A/C	A	1.13	6.00E-17	CARD11, GNA12, TTYH3	231296_at	(Intergenic)	↓	NS	2.00E-03	NS
chr3:49719729	rs9822268	A/G	A	1.21	2.00E-17	MST1, UBA7, APEH, AMIGO3, GMPPB, BSN	242015_x_at	**APEH**	NS	↓	NS	6.40E-04
chr11:76299194	rs2155219	T/G	T	1.13	5.00E-16	Intergenic	222806_s_at	**C11orf30**	↓	NS	2.00E-03	NS
chr9:139266405	rs10781499	A/G	A	1.12	3.00E-19	CARD9, INPP5E, SDCCAG3, SEC16A, SNAPC4	220162_s_at	**CARD9**	↑	NS	2.70E-08	NS
chr9:139266496	rs4077515	C/T	C	1.14	5.00E-08	CARD9	220162_s_at	**CARD9**	↓	NS	2.50E-08	NS
chr9:139269338	rs10781500	C/T	NA	NA	7.00E-06	CARD9	220162_s_at	**CARD9**	↓	NS	1.00E-07	NS
chr15:41563950	rs28374715	A/G	A	1.08	2.00E-08	ITPKA, NDUFAF1, NUSAP1	207993_s_at	**CHP1**	↓	NS	3.20E-03	NS
chr5:10752315	rs267939	C/T	C	1.10	6.00E-12	DAP	1556806_at	DAP	↓	↓	7.80E-19	6.80E-19
chr5:10752315	rs267939	C/T	C	1.10	6.00E-12	DAP	201095_at	DAP	↓	NS	3.30E-03	NS
chr7:107484437	rs4730276	G/A	NA	1.22	9.00E-06	SLC26A3, DLD, LAMB1	209095_at	**DLD**	↓	↓	2.90E-11	2.50E-10
chr7:107492789	rs4510766	A/G	A	1.20	2.00E-16	Intergenic	209095_at	**DLD**	↓	↓	5.30E-13	7.10E-14
chr7:107495434	rs886774	G/A	G	1.11	3.00E-08	LAMB1	209095_at	**DLD**	↓	NS	1.50E-05	NS
chr7:107503441	rs4598195	A/C	NA	1.23	1.00E-06	SLC26A3, DLD, LAMB1	209095_at	**DLD**	↓	↓	7.90E-15	1.10E-16
chr7:107503441	rs4598195	A/C	A	1.09	8.00E-08	DLD, LAMB1	209095_at	**DLD**	↓	↓	7.90E-15	1.10E-16
chr7:107580839	rs2158836	A/G	A	1.21	7.00E-06	SLC26A3, DLD, LAMB1	209095_at	**DLD**	↓	NS	1.30E-06	NS
chr1:2501338	rs10797432	C/T	C	1.08	3.00E-12	TNFRSF14, MMEL1, PLCH2	231835_at	**FAM213B**	↑	NS	5.90E-05	NS
chr1:2513216	rs734999	C/T	C	1.05	3.00E-09	TNFRSF14, MMEL1, PLCH2, C1orf93	231835_at	**FAM213B**	↑	NS	1.30E-04	NS

Table 2 *(Continued)*

SNP position (hg19)	rsID	Alleles	GWAS			Reported gene(s)	eQTL		Effect of eff./risk allele on gene expression		eQTL *P* value	
			Risk All.	OR	*P* value		ProbeID	Gene(s)	Blood	Intestine	Blood	Intestine
chr7:2789880	rs798502	A/C	A	1.13	3.00E-15	GNA12	221737_at	GNA12	↓	NS	2.10E-04	NS
chr7:2789880	rs798502	A/C	A	1.13	3.00E-15	GNA12	242514_at	GNA12	↑	NS	4.50E-08	NS
chr7:2789880	rs798502	A/C	A	1.13	6.00E-17	CARD11, GNA12, TTYH3	221737_at	GNA12	↓	NS	2.10E-04	NS
chr7:2789880	rs798502	A/C	A	1.13	6.00E-17	CARD11, GNA12, TTYH3	242514_at	GNA12	↑	NS	4.50E-08	NS
chr19:47123783	rs1126510	G/A	G	1.08	2.00E-09	CALM3	234284_at	**GNG8**	↓	NS	2.80E-06	NS
chr17:38040763	rs2872507	A/G	A	1.15	5.00E-11	IKZF3, ORMDL3, IKZF3, PNMT, ZPBP2, GSDML	240701_at	GSDMB	↓	↓	6.60E-16	3.90E-13
chr17:38040763	rs2872507	A/G	A	1.15	5.00E-11	IKZF3, ORMDL3, IKZF3, PNMT, ZPBP2, GSDML	215659_at	GSDMB	↓	NS	7.90E-07	NS
chr17:38040763	rs2872507	A/G	A	1.15	5.00E-11	IKZF3, ORMDL3, IKZF3, PNMT, ZPBP2, GSDML	219233_s_at	GSDMB	↓	NS	7.10E-12	NS
chr17:38051348	rs8067378	A/G	A	1.12	1.00E-07	GSDMB	240701_at	GSDMB	↑	↑	8.70E-19	3.70E-18
chr17:38051348	rs8067378	A/G	A	1.12	1.00E-07	GSDMB	215659_at	GSDMB	↑	NS	5.90E-08	NS
chr17:38051348	rs8067378	A/G	A	1.12	1.00E-07	GSDMB	219233_s_at	GSDMB	↑	NS	1.50E-13	NS
chr17:38062196	rs2305480	A/G	A	1.15	3.00E-08	ORMDL3, ZPBP2M, GSDML	219233_s_at	GSDMB	↓	NS	7.50E-12	NS
chr17:38062196	rs2305480	A/G	A	1.15	3.00E-08	ORMDL3, ZPBP2M, GSDML	215659_at	GSDMB	↓	NS	4.50E-07	NS
chr17:38062196	rs2305480	A/G	A	1.15	3.00E-08	ORMDL3, ZPBP2M, GSDML	240701_at	GSDMB	↓	↓	1.30E-16	1.80E-13
chr6:29934163	rs6935053	A/C	NA	NA	2.00E-06	HCG9	213932_x_at	HLA-A	↓	NS	2.90E-03	NS
chr6:29934163	rs6935053	A/C	NA	NA	2.00E-06	HCG9	215313_x_at	HLA-A	↓	↓	3.40E-05	4.60E-04
chr6:29934163	rs6935053	A/C	NA	NA	2.00E-06	HCG9	237826_at	HLA-H, HLA-G, HLA-J	↑	NS	7.80E-04	NS
chr7:27231762	rs4722672	C/T	C	1.09	2.00E-08	Intergenic	1564069_at	**HOTTIP**	NS	↓	NS	2.20E-04
chr7:27231762	rs4722672	C/T	C	1.09	2.00E-08	Intergenic	1564070_s_at	**HOTTIP**	NS	↓	NS	7.40E-04
chr7:27231762	rs4722672	C/T	C	1.09	2.00E-08	Intergenic	231786_at	**HOXA13**	↑	NS	2.80E-03	NS
chr7:128573967	rs4728142	A/G	A	1.07	2.00E-08	IRF5, TNPO3	205469_s_at	IRF5	↑	↑	1.00E-16	1.10E-13
chr7:128573967	rs4728142	A/G	A	1.07	2.00E-08	IRF5, TNPO3	239412_at	IRF5	↓	↓	1.80E-13	1.00E-06
chr7:128573967	rs4728142	A/G	A	1.07	2.00E-08	IRF5, TNPO3	205468_s_at	IRF5	↑	NS	2.70E-04	NS
chr7:128573967	rs4728142	A/G	A	1.10	4.00E-14	IRF5, TNPO3, TSPAN33	205469_s_at	IRF5	↑	↑	1.00E-16	1.10E-13
chr7:128573967	rs4728142	A/G	A	1.10	4.00E-14	IRF5, TNPO3, TSPAN33	239412_at	IRF5	↓	↓	1.80E-13	1.00E-06
chr7:128573967	rs4728142	A/G	A	1.10	4.00E-14	IRF5, TNPO3, TSPAN33	205468_s_at	IRF5	↑	NS	2.70E-04	NS
chr7:107580839	rs2158836	A/G	A	1.21	7.00E-06	SLC26A3, DLD, LAMB1	238608_at	**LAMB1**	↑	NS	1.10E-12	NS
chr1:2501338	rs10797432	C/T	C	1.08	3.00E-12	TNFRSF14, MMEL1, PLCH2	233960_s_at	**LOC100133445, LOC115110**	↑	NS	1.30E-03	NS
chr1:2513216	rs734999	C/T	C	1.05	3.00E-09	TNFRSF14, MMEL1, PLCH2, C1orf93	233960_s_at	**LOC100133445, LOC115110**	↑	NS	1.30E-03	NS
chr1:2501338	rs10797432	C/T	C	1.08	3.00E-12	TNFRSF14, MMEL1, PLCH2	1552930_at	MMEL1	↑	NS	2.70E-05	NS
chr1:2513216	rs734999	C/T	C	1.05	3.00E-09	TNFRSF14, MMEL1, PLCH2, C1orf93	1552930_at	MMEL1	↑	NS	3.60E-05	NS
chr15:41563950	rs28374715	A/G	A	1.08	2.00E-08	ITPKA, NDUFAF1, NUSAP1	225225_at	**OIP5-AS1**	NS	↓	NS	2.60E-04
chr17:38040763	rs2872507	A/G	A	1.15	5.00E-11	IKZF3, ORMDL3, IKZF3, PNMT, ZPBP2, GSDML	235136_at	**ORMDL3**	↓	NS	4.90E-07	NS
chr17:38040763	rs2872507	A/G	A	1.15	5.00E-11	IKZF3, ORMDL3, IKZF3, PNMT, ZPBP2, GSDML	223259_at	**ORMDL3**	↓	NS	9.30E-08	NS
chr17:38051348	rs8067378	A/G	A	1.12	1.00E-07	GSDMB	235136_at	**ORMDL3**	↑	NS	1.00E-07	NS
chr17:38051348	rs8067378	A/G	A	1.12	1.00E-07	GSDMB	223259_at	**ORMDL3**	↑	NS	4.80E-09	NS
chr17:38062196	rs2305480	A/G	A	1.15	3.00E-08	ORMDL3, ZPBP2M, GSDML	235136_at	**ORMDL3**	↓	NS	2.60E-07	NS
chr17:38062196	rs2305480	A/G	A	1.15	3.00E-08	ORMDL3, ZPBP2M, GSDML	223259_at	**ORMDL3**	↓	NS	1.30E-08	NS
chr19:47123783	rs1126510	G/A	G	1.08	2.00E-09	CALM3	206187_at	**PTGIR**	↓	NS	1.30E-04	NS
chr20:33799280	rs6088765	G/T	G	1.08	2.00E-08	PROCR, UQCC, CEP250	234340_at	**RP4-614O4.12**	↓	NS	6.40E-06	NS
chr16:30482494	rs11150589	T/C	T	1.09	6.00E-10	ITGAL	200961_at	**SEPHS2**	↓	NS	3.10E-03	NS
chr7:107492789	rs4510766	A/G	A	1.20	2.00E-16	Intergenic	206143_at	**SLC26A3**	↓	NS	3.00E-03	NS
chr20:62327582	rs2297441	A/G	A	1.09	2.00E-10	SLC2A4RG, STMN3, ZBTB46, ZGPAT, RTEL1, TNFRSF6B	222557_at	**STMN3**	↑	NS	2.90E-03	NS
chr9:117553249	rs4246905	C/T	C	1.10	6.00E-12	TNFSF8, TNFSF15	229242_at	**TNFSF15**	↓	NS	2.70E-05	NS
chr7:128573967	rs4728142	A/G	A	1.07	2.00E-08	IRF5, TNPO3	212318_at	**TNPO3**	↓	NS	5.10E-10	NS
chr7:128573967	rs4728142	A/G	A	1.07	2.00E-08	IRF5, TNPO3	214550_s_at	**TNPO3**	↓	NS	4.30E-06	NS
chr7:128573967	rs4728142	A/G	A	1.10	4.00E-14	IRF5, TNPO3, TSPAN33	212318_at	**TNPO3**	↓	NS	5.10E-10	NS
chr7:128573967	rs4728142	A/G	A	1.10	4.00E-14	IRF5, TNPO3, TSPAN33	214550_s_at	**TNPO3**	↓	NS	4.30E-06	NS
chr16:68591230	rs1728785	C/A	C	1.08	4.00E-08	ZFP90	235698_at	ZFP90	↑	NS	6.10E-12	NS
chr16:68591230	rs1728785	C/A	C	1.08	4.00E-08	ZFP90	241818_at	ZFP90	↑	NS	2.80E-05	NS
chr16:68591230	rs1728785	C/A	C	1.08	4.00E-08	ZFP90	242400_at	ZFP90	↑	NS	5.70E-07	NS
chr16:68591230	rs1728785	C/A	C	1.08	4.00E-08	ZFP90	226124_at	ZFP90	↑	NS	1.90E-18	NS
chr16:68591230	rs1728785	C/A	C	1.17	3.00E-08	CDH1	235698_at	ZFP90	↑	NS	6.10E-12	NS
chr16:68591230	rs1728785	C/A	C	1.17	3.00E-08	CDH1	241818_at	ZFP90	↑	NS	2.80E-05	NS

Table 2 *(Continued)*

SNP position (hg19)	rsID	Alleles	GWAS			Reported gene(s)	eQTL		Effect of eff./risk allele on gene expression		eQTL *P* value	
			Risk All.	OR	*P* value		ProbeID	Gene(s)	Blood	Intestine	Blood	Intestine
chr16:68591230	rs1728785	C/A	C	1.17	3.00E-08	CDH1	242400_at	ZFP90	↑	NS	5.70E-07	NS
chr16:68591230	rs1728785	C/A	C	1.17	3.00E-08	CDH1	226124_at	ZFP90	↑	NS	1.90E-18	NS
chr6:29934163	rs6935053	A/C	NA	NA	2.00E-06	HCG9	242557_at	ZNRD1-AS1	↑	NS	2.20E-03	NS
Intersection of blood and intestine eQTLs with Crohn's Disease GWAS hits[a]												
chr2:27635463	rs1728918	A/G	A	1.12	5.00E-16	UCN	240330_at	(Intergenic)	NS	↓	NS	1.20E-03
chr6:167371110	rs2149085	T/C	T	1.34	8.00E-12	RNASET2, FGFR1OP, CCR6, MIR3939	240720_at	(Intergenic)	↓	NS	9.50E-05	NS
chr6:167371110	rs2149085	T/C	T	1.34	8.00E-12	RNASET2, FGFR1OP, CCR6, MIR3939	239388_at	(Intergenic)	↓	NS	3.00E-20	NS
chr6:167371110	rs2149085	T/C	T	1.34	8.00E-12	RNASET2, FGFR1OP, CCR6, MIR3939	241838_at	(Intergenic)	↓	NS	1.50E-04	NS
chr6:167406633	rs415890	C/G	C	1.17	3.00E-12	CCR6	241838_at	(Intergenic)	↓	NS	1.30E-04	NS
chr6:31575276	rs9348876	T/C	T	1.41	3.00E-06	AIF1	209901_x_at	**AIF1**	↑	NS	1.40E-03	NS
chr6:31575276	rs9348876	T/C	T	1.41	3.00E-06	AIF1	213095_x_at	**AIF1**	↑	NS	2.20E-03	NS
chr11:76301316	rs7927894	T/C	T	1.16	1.00E-09	C11orf30	222806_s_at	**C11orf30**	↓	NS	1.10E-04	NS
chr11:76301375	rs7927997	T/C	T	1.17	6.00E-13	C11orf30	222806_s_at	**C11orf30**	↓	NS	1.70E-04	NS
chr9:139266496	rs4077515	T/C	T	1.18	1.00E-36	CARD9, SNAPC4	220162_s_at	**CARD9**	↑	NS	2.50E-08	NS
chr9:139266496	rs4077515	T/C	T	1.29	4.00E-06	CARD9, SNAPC4	220162_s_at	**CARD9**	↑	NS	2.50E-08	NS
chr11:64097233	rs694739	A/G	A	1.10	6.00E-10	PRDX5, ESRRA	223663_at	**CCDC88B**	↑	NS	3.20E-03	NS
chr6:31142245	rs3094188	C/A	C	1.61	7.00E-07	PSORS1C3	37425_g_at	CCHCR1	↓	NS	4.50E-03	NS
chr1:160830268	rs4656940	A/G	A	1.15	6.00E-07	CD244, ITLN1	220307_at	**CD244**	↓	NS	2.50E-04	NS
chr1:160852046	rs2274910	C/T	C	1.14	1.00E-09	ITLN1	220307_at	**CD244**	↓	NS	2.30E-04	NS
chr5:173279842	rs359457	T/C	T	1.08	3.00E-12	CPEB4	224828_at	CPEB4	↓	NS	1.50E-03	NS
chr5:173337853	rs17695092	T/G	T	1.10	5.00E-09	CPEB4	224828_at	CPEB4	↓	NS	8.10E-07	NS
chr10:35535695	rs12242110	G/A	G	1.15	1.00E-09	CREM	230511_at	**CREM**	↓	NS	3.40E-03	NS
chr5:96244549	rs2549794	C/T	C	1.05	1.00E-10	ERAP2, LRAP	1569521_s_at	**CTD-2260A17.2**	↓	NS	1.90E-03	NS
chr10:35287650	rs17582416	G/T	G	1.16	2.00E-09	Intergenic	203078_at	**CUL2**	↓	NS	1.70E-05	NS
chr5:96244549	rs2549794	C/T	C	1.05	1.00E-10	ERAP2, LRAP	227462_at	ERAP2	↑	↑	1.00E-36	1.90E-12
chr5:96244549	rs2549794	C/T	C	1.05	1.00E-10	ERAP2, LRAP	1554273_a_at	ERAP2	↑	NS	5.50E-13	NS
chr5:96244549	rs2549794	C/T	C	1.05	1.00E-10	ERAP2, LRAP	219759_at	ERAP2	↑	↑	1.30E-38	8.40E-14
chr5:96244549	rs2549794	C/T	C	1.05	1.00E-10	ERAP2, LRAP	235104_at	ERAP2	↑	↑	3.70E-35	5.90E-10
chr11:61557803	rs102275	C/T	C	1.08	2.00E-11	FADS1	208962_s_at	**FADS1, MIR1908**	↑	NS	5.30E-04	NS
chr11:61557803	rs102275	C/T	C	1.08	2.00E-11	FADS1	202218_s_at	FADS2	↑	NS	2.10E-08	NS
chr1:155230131	rs3180018	T/C	T	1.13	2.00E-13	SCAMP3, MUC1	201275_at	**FDPS**	↓	NS	4.90E-06	NS
chr1:155230131	rs3180018	T/C	T	1.13	2.00E-13	SCAMP3, MUC1	209093_s_at	GBA, GBAP1	↑	NS	9.50E-04	NS
chr1:155230131	rs3180018	T/C	T	1.13	2.00E-13	SCAMP3, MUC1	210589_s_at	GBAP1	↑	NS	1.90E-04	NS
chr1:155230131	rs3180018	T/C	T	1.13	2.00E-13	SCAMP3, MUC1	213448_at	GBAP1	↑	NS	1.20E-10	NS
chr17:38040763	rs2872507	A/G	A	1.14	2.00E-09	GSMDL, ZPBP2, ORMDL3, IKZF3	240701_at	GSDMB	↓	↓	6.60E-16	3.90E-13
chr17:38040763	rs2872507	A/G	A	1.14	2.00E-09	GSMDL, ZPBP2, ORMDL3, IKZF3	215659_at	GSDMB	↓	NS	7.90E-07	NS
chr17:38040763	rs2872507	A/G	A	1.14	2.00E-09	GSMDL, ZPBP2, ORMDL3, IKZF3	219233_s_at	GSDMB	↓	NS	7.10E-12	NS
chr17:38040763	rs2872507	A/G	A	1.12	5.00E-09	ORMDL3	240701_at	GSDMB	↓	↓	6.60E-16	3.90E-13
chr17:38040763	rs2872507	A/G	A	1.12	5.00E-09	ORMDL3	215659_at	GSDMB	↓	NS	7.90E-07	NS
chr17:38040763	rs2872507	A/G	A	1.12	5.00E-09	ORMDL3	219233_s_at	GSDMB	↓	NS	7.10E-12	NS
chr6:31142245	rs3094188	C/A	C	1.61	7.00E-07	PSORS1C3	1559050_at	HCG27	↓	NS	4.30E-04	NS
chr6:31274380	rs9264942	C/T	C	1.15	5.00E-28	HLA-C, PSORS1C1, NFKBIL1, MICB	209140_x_at	**HLA-B**	↓	NS	4.00E-03	NS
chr6:31274380	rs9264942	C/T	C	1.15	5.00E-28	HLA-C, PSORS1C1, NFKBIL1, MICB	216526_x_at	HLA-C	↓	NS	2.30E-06	NS
chr6:32658310	rs9469220	A/G	A	1.14	2.00E-06	NR	236203_at	HLA-DQA1, LOC100507718, LOC100509457	↓	NS	1.60E-03	NS
chr6:32658310	rs9469220	A/G	A	1.14	2.00E-06	NR	209480_at	HLA-DQB1	↓	NS	1.80E-03	NS
chr6:32658310	rs9469220	A/G	A	1.14	2.00E-06	NR	210747_at	HLA-DQB1	↑	NS	5.30E-03	NS
chr6:32658310	rs9469220	A/G	A	1.14	2.00E-06	NR	211654_x_at	HLA-DQB1	↓	NS	2.50E-03	NS
chr6:32658310	rs9469220	A/G	A	1.14	2.00E-06	NR	212998_x_at	HLA-DQB1, LOC100293977	↓	NS	4.40E-05	NS
chr21:34776695	rs2284553	G/A	G	1.12	2.00E-16	IFNGR2, IFNAR1, IFNAR2, IL10RB, GART, TMEM50B	204191_at	**IFNAR1**	↓	NS	3.70E-03	NS
chr21:34796886	rs2834215	A/G	NA	1.22	3.00E-07	IFNGR2	201642_at	**IFNGR2**	↑	NS	1.10E-04	NS
chr10:59913151	rs1819658	C/T	C	1.19	9.00E-17	UBE2D1	238739_at	**IPMK**	↑	NS	1.50E-03	NS
chr5:131770805	rs2188962	T/C	T	1.25	2.00E-18	Intergenic	238725_at	**IRF1**	↑	NS	3.00E-03	NS
chr5:131770805	rs2188962	C/T	NA	1.36	1.00E-07	IBD5	238725_at	**IRF1**	↓	NS	3.00E-03	NS

Table 2 *(Continued)*

SNP position (hg19)	rsID	Alleles	GWAS			Reported gene(s)	eQTL		Effect of eff./risk allele on gene expression		eQTL *P* value	
			Risk All.	OR	*P* value		ProbeID	Gene(s)	Blood	Intestine	Blood	Intestine
chr5:131784393	rs12521868	T/G	T	1.23	1.00E-20	SLC22A4, SLC22A5, IRF1, IL3	238725_at	**IRF1**	↑	NS	2.70E-03	NS
chr1:160852046	rs2274910	C/T	C	1.14	1.00E-09	ITLN1	223597_at	**ITLN1**	NS	↓	NS	1.50E-04
chr6:33764033	rs751728	T/C	T	1.32	1.00E-08	ITPR3, MIF1, IP6K3, LEMD2, MLN	224980_at	**LEMD2**	↑	NS	3.80E-06	NS
chr5:96244549	rs2549794	C/T	C	1.05	1.00E-10	ERAP2, LRAP	207904_s_at	**LNPEP**	↑	NS	7.10E-05	NS
chr5:96244549	rs2549794	C/T	C	1.05	1.00E-10	ERAP2, LRAP	236728_at	**LNPEP**	↑	NS	5.20E-16	NS
chr6:31575276	rs9348876	T/C	T	1.41	3.00E-06	AIF1	214574_x_at	**LST1**	↑	NS	4.30E-03	NS
chr6:31575276	rs9348876	T/C	T	1.41	3.00E-06	AIF1	215633_x_at	**LST1**	↑	NS	6.10E-03	NS
chr6:31575276	rs9348876	T/C	T	1.41	3.00E-06	AIF1	211582_x_at	**LST1**	↑	NS	9.60E-04	NS
chr6:31575276	rs9348876	T/C	T	1.41	3.00E-06	AIF1	210629_x_at	**LST1**	↑	NS	6.40E-04	NS
chr6:31575276	rs9348876	T/C	T	1.41	3.00E-06	AIF1	211581_x_at	**LST1**	↑	NS	3.30E-04	NS
chr16:50739582	rs17221417	G/C	G	1.29	4.00E-11	NOD2	220066_at	**NOD2**	↓	NS	9.20E-06	NS
chr16:50756881	rs2076756	G/A	G	1.66	1.00E-37	NOD2, CYLD, SNX20, NKD1	220066_at	**NOD2**	↓	NS	4.40E-05	NS
chr16:50756881	rs2076756	G/A	G	1.46	3.00E-10	NOD2	220066_at	**NOD2**	↓	NS	4.40E-05	NS
chr16:50756881	rs2076756	A/G	NA	NA	7.00E-14	CARD15	220066_at	**NOD2**	↑	NS	4.40E-05	NS
chr16:50756881	rs2076756	A/G	NA	1.71	1.00E-21	CARD15	220066_at	**NOD2**	↑	NS	4.40E-05	NS
chr16:50756881	rs2076756	G/A	G	1.53	4.00E-69	NOD2	220066_at	**NOD2**	↓	NS	4.40E-05	NS
chr17:38040763	rs2872507	A/G	A	1.14	2.00E-09	GSMDL, ZPBP2, ORMDL3, IKZF3	235136_at	**ORMDL3**	↓	NS	4.90E-07	NS
chr17:38040763	rs2872507	A/G	A	1.14	2.00E-09	GSMDL, ZPBP2, ORMDL3, IKZF3	223259_at	**ORMDL3**	↓	NS	9.30E-08	NS
chr17:38040763	rs2872507	A/G	A	1.12	5.00E-09	ORMDL3	235136_at	**ORMDL3**	↓	NS	4.90E-07	NS
chr17:38040763	rs2872507	A/G	A	1.12	5.00E-09	ORMDL3	223259_at	**ORMDL3**	↓	NS	9.30E-08	NS
chr2:198896895	rs6738825	A/G	A	1.06	4.00E-09	PLCL1	234009_at	**PLCL1**	↓	NS	4.20E-03	NS
chr10:81060317	rs1250550	C/A	C	1.19	1.00E-30	ZMIZ1	201490_s_at	**PPIF**	↑	NS	8.70E-04	NS
chr19:46849806	rs4802307	G/T	G	1.10	2.00E-10	Intergenic	201979_s_at	**PPP5C**	↑	NS	3.60E-03	NS
chr18:12779947	rs2542151	T/G	NA	1.15	3.00E-08	PTPN2	240843_at	**PTPN2**	↓	NS	1.20E-03	NS
chr18:12779947	rs2542151	G/T	G	1.30	2.00E-07	PTPN2	240843_at	**PTPN2**	↑	NS	1.20E-03	NS
chr18:12779947	rs2542151	G/T	G	1.35	5.00E-17	PTPN2	240843_at	**PTPN2**	↑	NS	1.20E-03	NS
chr18:12809340	rs1893217	G/A	G	1.25	1.00E-14	PTPN2	240843_at	**PTPN2**	↑	NS	8.40E-04	NS
chr6:167371110	rs2149085	T/C	T	1.34	8.00E-12	RNASET2, FGFR1OP, CCR6, MIR3939	217984_at	RNASET2	↓	NS	5.10E-20	NS
chr6:167371110	rs2149085	T/C	T	1.34	8.00E-12	RNASET2, FGFR1OP, CCR6, MIR3939	1556201_at	RNASET2	↓	NS	3.60E-08	NS
chr6:167371110	rs2149085	T/C	T	1.34	8.00E-12	RNASET2, FGFR1OP, CCR6, MIR3939	217983_s_at	RNASET2	↓	NS	5.40E-26	NS
chr6:167371110	rs2149085	T/C	T	1.34	8.00E-12	RNASET2, FGFR1OP, CCR6, MIR3939	1568977_at	RNASET2	↓	NS	2.00E-06	NS
chr6:167371110	rs2149085	T/C	T	1.34	8.00E-12	RNASET2, FGFR1OP, CCR6, MIR3939	232722_at	RNASET2	↓	NS	1.10E-17	NS
chr6:167406633	rs415890	C/G	C	1.17	3.00E-12	CCR6	1556201_at	RNASET2	↓	NS	4.60E-08	NS
chr6:167406633	rs415890	C/G	C	1.17	3.00E-12	CCR6	1568977_at	RNASET2	↓	NS	3.70E-06	NS
chr6:167406633	rs415890	C/G	C	1.17	3.00E-12	CCR6	232722_at	RNASET2	↓	NS	2.50E-17	NS
chr6:167406633	rs415890	C/G	C	1.17	3.00E-12	CCR6	217984_at	RNASET2	↓	NS	1.00E-19	NS
chr6:167406633	rs415890	C/G	C	1.17	3.00E-12	CCR6	217983_s_at	RNASET2	↓	NS	4.10E-25	NS
chr1:114377568	rs2476601	G/A	G	1.26	4.00E-09	PTPN22	222790_s_at	**RSBN1**	↓	NS	4.40E-03	NS
chr1:114377568	rs2476601	G/A	G	1.31	1.00E-08	PTPN22	222790_s_at	**RSBN1**	↓	NS	4.40E-03	NS
chr8:74007347	rs12677663	T/G	T	1.15	2.00E-08	C8orf84, TERF1, RPL7, RDH10, KCNB2	235210_s_at	**SBSPON**	NS	↑	NS	3.80E-04
chr7:26892440	rs10486483	A/G	A	1.09	3.00E-08	Intergenic	204361_s_at	**SKAP2**	↑	NS	6.10E-04	NS
chr7:26892440	rs10486483	A/G	A	1.09	3.00E-08	Intergenic	204362_at	**SKAP2**	↑	NS	6.00E-05	NS
chr5:131742228	rs6596075	C/G	C	1.55	3.00E-06	Intergenic	205074_at	SLC22A5	↓	NS	4.10E-06	NS
chr5:131770805	rs2188962	T/C	T	1.25	2.00E-18	Intergenic	205074_at	SLC22A5	↓	↓	2.50E-10	4.60E-06
chr5:131770805	rs2188962	C/T	NA	1.36	1.00E-07	IBD5	205074_at	SLC22A5	↑	↑	2.50E-10	4.60E-06
chr1:160830268	rs4656940	A/G	A	1.15	6.00E-07	CD244, ITLN1	202043_s_at	**SMS**	↓	NS	2.30E-03	NS
chr1:160852046	rs2274910	C/T	C	1.14	1.00E-09	ITLN1	202043_s_at	**SMS**	↓	NS	1.20E-04	NS
chr17:40514201	rs744166	A/G	A	1.18	7.00E-12	STAT3	235680_at	STAT3	↑	NS	1.00E-06	NS
chr6:31142245	rs3094188	C/A	C	1.61	7.00E-07	PSORS1C3	223274_at	**TCF19**	↓	NS	3.30E-04	NS
chr2:43806918	rs10495903	T/C	T	1.14	2.00E-14	THADA	1566888_at	**THADA**	↑	NS	3.00E-10	NS
chr2:43806918	rs10495903	T/C	T	1.14	2.00E-14	THADA	1566889_at	**THADA**	↑	↑	6.00E-10	8.40E-08
chr21:34796886	rs2834215	A/G	NA	1.22	3.00E-07	IFNGR2	222907_x_at	TMEM50B	↓	↓	3.10E-08	7.50E-05
chr21:34796886	rs2834215	A/G	NA	1.22	3.00E-07	IFNGR2	228001_at	TMEM50B	↓	↓	4.20E-19	1.20E-11
chr21:34796886	rs2834215	A/G	NA	1.22	3.00E-07	IFNGR2	225182_at	TMEM50B	↑	NS	1.10E-04	NS
chr21:34796886	rs2834215	A/G	NA	1.22	3.00E-07	IFNGR2	219600_s_at	TMEM50B	↓	↓	1.70E-05	1.00E-03
chr9:117545666	rs6478106	T/C	T	1.73	5.00E-46	TNFSF15, LOC100129633, LOC645266, TNFSF8	229242_at	**TNFSF15**	↓	NS	4.50E-03	NS
chr9:117552885	rs3810936	C/T	C	1.21	1.00E-15	TNFSF15, TNFSF8	229242_at	**TNFSF15**	↓	NS	3.30E-05	NS

Table 2 *(Continued)*

SNP position (hg19)	rsID	Alleles		GWAS		Reported gene(s)	eQTL		Effect of eff./risk allele on gene expression		eQTL *P* value	
		Risk All.		OR	*P* value		ProbeID	Gene(s)	Blood	Intestine	Blood	Intestine
chr9:117552885	rs3810936	C/T	C	1.21	1.00E-15	TNFSF15, TNFSF8	221085_at	**TNFSF15**	↓	NS	4.80E-03	NS
chr9:117566440	rs4263839	G/A	G	1.22	3.00E-10	TNFSF15	229242_at	**TNFSF15**	↓	NS	1.70E-05	NS
chr9:117566440	rs4263839	G/A	G	1.22	3.00E-10	TNFSF15	221085_at	**TNFSF15**	↓	NS	2.20E-03	NS
chr22:21928641	rs181359	A/G	A	1.10	5.00E-16	YDJC	200684_s_at	UBE2L3	↑	NS	3.00E-04	NS
chr22:21928641	rs181359	A/G	A	1.10	5.00E-16	YDJC	200682_s_at	UBE2L3	↓	NS	1.10E-07	NS
chr22:21928641	rs181359	A/G	A	1.10	5.00E-16	YDJC	200676_s_at	UBE2L3	↑	NS	3.10E-09	NS
chr22:21928641	rs181359	A/G	A	1.10	5.00E-16	YDJC	200683_s_at	UBE2L3	↑	NS	6.00E-03	NS
chr20:62349586	rs4809330	G/A	G	1.12	3.00E-15	RTEL1, TNFRSF6B, SLC2A4RG	221848_at	**ZGPAT**	↑	NS	1.90E-03	NS
chr5:150258867	rs11747270	G/A	G	1.33	3.00E-16	IRGM	228144_at	**ZNF300**	↓	NS	4.70E-03	NS
chr5:150270420	rs7714584	G/A	G	1.37	8.00E-19	IRGM	228144_at	**ZNF300**	↓	NS	4.00E-03	NS
chr5:150270420	rs7714584	G/A	G	1.37	8.00E-19	IRGM	244289_at	ZNF300P1	NS	↑	NS	1.70E-09

[a]Expressional QTLs empirically reveal the genetic polymorphisms influence gene expression level and potential in turn modify disease susceptibility (supported by GWAS findings), moreover eQTLs point out the direction of the possible causality mechanism. ↑ denotes the GWAS risk allele increases expression level of the eQTL gene; ↓ denotes the GWAS risk allele decreases the expression level of the eQTL gene; and NS denotes no significant eQTLs were detected in our dataset. Novel eGenes with respect to previous published findings from IBD, UC and FAP patients are highlighted in bold.

and *P* value = 1.50E-13 in intestine) and LNPEP (eQTL *P* value = 3.2E-16 in blood but not significant in intestine) through cis-eQTLs (Table 2). ERAP2 and LNPEP are both aminopeptidases, which are involved in antigen presentation. ERAP2, a highly conserved, interferon γ inducible gene,[23] is involved in peptide trimming in the endoplasmic reticulum required for major histocompatibility complex class 1 presentation, and has been previously described in other genetic studies of IBD.

Pathway enrichment analysis of genes controlled by CD risk loci in blood and intestine. Whereas the NHGRI GWAS catalog and most publications only report the top signals as in those a passing genome-wide significant threshold of 5e-8, most of the existing GWAS only have moderate statistical power, therefore many true disease-associating SNPs may only show a suggestive *P* value (e.g., *P* value < 1e-3). Thus, it is generally considered that eQTLs can guide identification of susceptibility genes and active pathways by utilizing a full dataset rather than just the published top hits of GWAS signals. In this paper, we leveraged the full results of large IBD GWAS,[6] filtered by *P* value ≤ 0.001 (Supplementary Information), and termed these as "IBD SNPs". Importantly, through integrating these "IBD SNPs" with our newly discovered intestine and blood eQTLs (10% false discovery rate) we obtained a list of 96 and 335 genes, respectively, that were controlled by these genetic loci. These blood and intestine genes were subsequently submitted for biological pathway analysis using Ingenuity Pathway Analysis to determine their enrichment in canonical pathways and predicted upstream regulators.

Genes influenced by IBD GWAS SNPs in blood (through eQTLs) were enriched for several canonical pathways: T-cell signaling, antigen presentation, JAK/STAT signaling, interferon response, and pathways related to inositol metabolism (Figure 4a). Although the pathways enriched in blood and intestine eSNPs were highly overlapping (Figure 4b), there were also a number of pathways that showed tissue-specific enrichment. Enrichment in common pathways between blood and intestine are driven by shared eSNPs in human leukocyte antigen and JAK/STAT signaling genes, whereas pathways uniquely enriched in blood eSNPs included protein ubiquitination, Systemic Lupus Erythematosis signaling and PPARa/RXRa activation (Supplementary Tables S6 and S7).

Compared with blood eSNPs, intestine eSNPs gave rise to fewer enriched pathways with less coverage (Supplementary Table S6 vs. Supplementary Table S7), therefore we have focused on the blood eSNPs for upstream regulator analysis. In this analysis Ingenuity Pathway Analysis software predicts for any given gene list, the potential upstream regulators or transcription factors of these genes, based on their databases containing literature supported downstream targets of genes Because our submitted gene list did not include information on changes in gene expression, the predicted upstream regulators do not have an associated likelihood of being activated or inhibited. For blood eSNPs, the top predicted upstream regulators included IFNγ, lipopolysaccharide, and genes involved in antigen presentation and T-cell signaling (Supplementary Table S11-A). Interestingly, the top predicted upstream master transcription factors included the forkhead

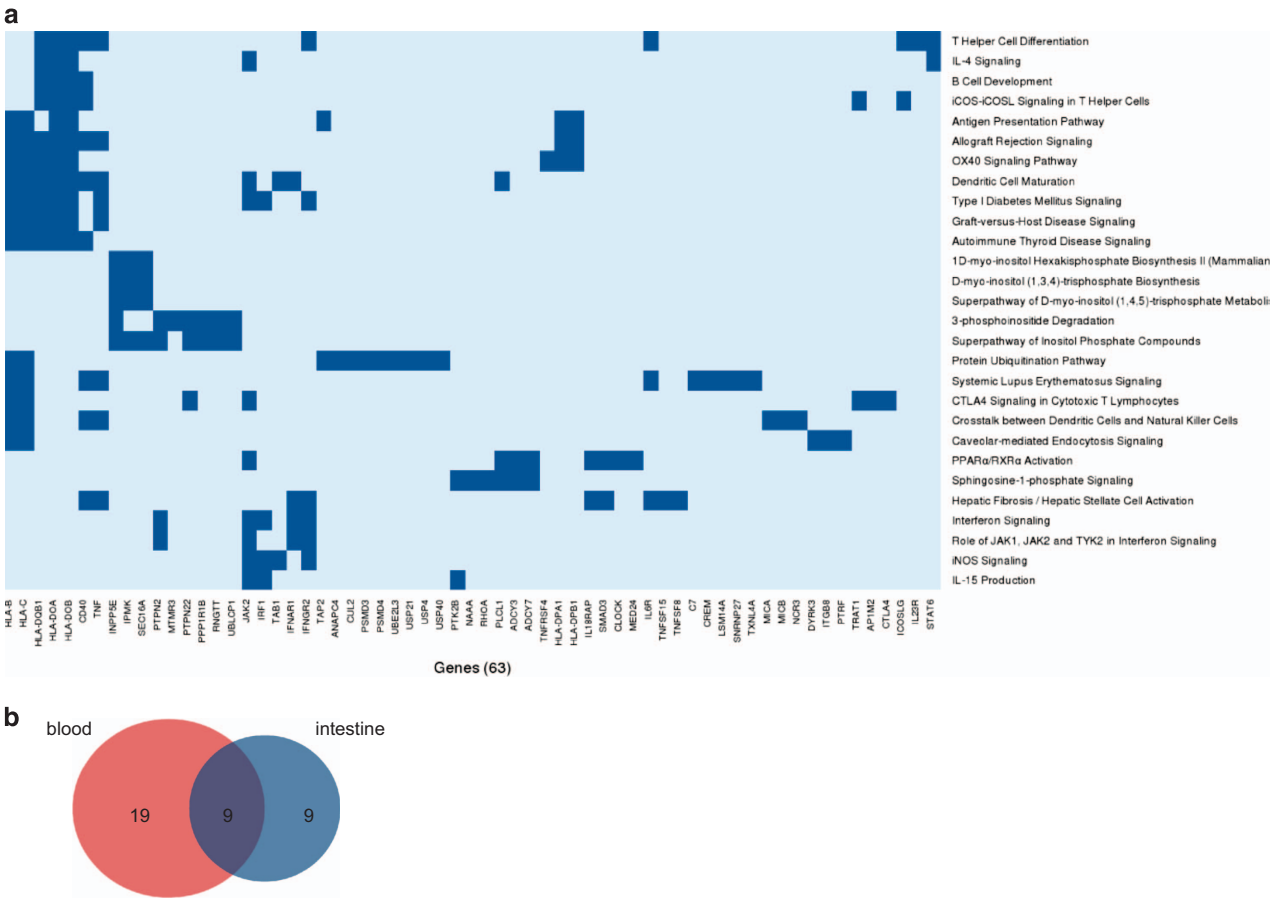

Figure 4 Ingenuity pathway analysis of genes controlled by IBD-associated loci. (**a**) Heatmap displaying clustering of canonical pathways enriched genes (enrichment *P* value <0.01) whose blood expression is controlled by an IBD-associated locus ('eGenes' henceforth); pathways on *y* axis and genes driving enrichment on the *x* axis. Dark blue squares indicate a gene is present in the corresponding pathway listed to the right. (**b**) Venn diagram of the intersection of Ingenuity pathways enriched in blood and intestine (refer to Supplementary Table S6 and Supplementary Table S7).

(Fox) family members FOXD1 and FOXJ1, both of which have been predicted to have roles in inhibiting inflammation through negative regulation of NFAT (nuclear factor of activated T cells) and NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) gene pathways (Supplementary Table S11-B).

Cell type-specific enrichment of genes influenced by eQTLs. Given that blood and intestinal mRNA expression analysis is the summation of expression of mRNA's from potentially multiple cell types within a particular tissue type, we attempted to further refine our eQTL analysis by determining the cell types most likely expressing the genes associated with IBD SNPs. To do this we took advantage of the (GEB) Gene Expression Barcode database, which provides reliable absolute measures of expression for most annotated genes for over 100 human tissue types, including diseased tissue. To determine cell types associated with genes with eSNPs we retrieved the GEB 3.0 dataset, which assigns each probeset targeting a gene, to the tissues and cell types where that probeset is expressed.[24] Note that there can be multiple probesets targeting a single gene. We mapped all eSNP expression probesets with IBD GWAS *P* value $<$1e-3 to their corresponding cell types and gene labels. The summary of all eSNP probesets according to GEB classification and cell type-specificity is shown in Table 3. Blood eSNP probesets showed enrichment in 24 cell types (Supplementary Methods), whereas intestine eSNP probesets did not show significant enrichment (e-value <0.05) in any cell type, possibility owing to the smaller number of intestine eSNPs than blood and consequently lower statistical power. Figure 5 shows the mapping of blood eSNP genes to the 24 significantly enriched cell types. Blood eSNP genes showed strongest enrichment in T cells, neutrophils, monocytes, and natural killer cells (Figure 5). Of note, the enriched T-cell subsets are specific to naive T cells, regulatory T cells and CD161+CD8 T cells. Genetic perturbation of pathways associated with regulatory T-cell development or cytokines produced by regulatory T cells are strongly implicated in IBD pathogenesis in murine models of colitis, monogenic very early-onset IBD and GWAS loci identified in adult-onset IBD patients[25,26] thus supporting our observations. Interestingly, CD161+CD8 T cells have a phenotype consistent with mucosal-associated invariant T cells, which have semi-invariant T-cell receptors that recognize bacterial metabolites[27,28] and have been recently proposed to have

Table 3 Mapping of eSNP probesets to gene expression barcodes cell types

Tissue	High entropy	Mapping to many cell types	No cell type mapping	Specific cell type mapping	Total
Blood	139	77	75	300	519
Intestine	33	11	29	76	149

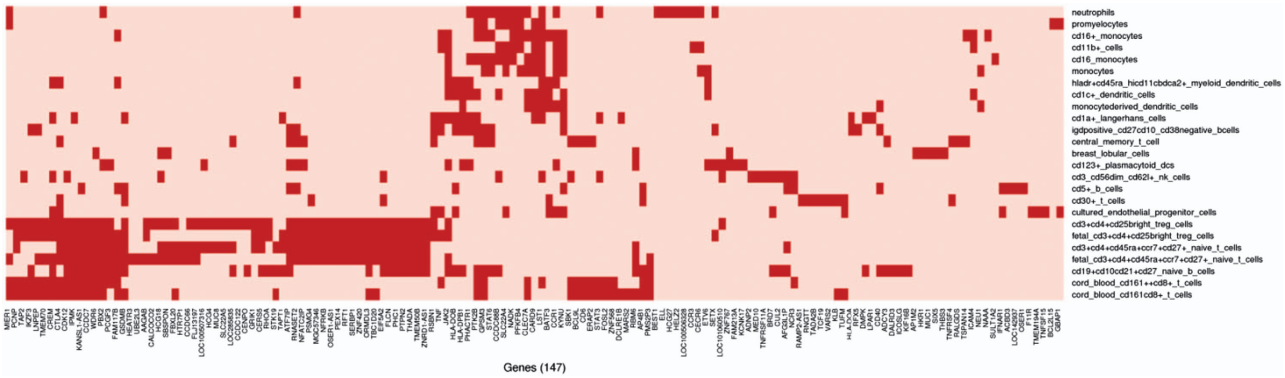

Figure 5 Cell type enrichment of blood eSNPs. Heatmap displaying clustering of cell types enriched in blood eSNPs (enrichment *P* value <0.05); cell types on *y* axis and genes driving enrichment on the *x* axis. Dark red squares indicate a gene is present in the corresponding pathway listed to the right.

a role in IBD, though whether protective or pathological is still unclear.

DISCUSSION

In this paper, we report two key results.[1] A systematic identification of a large number of eQTLs in two CD-related tissues the blood and intestine from anti-TN- resistant Crohn's patients and[2] the novel characterization that many known IBD GWAS loci were actually eQTLs in blood and intestine. Based on empirical evidence, our approach elucidates a large number of genes driven by IBD loci, which potentially mediate the disease etiology.

Both sample availability and tissue relevance have been taken into account when designing this eQTL study. Although a much smaller number of subjects was available for the study of the intestine limiting power to detect association, the intestine-derived eQTLs, location of disease manifestation, proved crucial to orient the disease role of the GWAS hits, which were otherwise unsupported by the whole blood data. Our results indicate that the analysis of tissues more directly involved in a disease (e.g., the intestine of Crohn's patients) can highlight pathways that would not be otherwise detected in different tissues, even if bigger sample sizes were available. For instance, in Supplementary Tables S6 and S7 we show pathways that are enriched in either blood or intestine, but not in both. This can possibly be due to that disease mechanisms are not active in all tissues.

In the current study, we utilized blood and intestine tissue samples[15] to systematically discover eQTLs, and further related the eQTLs to IBD GWAS loci. In agreement with previous findings,[29–32] we found that a large proportion of eQTLs are shared across blood and intestine. Specifically, we found that $>60\%$ of the intestine SNP-controlled genes were also influenced by eQTLs in blood. Given the stringent cutoff we imposed on such comparison (i.e., we required eQTLs to pass 10% false discovery rate in both tissues), this is a conservative estimate of the amount of sharing between the two tissues, and a relaxation of the significance threshold would likely result in an even higher overlap.[32] The high overlap between the two tissues is further confirmed within the disease/trait-associated SNPs reported in the NHGRI catalog, where the number of GWAS peaks shared between intestine and blood is higher than what would be expected by random chance alone. This finding holds true across all the traits we surveyed (Figure 3a), however we also replicated and discovered a large number of blood- and intestine-specific eQTLs underlying disease GWAS hits, pointing to tissue-specific roles of an IBD genetic variant. We also observe a few eQTLs we discovered in this study overlap with previously reported eQTLs by Kabakchiev *et al.* [17] and by Singh T *et al.*[33]

More specifically, we compared our newly discovered eQTLs with previously published eQTLs from a number of tissues and from subjects of different disease conditions (Supplementary Table S10). Besides the already highlighted high overlap between intestine and whole-blood eQTLs of the present study, we observed a particularly high overlap with previously published ileum and rectum eQTLs (odds ratios = 3.09 and 2.93, respectively) obtained from independent populations composed of UC[17] and Familial Adenomatous Polyposis[17] patients, as well as IBD and normal controls.[33] Surprisingly, our whole-blood eQTLs showed a much higher degree of overlap with ileum and rectum eQTLs from independent IBD cohorts (odds ratios = 1.54 and 1.70, respectively) than with whole blood eQTLs obtained from the meta-analysis of generically healthy subjects (odds ratio = 1.19). This finding suggests that, to some extent, the selection of subjects with the right disease context might be more

important than or as important as the collection of relevant tissues in the design of an eQTL study. It should be noted that tissue-level eQTLs in fact investigate expression level of a mixture of cell types. For example, intestine tissue of IBD subjects contains many type of cells, including various kinds of immune cells, which presumable in part are infiltrating via the blood. Therefore, the blood tissue and intestine tissue of Crohn subjects have shared cell types, and the eQTLs detected in these two tissues were somewhat overlapping.

It is important to highlight that our study cohort differs from a generic cohort of Crohn patients in that they were all resistant to anti-TNF therapy. This might have impacted our findings in at least two ways: (1) the genetic background of anti-TNF resistant CD patients might be slightly different from that of anti-TNF responders; and (2) exposure to anti-TNF therapy before the collection of blood and intestine samples, if unsuccessful in treating CD itself, might well have impacted the microbiome of the patients, thus revealing expression patterns not otherwise found in a more general patients' population.

Besides observing statistically significant overlap of eQTLs discoveries from different tissues from a same set of subjects (i.e., between intestine and blood eQTLs in the present study) and between subjects of different disease conditions (e.g., Supplementary Table S10), we also observed some degree of heterogeneity across different intestine sections within our cohort. Even though our small sample size does not allow us to report statistically significant differences across intestine sections in a genome-wide survey, we can report section-specific association patterns when we zoom on specific loci of interest. One such example is the IBD risk locus NOD2 (rs17221417, Figure 6b), for which terminal ileum and rectum display the same pattern of expression observed in whole blood, whereas ascending, transverse, descending, and sigmoid colon display a rather unclear, if opposite, direction of this same effect. This inconsistent association pattern of the risk locus with NOD2 gene expression allowed as to report a significant eQTL from the blood only, but not from the pooled intestine data analysis.

As in complex diseases, multiple pathways and gene networks are altered in IBD. We identified many genes relevant to IBD in the analysis of intersection between eQTLs and published association signals from GWAS studies focusing on IBD, UC and Crohn's (Table 2). The large number of biologically plausible findings indicate the eQTLs as powerful tools to interpret and dissect GWAS signals. In the vast majority of the genes listed in Table 2, the direction of transcription regulation (i.e., up- or downregulation) caused by GWAS SNPs on the genes, agree with our current understanding of IBD molecular etiology. To help the reader interpret our observations we have organized the genes influenced by IBD GWAS hits (mediated by blood and intestine eQTLs) by functional categories and discussed their potential relevance below. These types of insights are what we hope gives momentum to the task of unraveling the underlying causes of IBD and then how one could potentially intervene therapeutically.

Epithelial barrier. Increased levels of ADCY3 (Adenylate Cyclase 3) in intestine and blood eQTLs[34] have been linked through activation of the CREB pathway to upregulation of the levels and activity of MMP2 and MMP9 matrix metalloproteases involved in tissue re-modeling and wound repair, which are known effectors of tissue damage in IBD.[35] Another eQTL with an intestinal epithelial manifestation is *TSPAN14* (tetraspanin 14), whose gene expression is controlled by an IBD GWAS SNP (rs6586030) in both blood and intestine (Table 2). While also expressed in immune cells, TSPAN14 has an intestinal epithelial role as a positive regulator of ligand induced ADAM10-mediated Notch1 activation. ADAM10 is a sheddase expressed on the surface of intestinal epithelial cells and is important for intestinal epithelial cell lineage specification and crypt cell columnar cell maintenance. This eQTL, resulting in a decrease in transcript in IBD, could contribute to epithelial barrier and restitution defects.[36–38]

Metabolism. In accordance with the analysis of the highest trait enrichment in IBD for NHGRI GWAS, we identified several eQTLs involved in metabolism. We reproduced, from previous reports, (Repnik and Potocnik, 2011), a significant cis-eQTL for the solute carrier family 22 member 5 (SLC22A5) in both the blood and intestine in our Crohn's cohort. The T allele, which is associated with increased risk of CD/IBD was found to associate with decreased expression of SLC22A5. This decrease in expression in the intestine was also seen when each of the regions sampled were calculated separately (see Figure 6c). Similar observations were seen in a Slovenian cohort of refractory CD patients whereby lower expression of SLC22A5 gene was associated with disease-susceptible genotypes for two IBD disease-associated SNPs. SLC22A5 encodes a polyspecific organic cation transporter and has a high affinity for carnitine.[39] Autosomal recessive mutations cause primary carnitine deficiency, which leads to a defect in mitochondrial fatty acid oxidation. Furthermore, experimental validation in SLC22A5 knockout mice have pointed to expansion of activated CD4 T cells and increased enterocyte apoptosis in the small intestine. Lower levels of DLD (dihydrolipoamide dehydrogenase), another GWAS eQTL, can result in metabolic disturbances. DLD is the third subunit of the alpha-ketoglutarate dehydrogenase complex, which catalyses the decarboxylation of alpha-ketoglutarate into succinyl-coenzyme A in the Krebs cycle. This can lead to accumulation of pyruvate and branched-chain amino acids in plasma and branched-chain alpha-ketoacids in urine.[40] DLD has also been reported in lactic acidosis affecting carbohydrate fermentation, which has been implicated in ischemic colitis and short bowel syndrome.[40–43]

Monocytes/mcrophages. Several blood and intestine eQTLs have been identified as having specific roles in monocyte and macrophage function such as differentiation, polarization, and migration. LST1 is upregulated by Crohns GWAS risk alleles and has been reported as being a pro inflammatory marker expressed in the colon of IBD patients where its expression has a role in intestinal epithelial cells, monocyte differentiation, and nanotube formation.[44,45] IRF5, expressed in macrophages as well as T cells, is frequently upregulated by inflammatory stimuli in autoimmunity. We found various probesets of this gene were either up- or down-regulated by UC GWAS risk alleles (Table 2), suggesting different behavior of IRF5 splicing isoforms (Supplementary

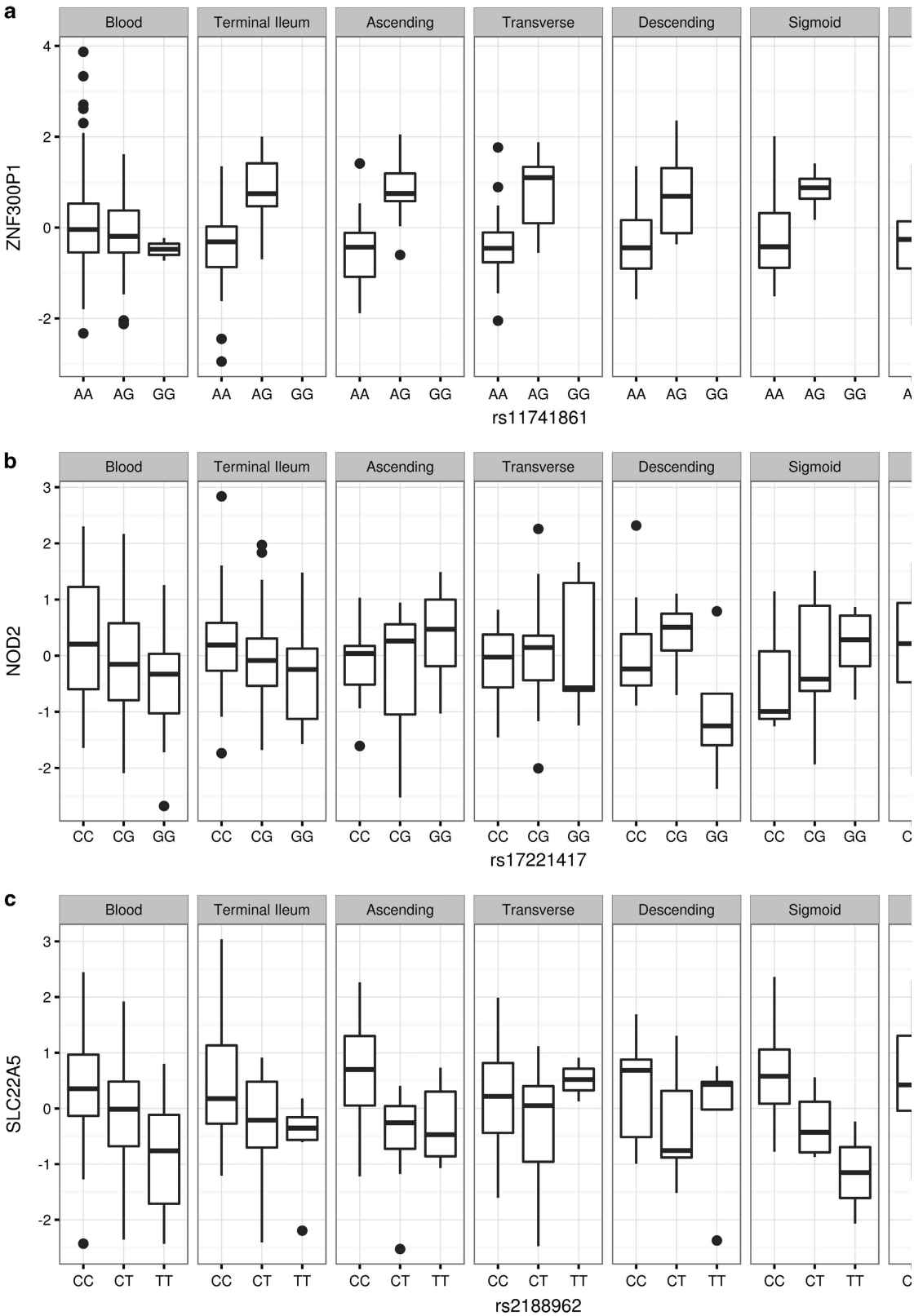

Figure 6 Tissue specificity of IBD-associated eSNPs. Some example of eSNPs that were previously reported to be associated with IBD, with different degree of tissue specificity in their gene expression signal. Genotype on the horizontal axis, mean-centered expression levels on the vertical axis. (**a**) Polymorphism rs11741861 shows a significant association with ZNF300P1 mRNA levels in all the intestine sections, but not in the blood; (**b**) polymorphism rs17221417 shows different effects on NOD2 in different tissues; (**c**) polymorphism rs2188962 controls SLC22A5 expression uniformly and with a similar effect across different tissues.

Table S9). IRF5 is a marker for M1 macrophages and leads to production of IL-12 p40, IL-12 p35, and IL-23p19 while repressing IL-10. These macrophages create an environment conducive for a potent T- helper type-1 T(H)1-T(H)17 response,[46] however, a downregulated variant may skew macrophage polarization to an M2 phenotype, which has been associated with ulcerative colitis.

Several identified GWAS enriched eQTLs are involved in migration. AIF1 is upregulated by Crohn GWAS risk allele, and has been shown to increase chemokine expression in monocytes in addition to having a putative role in T cells[47] (24796669). Increased SKAP2 transcription, caused by the UC GWAS risk allele (Table 2), is involved in cytoskeletal re-arrangement and macrophage migration for integrin induced responses. Other eQTLs are less studied, such as TM9SF4, which is upregulated by IBD GWAS risk allele and has a conserved immune function in adhesion and phagocytosis in drosophila.[48]

Eosinophils. GSDMB and ORMDL3 are controlled by both blood and intestine eQTLs, and are also associated with UC and Crohns in GWAS studies. This gene locus has been linked to alterations in eosinophillic number and hyper-inflammation in asthma.[49,50] An intestine-specific risk eQTL allele downregulates gene expression (Table 2). ITLN1 is also a serum biomarker for disease activity with lower levels found in IBD patients.[51]

Interferon response. As seen through the enrichment in the JAK STAT pathway of eQTLs of this TNF refractory population, genetic susceptibility in cytokine signaling can lead to dysregulated immune homeostasis in the intestine. EMSY (c11orf30), downregulated by IBD GWAS risk allele, is a transcriptional repressor in the PI3K/AKT pathway of the interferon response. Other interferon-responsive eQTLs are IRF1, whose upregulation has also been reported in IBD[52] and TNFSF15, an eQTL which induces IFNγ and IL17 through synergizing with IL18 and IL23 and can be both activated and repressed by NF-κB.[53]

NF-κB. Both the blood-specific eQTLs pathway enrichment and predicted regulators involve ubiquitination and NF-κB. CUL2 is part of a ubiquitin ligase complex involved in modulating the NF-KB pathway through proteosomal degradation of sub units.[54,55] DNMT3B, a DNA methyl transferase, is recruited by transcription factors such as NF-KB and TRAF1. Less methylation, resulting from downregulation of DNMT3B by the IBD risk allele could lead to more activation of NF-KB and TRAF1, which have been reported as being upregulated in IBD.[56,57] UBE2L3 is involved in regulating TNFα induced linear ubiquitination of NEMO, potentially having a critical role in assembling and orchestrating the componentry of the TNFR1 signaling platform.[58,59] Whereas, APEH, a negative effector of proteasome activity,[60] is downregulated by UC risk allele in intestine, potentially involving modulation of the NF-KB pathway.

Autophagy, inflammasome, and endoplasmic reticulum stress. IPMK that is upregulated by a risk allele identified in IBD and Crohn GWAS is involved in induction of early response genes in serum through stabilization of mechanistic target of rapamycin while acting as a co-activator for CREB-binding protein/E1A-binding protein p300.[61] The expression level of death-associated protein was profoundly downregulated by the UC risk allele in both blood and intestine. DAP was reported to be linked to TGFB-induced apoptosis (transforming growth factor, beta 1) through SMAD-mediated expression and is a putative regulator in the induction of autophagy.[62] Tu translation elongation factor also has a role in enhancement of autophagy and inhibition of the type I interferon response.[63] PRKCB, influenced by its blood expressed eQTL, is a negative regulator of autophagy and the mitochondrial energy supply.[64] MAPRE1, upregulated by IBD risk allele in blood, has a role in autophagy-mediated induction of the AIM1 inflammasome leading to secretion of IL1B.[65] CARD9 is also involved in inflammasome activation, acting as an adapter that mediates protein–protein interactions, interacts with NOD2 and is associated with anti-fungal response, the IL23R/IL17 pathway, and epithelial restitution.[66–68] CARD9, include variants both up- and down-regulated as blood eQTLs and has been reported as being differentially methylated between IBD cases and controls.[69] CCDC101, showed as the only gene to be influenced by rs26528-C (1.50E-11), was profoundly downregulated by the IBD risk allele (rs26528-C), a histone acetyltransferase important for response to endoplasmic reticulum stress.[70]

Lymphocytes. Through our eQTL enrichment analysis in cellular specific gene expression signatures, genes related to T-cell function and T-regulatory cells, in particular, were among the top hits in blood in Crohn's. CD244 (2B4), a non MHC-binding inhibitory receptor on activated NK and CD8 memory cells interacts with CD48 and has a role in regulating tolerance.[71] CD6 is involved with TCR signaling [72] and T regs are characterized by low CD6 expression.[73] NDFIP1, potentially a protective allele, is upregulated by its IBD GWAS risk allele in the blood where it acts as an adapter for ubiquitin ligase in induction of peripheral tolerance. NDFIP1 is activated by TGFB to suppress IL4 in inducible T regs.[74,75] Another blood-specific eQTL includes ZNF300, which is downregulated by Crohn risk allele and is involved in activating the IL2βR expressed highly on T-regulatory cells.[76] Other identified eQTLs were involved in T-cell skewing. For example, FOSL2 is an AP1 transcription factor, which is a putative regulator of plasticity and repressor of TH17 cells. In *in vitro* experiments, FOSL2 overexpression was shown to decrease the number of IL17A producing T cells, whereas FOSL2 deficiency enabled IFNγ production in Th17 and Th2 cell cultures when Th17 cells were subsequently exposed to Th1-skewing conditions.[77,78] CCDC88B is a regulator of T-cell function,[79] and is upregulated in Crohn's and can lead to excessive CD4+ and CD8+ activation and altered IL-12 and TNFα production. For B cell-related eQTLs, downregulation of ZFP36L1 is the directional consequence of IBD RISK allele rs194749C, and has been reported as negatively regulating plasma cell differentiation by targeting BLIMP1, of which lower levels could lead to enhanced antibody production.[80]

In summary, we systematically characterized eQTL architecture in two IBD relevant tissues (blood and intestine), and identified genes influenced by IBD GWAS loci known to date. Our approach revealed a large number of

genes driven by IBD loci which potentially mediate the disease etiology. For example, rs26528-C was strongly associated with IBD ($P = 1.00E-21$),[6] and RABEP2, IL27, EIF3C, SULT1A1, SULT1A2, NUPR1 were proposed as underlying genes.[6] Our results demonstrated eQTLs as a powerful approach in interpreting genetic study results. We found >200 eQTLs on known IBD GWAS loci (Table 2), and informed 109 out of 372 IBD GWAS SNPs documented in NHGRI catalog. Many of the genes mapped to these eQTLs have experimentally validated roles in cell types contributing to intestinal inflammation. These findings reflect our most up-to-date and comprehensive understanding of transcriptome regulation of IBD GWAS, and will serve as a valuable resource in further dissecting the molecular basis of this disorder.

CONFLICT OF INTEREST

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Potential competing interests: None.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Many genome-wide association studies (GWAS) identified genetic polymorphisms associated with inflammatory bowel disease (IBD).
- ✓ The etiological mechanisms of the discovered genetic loci and IBD risk alleles are mostly unknown.

WHAT IS NEW HERE

- ✓ To our knowledge, this is the most comprehensive expressional quantitative trait loci (eQTL) study on IBD related tissues (blood and intestine) to date.
- ✓ We constructed eQTL on an anti-TNF-resistant Crohn's disease (CD) cohort.
- ✓ We used eQTL to inform 109 out of 372 known IBD risk loci.
- ✓ We carefully aligned the effect direction in GWAS and eQTLs for the informed GWAS single-nucleotide polymorphisms (SNPs), and point out the possible molecular etiology of the IBD risk alleles.

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