1 Genome-wide association study implicates immune activation of

2 multiple integrin genes in inflammatory bowel disease

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10 **Genetic association studies have identified 210 risk loci for inflammatory bowel disease[1–7], which**

11 **have revealed fundamental aspects of the molecular biology of the disease, including the roles of**

12 **autophagy and Th17 cell signaling and development. We performed a genome-wide association**

13 **study of 25,305 individuals, and meta-analyzed with published summary statistics, yielding a total**

14 **sample size of 59,957 subjects. We identified 26 new genome-wide significant loci, three of which**

15 **contain integrin genes that encode molecules in pathways identified as important therapeutic**

16 **targets in inflammatory bowel disease. The associated variants are also correlated with**

17 **expression changes in response to immune stimulus at two of these genes (*ITGA4*, *ITGB8*) and at**

18 **two previously implicated integrin loci (*ITGAL*, *ICAM1*). In all four cases, the stimulus-dependent**

19 **expression increasing allele also increases disease risk. We applied summary statistic fine-**

20 **mapping and identified likely causal missense variants in the primary immune deficiency gene**

21 ***PLCG2* and the negative regulator of inflammation, *SLAMF8*. Our results demonstrate that new**

22 **common variant associations continue to identify genes and pathways of relevance to therapeutic**

23 **target identification and prioritization.**

24 Inflammatory bowel disease (IBD) is a chronic, debilitating, disorder of the gastrointestinal tract that

25 includes two common disease subtypes, Crohn's disease and ulcerative colitis. Disease pathogenesis is

26 poorly understood but is likely driven by a dysregulated immune response to unknown environmental

27 triggers in genetically susceptible individuals. Treatment regimes often use potent immunomodulators to

28 achieve and maintain remission of symptoms. However, patients commonly experience side effects, lose

29 response to treatment, or develop complications of IBD, with many ultimately requiring major abdominal

30 surgery. Previous genome-wide association studies (GWAS) and targeted follow-up using the

31 Immunochip have been very successful at identifying genetic risk loci for IBD, but increased biological

32 understanding has not yet had a significant impact on therapy for these disorders.

33 In order to further expand our understanding of the biology of these disorders we carried out a GWAS of

34 12,160 IBD cases and 13,145 population controls of European ancestry that had not been included in any

35 genome-wide meta-analysis of IBD to date (Supplementary Table 1, Online Methods). We imputed

36 genotypes using a reference panel comprising whole genome sequences from 4,686 IBD cases[8] and

37 6,285 publically available population controls[9,10]. Following quality control (Online Methods) we tested 9.7

38 million sites for association. At the 232 IBD associated SNPs in the latest meta-analysis by the

39 International IBD Genetics Consortium[1], 228 had effects in the same direction in our data, 188 showed at

40 least nominal evidence of replication (P<0.05) and none showed significant evidence of heterogeneity of

41 effect by Cochrane's Q test. Among these replicated loci was a genome-wide significant association on

42 chromosome 10q25 that was only previously significantly associated with Crohn's disease in individuals

43 of East Asian ancestry[3,7], further supporting near complete sharing of genetic risk loci across

44 populations[1]. We meta-analyzed our new GWAS data with previously published summary statistics from

45 12,882 IBD cases and 21,770 population controls imputed using the 1000 Genomes Project reference

46 panel[1] (Supplementary Figures 1-3, Supplementary Table 2). We observed inflation of the summary

47 statistics (λ_{GC} = 1.23 and 1.29 for Crohn's and ulcerative colitis, respectively), but LD score regression

48 demonstrated that this was due to broad polygenic signal, rather than confounding population

49 substructure (both intercepts = 1.09, Online Methods).

50 We identified 26 new loci at genome-wide significance (**Table 1**). In order to identify causal variants,

51 genes and mechanisms, we performed a summary-statistic fine-mapping analysis on these loci, as well

52 as 39 previously discovered loci where fine-mapping had not yet been attempted[11] (Online Methods,

53 Supplementary Table 3). In order to be confident about fine-mapping inferences, we restricted

54 subsequent analyses to 12 signals where we had high quality imputed data for all relevant variants

55 (Online Methods). At 6 of these 12 loci we identified a single variant with >50% probability of being causal

56 (**Table 2**, Supplementary Figures 4-6). Among these were two loci where a single variant had >99%

57 probability of being causal: a missense variant predicted to affect protein function in *SLAMF8*, (**Figure**

58 **1a**), and an intronic variant in the key regulator of Th17 cell differentiation, *RORC*[12]. SLAMF8 is a cell

59 surface receptor that is expressed on activated myeloid cells and has been reported to negatively

60 regulate inflammatory responses by repressing the production of reactive oxygen species (ROS)[13] and

61 inhibiting their migration to sites of inflammation[14]. *RORC* encodes RORγt, the master transcriptional

62 regulator of Th17 cells[12] and group 3 innate lymphoid cells[15]. Both of these cell types play important roles

63 in defence at mucosal surfaces, especially in the intestine, and have been shown to contribute to the

64 homeostasis between the intestinal immune system and gut microbiota[16,17], an equilibrium that is known

65 to be lost in inflammatory bowel disease[18]. Pharmacologic inhibition of RORγt has been shown to offer

66 therapeutic benefit in mouse models of intestinal inflammation, and reduces the frequency of Th17 cells

67 isolated from primary intestinal samples of IBD patients[19].

68 In loci where fine-mapping was less clearly resolved, we searched for likely functional variants, observing

69 a missense variant predicted to affect protein function (CADD = 16.45, 50.2% probability of causality) in

70 *PLCG2.* Furthermore, after conditioning on this variant, we discovered a second, independent, likely

71 functional (CADD = 34, 74.6% probability of causality) missense variant in the same gene (P=2x10^{-8}).

72 *PLCG2* encodes a phospholipase enzyme that plays a critical role in regulating immune pathway

73 signalling[20], and has previously been implicated in two autosomal dominant immune disorders. Intragenic

74 deletions in its autoinhibitory domain cause antibody deficiency and immune dysregulation (familial cold

75 autoinflammatory syndrome 3, MIM 614468)[21] and heterozygous missense variants (e.g. p.Ser707Tyr)

76 lead to a phenotype that includes intestinal inflammation[22] (**Figure 1b**).

77 A more general overlap between candidate IBD GWAS genes and Mendelian disorders of inflammation

78 and immunity has been previously observed[23]. In addition to *PLCG2* we identified an association between

79 Crohn's disease and an intronic variant in *NCF*4 (P=1.76 x 10^{-8}). This gene encodes p40phox, a

80 component of the NADPH-oxidase system that is responsible for the oxidative burst in innate immune

81 cells and which is a key mechanism of killing phagocytosed bacteria. Rare pathogenic variants in *NCF4*

82 cause autosomal recessive chronic granulomatous disease, characterized by Crohn's disease-like

83 intestinal inflammation and defective ROS production in neutrophils[24]. Our associated variant, rs4821544,

84 had previously been suggestively associated with small bowel Crohn's disease[25,26], and when we

85 stratified patients by disease location we found that the effect was consistently stronger for small bowel

86 compared to large bowel disease (Supplementary Figure 7).

87   Among the remaining 22 novel loci we noted three that were within 150kb of integrin genes (*ITGA4,*

88   *ITGAV* and *ITGB8*), while two previously associated loci overlap with a fourth integrin, *ITGAL*, and its

89   binding partner *ICAM1.* Integrins are cell adhesion mediators with bi-directional signalling capabilities that

90   play a crucial role in leukocyte homing and cell differentiation in inflammation and cancer[27]. Given the

91   strong candidacy of these genes, we sought potentially causal molecular mechanisms that would connect

92   the IBD associated SNPs to integrin regulation. Our fine-mapping analysis excluded the possibility that

93   these associations are caused by protein-coding changes, so we next tested for effects of IBD risk SNPs

94   on integrin gene expression in immune cells using nine publicly available eQTL datasets. While many

95   eQTLs and GWAS signals show some degree of correlation, inferences about causality require more

96   robust statistical co-localization of the two signals. Remarkably, we observed three of our five

97   associations had >90% probability of being driven by the same variants as monocyte-specific stimulus

98   response eQTLs (*ITGA4, P_{LPS_24hr}*=0.984; *ITGAL, P_{LPS_24hr}*=0.980; *ICAM1, P_{LPS_2hr}*=0.961; Supplementary

99   Table 4). A fourth association, *ITGB8*, is difficult to map due to extended linkage disequilibrium in the

100   locus, but shows intermediate evidence of co-localization (P_{LPS_24hr}=0.712) in response to the same

101   stimulus (**Figure 2**). These observations suggest upregulation of pro-inflammatory cell surface markers as

102   a potential mechanism of action, as all four of the IBD risk increasing alleles upregulate expression of

103   their respective genes.

104   Integrins and their counter-receptors have recently emerged as important therapeutic targets in IBD. Most

105   promisingly monoclonal antibodies that target the components of the α4β7 dimer, responsible for the gut-

106   homing specificity of leukocyte subsets, have demonstrated efficacy in IBD[28–30]. Additionally, an antisense

107   oligonucleotide targeting *ICAM1* has shown promise in the treatment of ulcerative colitis and pouchitis[31].

108   The importance of gut-selectivity for therapeutic approaches is highlighted by the success of antibodies

109   that bind the αL and α4 integrin subunits. Whilst αL-directed therapy with efalizumab demonstrated

110   potential in Crohn's disease[32], and α4-directed therapy (which binds α4β1 in addition to α4β7 integrin)

111   with natalizumab is licensed in the USA for Crohn's disease[33], both medications have been associated

112   with occurrences of progressive multifocal leukoencephalopathy (PML). This potentially fatal condition is

113   likely mediated by impaired leukocyte migration to the central nervous system leading to JC virus infection

114   of the brain. Owing to the risk of PML, efalizumab has been withdrawn from the market and natalizumab

115   is not licensed for Crohn's disease in Europe.

116   Integrins are not only important in cell trafficking, but can also participate in cellular signalling. For

117   example, the αVβ8 heterodimer – both subunits of which are now within confirmed IBD loci – is a potent

118   activator of TGFβ[34], with a range of cell-type specific effects. Furthermore, mice with dendritic-cell specific

119   deletion of this complex had impaired regulatory T cell function and severe colitis[35], whereas deleting the

120   complex in regulatory T cells themselves prevented them from suppressing pathogenic T cell responses

121   during active inflammation[36]. While no current IBD therapeutics target αVβ8 directly, promising early

122   results of an oral antisense oligonucleotide to the inhibitory TGFβ-signalling protein SMAD7[37], itself

123   encoded by a locus identified by genetic association studies[23], demonstrate the therapeutic potential of

124   modifying TGFβ signaling in Crohn's disease.

125   In addition to the connections to anti-integrin and anti-TGFβ therapies described above, IBD GWAS have

126   previously implicated loci containing other therapeutically relevant genes, such as those in pathways

127   targeted by anti-TNF and anti-p40 IBD therapies (**Figure 3**). These discoveries have demonstrated that

128   the importance of the biological pathways underlying associations, and their potential therapeutic

129   relevance, are not necessarily reflected in their GWAS effect sizes. For example, the modest odds ratios

130   of the signals near integrin genes (1.10-1.12) required tens of thousands of samples to detect at genome-

131   wide significance. Furthermore, analyses aimed at understanding the specific cellular contexts in which

132   these genes are active in IBD, as well as the risk-increasing direction of effect (e.g. consistent up-

133   regulation of integrins in response to LPS stimulus), are only beginning to bear fruit.

134   Our study has demonstrated that continuing to pursue GWAS, even in a well studied complex disease

135   like IBD, has the potential to complement other powerful approaches, such as targeted genotyping (via

136   the Immunochip) and large-scale genome and exome sequencing. In two cases we have implicated

137   genes in which different variants have previously been shown to cause immune-related Mendelian

138   disorders, echoing a connection made to the very first Crohn's disease risk gene, *NOD2*, in which rare

139   missense mutations cause the autosomal dominant granulomatous disorder Blau syndrome[38]. Finally,

140   while the individual effect sizes of our newly discovered associations are modest, we believe that our

141   results show that GWAS continues to deliver new understanding of disease biology and new therapeutic

142   opportunities.

143

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Competing financial interests:

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Online Methods

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New genome-wide genetic data

209 *GWAS samples and genotyping.* 11,768 British IBD cases, diagnosed using accepted endoscopic,

210 histopathological and radiological criteria, were genotyped on the Human Core Exome v12.1. 10,484

211 population control samples genotyped on the Human Core Exome v12.0 were obtained from the

212 Understanding Society Project. Genotypes were called using optiCall[39].

213 *GWAS quality control.* We removed variants that did not overlap between the two versions of the chip,

214 had missingness > 5%, a significant difference in call rate between cases and controls ($P < 1\times10^{-5}$),

215 deviated from Hardy-Weinberg equilibrium (HWE) in controls ($P < 1\times10^{-5}$), or that were affected by a

216 genotyping batch effect (significant association [$P < 1\times10^{-5}$] between an outlier group of cases discovered

217 using principal component analysis [PC1 < -0.005], and the remainder of the samples). We then removed

218 samples with missingness > 1%, heterozygosity ±3 standard deviations from the mean, mismatch

219 between reported and genotypic sex, first-degree relatives or closer (kinship coefficient > 0.177), and

220 non-European samples identified through principal component analysis with HapMap3 populations. After

221 quality control, data were available for 4,474 Crohn's disease, 4,173 ulcerative colitis, 592 IBD-

222 unclassified cases and 9,500 controls for 296,203 variants.

223 *Whole-genome sequenced samples.* We generated low-coverage whole genome sequences for 4,686

224 IBD cases and 3,781 population controls from the UK IBD Genetics Consortium (UKIBDGC) and UK10K

225 Consortium, respectively. Detailed information on sequencing, genotype refinement and quality control

226 are described elsewhere[8].

227 *Imputation.* These sequences were combined with 2,504 samples from the Phase 3 v5 release of the

228 1000 Genomes project (2013-05-02 sequence freeze) to create a phased imputation reference panel

229 enriched in IBD-associated variants. We used PBWT[40] to impute from this reference panel (114.2 million

230 total variants) into our new GWAS described above.

231

232

233 **Association testing, meta-analysis, and quality control.**

234 *Association testing.* Prior to association testing, we removed all samples that were included in previous

235 IBD GWAS meta-analyses (Supplementary Table 1). We then tested for association to ulcerative colitis,

236 Crohn's disease and IBD separately within the sequenced samples and new GWAS using SNPTEST

237 v2.5, performing an additive frequentist association test conditioned on the first ten principal components

238 for each cohort. We filtered out variants with minor allele frequency (MAF) < 0.1%, INFO < 0.4, or strong

239 evidence for deviations from HWE in controls ($p_{HWE}<1x10^{-7}$).

240 *Meta-analysis.* We used METAL (release 2011-03-05) to perform a standard error weighted meta-

241 analysis of our sequencing and GWAS cohorts with the publicly available International Inflammatory

242 Bowel Disease Genetics Consortium (IIBDGC) meta-analysis summary statistics[1], after applying the

243 additional MAF ≥0.1%, and INFO ≥0.4 filters to the IIBDGC data.

244 *Quality control.* The output of the fixed-effects meta-analysis was further filtered, and sites with high

245 evidence for heterogeneity ($I^2>0.90$) were discarded. Only sites for which all cohorts passed our quality

246 control filters were included in our analysis. In addition, we discarded genome-wide significant variants for

247 which the meta-analysis p-value was not lower than all of the cohort-specific p-values.

248 *LD score regression.* We performed LD score regression using LDSC v1.0.0 and European linkage

249 disequilibrium (LD) scores from the 1000 Genomes Project (downloaded from

250 https://data.broadinstitute.org/alkesgroup/LDSCORE/eur_w_ld_chr.tar.bz2) on our filtered meta-analysis

251 summary statistics for all sites with INFO > 0.95. This INFO threshold is to avoid confounding due to poor

252 imputation, as recommended by the authors[41].

253 **Locus definition**

254 *Computing LD windows.* An LD window was calculated for every genome-wide significant variant in any

255 of the three traits (Crohn's disease, ulcerative colitis, IBD), defined by the left-most and right-most

256 variants that are correlated with the main variant with an r^2 of 0.6 or more. The LD was calculated in the

257 GBR and CEU samples from the 1000 Genomes Phase 3, release v5 (based on 20130502 sequence

258 freeze and alignments). Loci with overlapping LD windows, as well as loci whose lead variants were

259 separated by 500kb or less, were subsequently merged, and the variant with the strongest evidence of

260 being associated was kept as the lead variant for each merged locus.

9

261   *Identifying novel loci.* A locus was annotated as known if it contained at least one variant previously

262   reported at genome-wide significance (irrespective of the LD between that variant and the most

263   associated variants in the locus). To ensure that putatively novel signals were not due to long-range LD

264   with variants in previously reported loci, we conducted conditional analysis in our new GWAS for all

265   variants in loci which were less than 3Mb away from a known locus. Putatively novel loci already known in

266   a lower order IBD trait (e.g. a previously known Crohn's disease locus coming up as an IBD locus) were

267   also removed from this list. This did not apply where, for example, a known Crohn's disease locus was

268   now associated with ulcerative colitis, or vice versa.

269   **Fine-mapping**

270   Approximate Bayes factors were calculated from the meta-analysis effect sizes and standard errors

271   described above by applying equation (2) of Wakefield[42], assuming a prior variance on the log odds ratios

272   of 0.04 (the default prior used by the software SNPTest, and used by Maller *et al*[43]). We then performed

273   fine-mapping using these Bayes factors as described in Maller et al to calculate the posterior that each

274   variant is causal, and the 95% credible set for each association (the smallest set of variants with

275   posteriors that sum to at least 95%). For each association we use the meta-analysis results for the

276   phenotype (Crohn's disease, ulcerative colitis or IBD) specified in Table 1. We only consider a locus to be

277   confidently fine-mapped if there are no variants in the Phase 3 v5 release of the 1000 Genomes project

278   (2013-05-02 sequence freeze) in high LD ($r^2 \geq 0.6$) with our hit SNP, but missing from our dataset, and no

279   variants in our data within high LD ($r^2 > 0.8$) that fail during our QC procedure.

280   **eQTL overlap**

281   *Identifying eQTL overlaps.* Nine eQTL datasets were searched to identify variants within the 26 newly

282   identified IBD risk loci that are associated with variation in gene expression (Supplementary Table 5).

283   Splice-QTLs based on exon-ratio[44] and transcript-ratio[45–47] were also included in the search where

284   available (Supplementary Table 5). The most significant variant-gene associations were extracted from

285   each eQTL/splice-QTL dataset and were reported as candidates if that variant had r2 > 0.8 with any of

286   the lead SNPs in the 26 IBD risk loci.

287   *Testing for co-localization.* We tested for co-localization between IBD association signals and eQTLs

288   using the coloc2 method[48], implemented in the R package coloc. We used a window size of 250kb on

289   either side of the IBD association, and implemented the default settings as recommended. Each test was

290   repeated using two different values for the prior probability of co-localization, p_{12}: $1\text{x}10^{-5}$ and $1\text{x}10^{-6}$.

11

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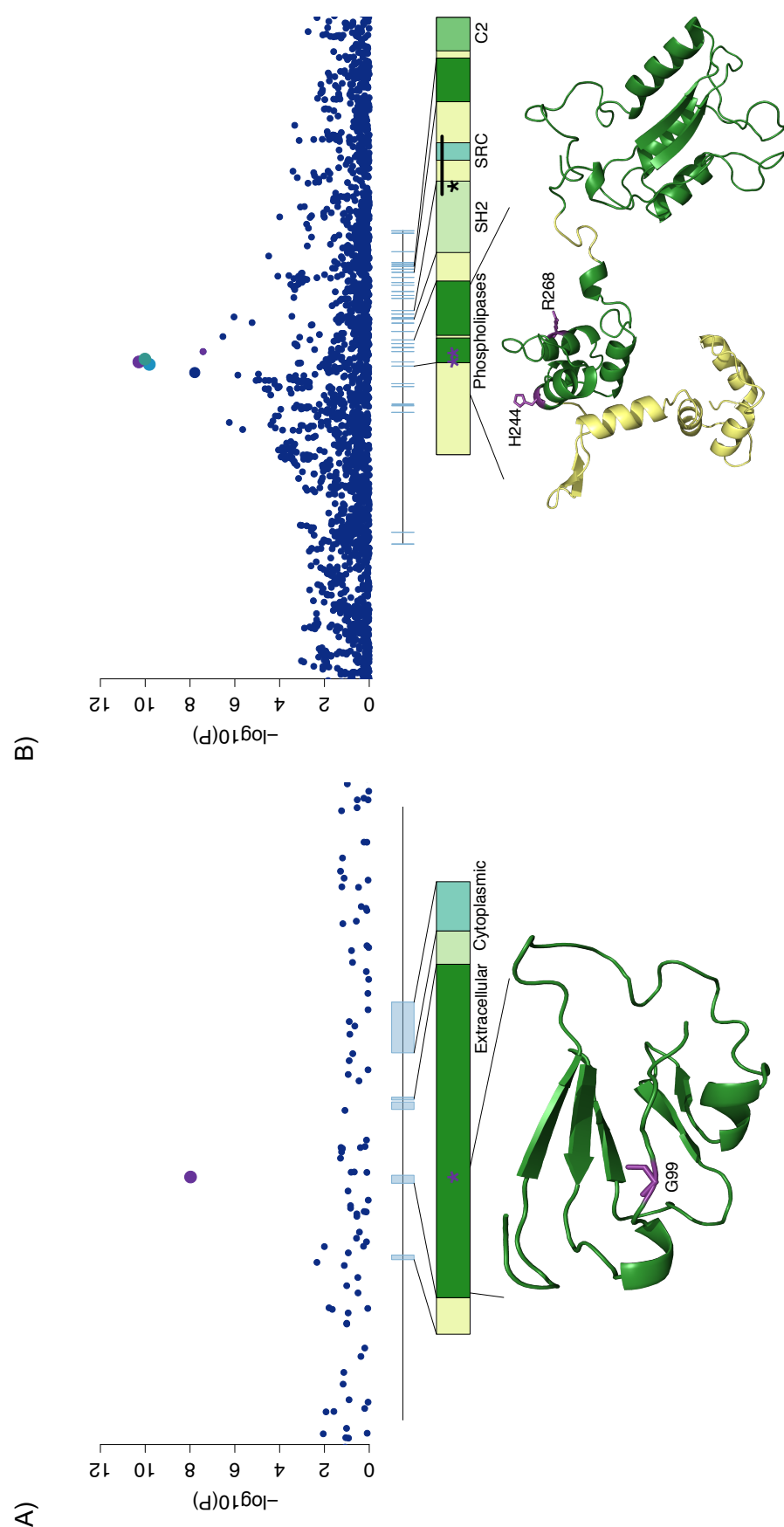
Figure 1. Likely causal missense variants. For A) SLAMF8 and B) PLCG2, local association results are plotted with point size corresponding to LD to our lead variant and color to fine-mapping probability (purple > 50%, intermediate blue 10-50%, navy blue <10%). Gene body diagrams and protein domain annotations are taken from ENSEMBL, and partial predicted crystal structures for both proteins are obtained from the SWISS-MODEL respository.

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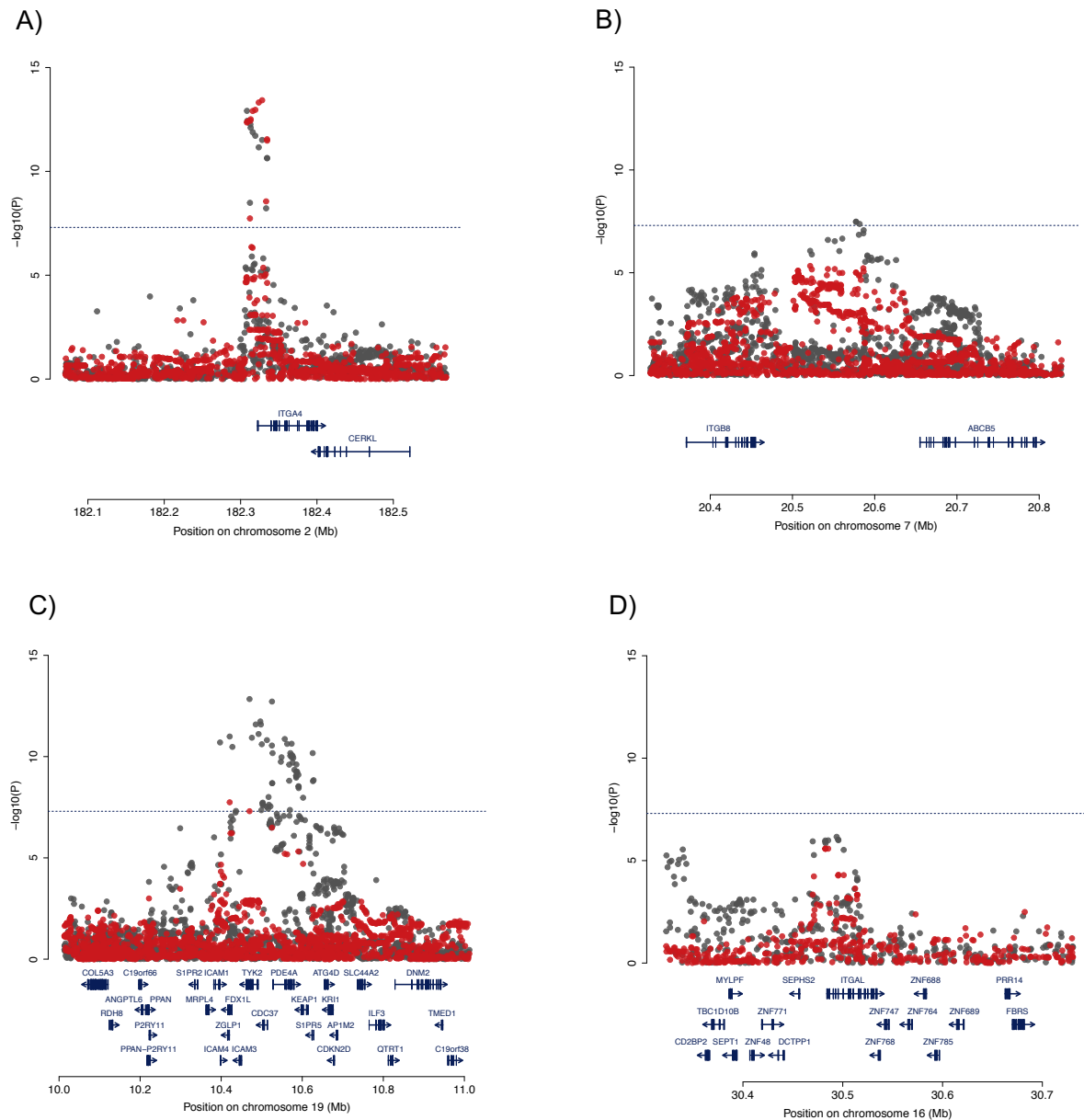
Figure 2. Co-localization of disease association and stimulus response eQTLs in monocytes. The local pattern of disease association (IBD: (A) *ITGA4,* (B) *ITGB8*, (C) *ICAM1*; (D) UC: *ITGAL*) in grey, and the association of that variant with response to LPS (lipopolysaccharide) stimulation in red. Evidence of co-localization (probability > 70%) is observed for all for signals.

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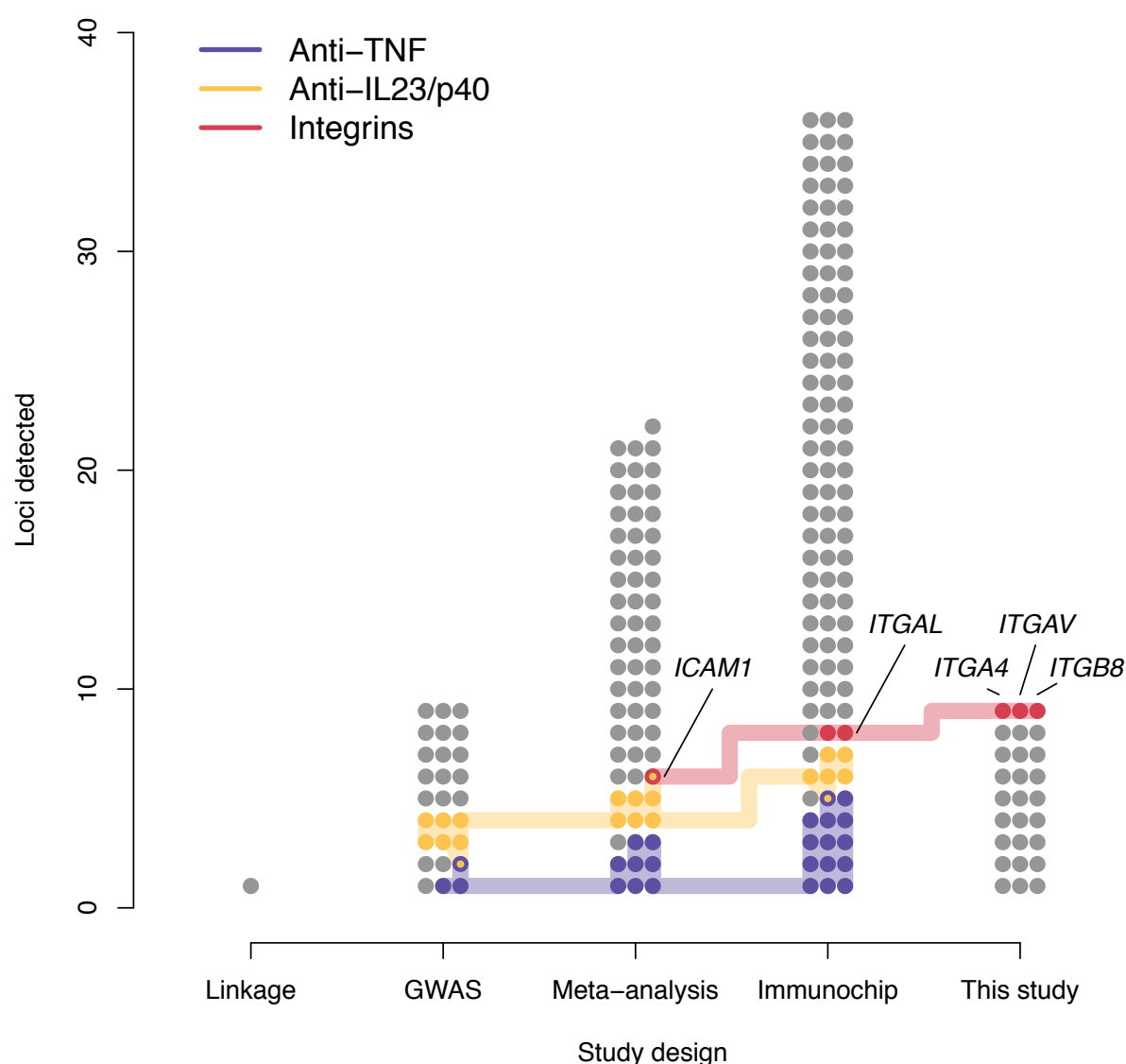
Figure 3. IBD-associated loci containing genes related to known drug targets. All IBD loci are divided into the studies where they were first identified[1]. The direct targets and closely related genes of three classes of IBD therapeutics are highlighted, with particular focus on the newly discovered integrin associations. Despite the general pattern that effect size decreases from left to right, therapeutically relevant associations continue to be found.

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Table 1. Novel IBD-associated loci.

Rsid	Chr	Position (bp)	Left-right (Mb)	Risk Allele	Non-risk Allele	Risk Allele Frequency in 1000 Genomes CEU+GBR	P_{Meta}	OR (95% CI)	Phenotype
rs34687326	1	159799910	159.8-159.8	G	A	0.9	1.06×10^{-08}	1.18 (1.12-1.24)	CD
rs59043219	1	209970610	209.97-210.02	A	G	0.379	1.09×10^{-08}	1.08 (1.05-1.10)	IBD
rs6740847	2	182308352	182.31-182.33	A	G	0.508	1.22×10^{-13}	1.10 (1.07-1.12)	IBD
rs144344067	2	187576378	187.5-187.68	A	AT	0.895	1.29×10^{-08}	1.12 (1.08-1.16)	IBD
rs1811711	2	228670476	228.67-228.67	C	G	0.826	6.09×10^{-09}	1.14 (1.1-1.18)	UC
rs76527535	2	242484701	242.47-242.49	C	T	0.745	2.87×10^{-08}	1.09 (1.06-1.12)	IBD
rs2581828	3	53133149	53.1-53.17	C	G	0.597	6.46×10^{-09}	1.10 (1.07-1.13)	CD
rs2593855	3	71175495	71.16-71.19	C	T	0.663	2.54×10^{-09}	1.09 (1.06-1.11)	IBD
rs503734	3	101023748	100.91-101.27	A	G	0.513	2.67×10^{-08}	1.07 (1.05-1.10)	IBD
rs56116661	3	188401160	188.4-188.4	C	T	0.795	5.67×10^{-10}	1.14 (1.10-1.18)	CD
rs11734570	4	38588453	38.58-38.59	A	G	0.368	4.80×10^{-08}	1.07 (1.05-1.10)	IBD
rs17656349	5	149605994	149.59-149.63	T	C	0.466	1.54×10^{-08}	1.09 (1.06-1.13)	UC
rs113986290	6	19781009	19.72-19.83	C	T	0.989	7.59×10^{-09}	1.36 (1.25-1.46)	UC
rs67289879	6	42007403	42-42.01	T	C	0.179	3.04×10^{-08}	1.09 (1.06-1.13)	IBD
rs11768365	7	6545188	6.5-6.55	A	G	0.816	3.88×10^{-08}	1.09 (1.06-1.12)	IBD
rs149169037	7	20577298	20.58-20.58	G	A	0.895	3.26×10^{-08}	1.14 (1.10-1.19)	IBD
rs243505	7	148435339	148.4-148.58	A	G	0.624	3.04×10^{-10}	1.08 (1.06-1.11)	IBD
rs7911117	10	27179596	27.16-27.18	T	G	0.871	1.84×10^{-08}	1.14 (1.10-1.19)	UC
rs111456533	10	126439381	126.32-126.55	G	A	0.829	1.18×10^{-09}	1.11 (1.08-1.14)	IBD
rs11221335	11	128385906	128.38-128.4	C	T	0.224	2.44×10^{-08}	1.09 (1.06-1.12)	IBD
rs80244186	13	42917861	42.84-42.94	A	T	0.111	3.66×10^{-08}	1.13 (1.09-1.18)	CD
rs11548656	16	81916912	81.91-81.92	A	G	0.961	5.18×10^{-11}	1.27 (1.20-1.34)	IBD
rs10492862	16	82867456	82.87-82.92	A	C	0.308	1.26×10^{-09}	1.11 (1.08-1.15)	CD
rs4256018	20	6093889	6.08-6.1	G	T	0.25	1.23×10^{-08}	1.08 (1.05-1.11)	IBD
rs138788	22	35729721	35.72-35.74	A	G	0.418	2.95×10^{-08}	1.09 (1.06-1.13)	UC
rs4821544	22	37258503	37.26-37.26	C	T	0.321	1.76×10^{-08}	1.10 (1.07-1.13)	CD

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Table 2. Variants fine-mapped to >50% probability of being causal in their given locus.

Rsid	Chr	Position (bp)	P_{Causal}	Effect	Credible set size	Phenotype	P_{Meta}	Locus type
rs34687326	1	159799910	1.000	SLAMF8 p.Gly99Ser (missense)	1	CD	1.06×10^{-08}	Novel
rs4845604	1	151801680	0.999	RORC (intronic)	1	IBD	7.09×10^{-14}	Known
rs1811711	2	228670476	0.914		2	UC	6.09×10^{-09}	Novel
rs56116661	3	188401160	0.561	LPP (intronic)	11	CD	5.67×10^{-10}	Novel
rs11548656	16	81916912	0.502	PLCG2 p.His244Arg (missense)	3	IBD	5.18×10^{-11}	Novel
rs1143687	16	81922813	0.746	PLCG2 p.Arg268Trp (missense)	5	IBD	3.83×10^{-08}	Novel
rs4821544	22	37258503	0.804	NCF4 (intronic)	2	CD	1.76×10^{-08}	Novel