Supplementary Materials for

Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci

Supplementary Tables

Supplementary Table 1. Case/control panels used in the analysis before/after quality control. 'Consortium' refers to the scientific group that provided DNA samples. All study subjects are of European ancestry.

Phenotype	Consortium	#Cases preQC	#Controls preQC	#Cases QCed	#Controls QCed	Platform
Ankylosing spondylitis	International Genetics of Ankylosing Spondylitis Consortium (IGAS)	10,417	12,338	8,726	-	Immunochip
Crohn's disease	International Inflammatory Bowel Disease Genetics Consortium (IIBDGC)	19,761	28,999	19,085	-	Immunochip
Psoriasis	Collaborative Association Study of Psoriasis (CASP) Genetic Analysis of Psoriasis Consortium Psoriasis Association Genetics Extension Wellcome Trust Case Control Consortium 2	6,577	15,085	6,530	-	Immunochip
Primary sclerosing cholangitis	The International PSC Study Group The UK-PSC Consortium International IBD Genetics Consortium	3,789	25,079	3,408	-	Immunochip
Ulcerative colitis	International Inflammatory Bowel Disease Genetics Consortium (IIBDGC)	14,833	-	14,513	-	Immunochip
Unique controls	Across all consortia	-	-	-	34,213	Immunochip
Total		55,377	81,051	52,262	34,213	Immunochip

Supplementary Table 2. 27 newly identified single disease associations with genome-wide significance ($P_{SBM}<5\times10^{-7}$ and $P_{disease}<5\times10^{-8}$). All variants were annotated used the variant effect predictor (VEP, release-77) from Ensembl (see **Methods**).

SEE EXCEL file.

Pheno new gws locus: phenotype with new genome-wide significant association signal ($P_{disease}<5\times10^{-8}$); **Chr:** chromosome; **BP_B37:** base pair position from dbSNP build v142 (genome build hg19); **SNP:** rs ID; **IchipSNP:** original SNP chip ID; **A1:** minor allele in controls; **A2:** major allele in controls; **SNP_pos_l/SNP_pos_r:** left/right association boundaries for each index SNP (see **Methods** section). Genomic positions were retrieved from NCBI's dbSNP build v142 (genome build hg19); **P_adj_SBM:** adjusted (disease-combined) *P*-value (P_{SBM}) from subset-based meta-analysis (SBM) (see **Methods**); **P/OR/CI95_L/CI95_R:** single disease *P*-value ($P_{disease}$) and corresponding odds ratio and 95% confidence interval with respect to minor allele. **MAF:** disease-specific/control minor allele frequency.

Consequence: consequence type of this variation due to the VEP annotation tool; **Transcript_id:** Ensembl RNA transcript ID; **Tssdistance:** distance to transcription start site; **sift_prediction:** the SIFT prediction if available; **polyphen_prediction:** the PolyPhen prediction if available; **gene_symbol:** Ensembl stable ID of affected gene; **Immunobase codes 0:**no match **other than 0:**lead SNP (incl. SNPs in r2>0.8 with lead SNP) has a match in Immunobase for ankylosing spondylitis (AS), autoimmune thyroid disease (ATD), celiac disease (CEL), Crohn's disease (CRO) CRO, juvenile idiopathic arthritis (JIA), multiple sclerosis (MS), primary biliary cirrhosis (PBS), psoriasis (PSO), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), type 1 diabetes (T1D), ulcerative colitis (UC), other disease (OS). The numbers are internal scores assigned to tag each feature to a particular phenotype, see http://www.immunobase.org/page/CriteriaDossierHome.

Supplementary Table 3. (a) Summary table of 169 non-MHC genome-wide significant susceptibility loci including 244 independent association signals with $P_{SBM}<5\times10^{-8}$ or ($P_{SBM}<5\times10^{-7}$ and $P_{disease}<5\times10^{-8}$) identified through the (conditional) subset-based meta-analysis of ankylosing spondylitis (AS), Crohn's disease (CD), psoriasis (PS), primary sclerosing cholangitis (PSC) and ulcerative colitis (UC). (b) Summary table of results from Bayesian multinomial regression to calculate the posterior probability ($Prob_{model}$) for each possible disease model using a uniform prior across all models. (c) Summary table of results from Bayesian multinomial regression to calculate the mean posterior probability ($MeanProb_{model}$) for each possible disease model using six different priors across all models.

SEE EXCEL file.

Locus: number of locus defined by annotation of association boundaries (see **Methods**); **Num_independent_signal:** number of independent signal within a certain locus; **Chr:** chromosome; **Locus_pos_l/Locus_pos_r:** left/right association boundaries for locus (see **Methods** section). Genomic positions were retrieved from NCBI's dbSNP build v142 (genome build hg19); **Pheno_SBM_risk:** risk (OR>1) disease subset based from subset-based meta-analysis; **Pheno_SBM_protective:** protective (OR<1) disease subset from subset-based meta-analysis; **SNP:** rs ID; **IchipSNP:** original SNP chip ID; **Gene:** gene nearest to the index SNP as long as a gene was with 10kb of the SNP; **Strand:** strand information for A1/A2; **A1:** minor allele in controls; **A2:** major allele in controls; **BP_B37:** base pair position from dbSNP build v142 (genome build hg19); **SNP_pos_l/SNP_pos_r:** left/right association boundaries for each index SNP (see **Methods** section). Genomic positions were retrieved from NCBI's dbSNP build v142 (genome build hg19); **P_adj_SBM:** adjusted (disease-combined) *P*-value (P_{SBM}) from subset-based meta-analysis (SBM) (see **Methods**); **P/OR/CI95_L/CI95_R:** single disease *P*-value ($P_{disease}$) and corresponding odds ratio and 95% confidence interval with respect to minor allele. **MAF:** disease-specific/control minor allele frequency. We tested for significantly different allele frequencies of variants across the batches from a particular disease or the control group (with at most one batch being removed) with a false discovery rate (FDR) threshold of 0.01 (**Supplementary Fig. 11**); **Known:** Best association signal from previous Immunochip/GWAS studies[1-4]. **Country allele freqs:** Allele frequencies by country information

SNP: rs ID; **BestModel**: disease model with highest probability ($Prob_{model}$); **BestModelP**: Probability ($Prob_{model}$) of disease model with highest probability; **BestModelPhenos**: Number of diseases involved in disease model with highest probability ($Prob_{model}$); **ConfSetSize:** Number of disease models with $Prob_{model}$ >0.01; **ConfSet**: Posterior probability ($Prob_{model}$) for each of these disease models with Prob>0.01, conditional on the genotype and phenotype data we have seen.

VoteWinner: Best disease model with highest posterior probability under six different priors; **VoteCount:** we counted how many priors voted for that model, and calculated the mean posterior from six different priors; **MeanP**: Mean posterior probability ($MeanProb_{model}$) for the proposed model and risk variant of six different priors; **MinP:** Minimum posterior probability when using six different priors; **MaxP:** Maximum posterior probability when using six different priors;

Supplementary Table 4. Summary table of different functional *in-silico* annotations for 244 risk SNPs from Supplementary table 3a.

Functional Consequence	No.
intron_variant	118
upstream_gene_variant	42
intergenic_variant	34
downstream_gene_variant	19
missense_variant	14
regulatory_region_variant	5
3_prime_UTR_variant	4
5_prime_UTR_variant	1
synonymous_variant	2
splice_donor_variant	1
splice_region_variant	1
frameshift_variant	1
Total	244

Supplementary Table 5. Functional *in-silico* annotations of Supplementary table 3a risk SNPs.

SEE EXCEL file.

Consequence: consequence type of this variation due to the VEP annotation tool; **Transcript_id:** Ensembl RNA transcript ID; **Tssdistance:** distance to transcription start site; **sift_prediction:** the SIFT prediction if available; **polyphen_prediction:** the PolyPhen prediction if available; **gene_symbol:** Ensembl stable ID of affected gene; **Immunobase codes 0:**no match **1:**lead SNP (incl. SNPs in r^2>0.8 with lead SNP) has a match in Immunobase for ankylosing spondylitis (AS), autoimmune thyroid disease (ATD), celiac disease (CEL), Crohn's disease (CRO) CRO, juvenile idiopathic arthritis (JIA), multiple sclerosis (MS), primary biliary cirrhosis (PBS), psoriasis (PSO), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), type 1 diabetes (T1D), ulcerative colitis (UC), other disease (OS). The DNA Hypersensitivity sites (DHS) and Promoter annotations were taken from 1KGP annotations[5].

Supplementary Table 6. Analysis of *cis*-eQTL data from whole peripheral samples of 2,360 unrelated individuals[6,7].

SEE EXCEL file.

Shown are all significant (at FDR<5%) expression probes within 1Mb from our trait associated SNPs. For each trait SNP–probe pair we provide the following: 1) the best eQTL SNP; 2) LD between trait SNP and best eQTL SNP; 3) association statistics for trait SNP (P-value, z-score, FDR); 4) association statistics for best eQTL SNP (P-value, z-score, FDR); 5) trait SNP association statistics after conditioning on best eQTL SNP-effects (P-value, z-score, FDR); and 6) best eQTL SNP association statistics after conditioning on trait SNP-effects (P-value, z-score, FDR). Cis-effects in green mark the overlap of 5 gSNPs (from **Supplementary table 3a**) with the best eQTL SNP from this independent control cohort; cis-effects in yellow mark the overlap of another 5 gSNPs (from **Supplementary table 3a**) with the best secondary eQTL SNP from this independent control cohort; cis-effects marked in bold are conditionally independent from best eSNP.

Supplementary Table 7. Cell/tissue types, enhancer types and number of facets that were tested in Fantom5 data[8]. Cell/tissue id begins 'CL' these are cell types, those beginning 'UBERON' are tissues.

Cells or Tissues	Enhancer Type	Number of facets tested
Cells (CL:xx)	Differentially Expressed	69
	Expressed	71
Tissues (UBERON:xx)	Differentially Expressed	41
	Expressed	41

Supplementary Table 8. Number of annotation cell types, modification type and suggested function in Roadmap annotations[9]. We used the peak regions for the histone modifications H3K27ac, H3K4me3, H3K4me1, H3K9me3, and H3K9ac. These marks are enriched at active promoters and enhancers or transcriptionally silent or repressed regions.

Histone Modification	Number of cell types with annotation data	Modification Type	Function
H3K27ac	86	Acetylation	Transcriptional Activation
H3K4me3	120	Tri-methylation	Actively transcribed promoters/TSS
H3K4me1	108	Mono-methylation	Actively transcribed enhancers
H3K9me3	35	Tri-methylation	Transcriptionally silent heterochromatin regions
H3K9ac	49	Acetylation	Actively Transcribed Promoters

Supplementary Table 9. Results from the association analysis (Supplementary table 3a) where separated into groups based on phenotype. Shared3+: variants that were associated with 3 or more phenotypes; **IBD**: variants associated with IBD, UC or CD; **All variants**: all variants identified in the study regardless of phenotype. SNPs that were not present in the 1000 genomes dataset were removed from this analysis.

Group	No of variants for analysis	No. of variants excluded (not in 1KGP)
All variants	234	10
Shared 3+	110	4
IBD	209	9
PS	66	0
AS	106	7
CD	177	8
UC	159	5
PSC	60	1

Supplementary Table 10. Enrichment analysis between SNPs in associated loci and various types of genomic annotations using GoShifter. The table below shows the annotations that were enriched (with $P<10^{-3}$) for each tested group of SNPs. The analysis was performed using Goshifter and genomic annotations from Roadmap[9] and Fantom5[8]. GoShifter was run with 10,000 permutations; the *P* values labelled with a '*' were calculated from 1 million permutations. For the Roadmap annotations, the peak regions were used to define the annotation region. 'Facet expressed' annotations are robustly expressed enhancers that were significantly expressed in each contained sample within a facet. 'Facet differentially expressed' annotations are expressed enhancers that significantly deviate in expression between facets (Bonferroni corrected $P<0.05$). For information on grouping (Shared3+; IBD; All variants), see **Supplementary Table 9.**

Phenotype	Dataset	Tested Annotation	Cell Type	Pvalue
CD	Fantom5	Facet Differentially Expressed	T_cell	0.0003
CD	Fantom5	Facet Expressed	T_cell	0.0003
All variants	Fantom5	Facet Differentially Expressed	T_cell	0.0001
All variants	Fantom5	Facet Expressed	T_cell	0.0001
All variants	Fantom5	Facet Differentially Expressed	T_cell	0.0001
All variants	Fantom5	Facet Expressed	T_cell	$1.2\times10^{-5*}$
All variants	Fantom5	Facet Expressed	Natural killer cells	0.0004
PS	Roadmap	H3K27ac	Adipose Tissue	0.0001
IBD	Roadmap	H3K4me3	CD3 Primary Cells	0.0009
All variants	Roadmap	H3K4me3	HUES64 Cell Line	0.0001
All variants	Roadmap	H3K4me3	Mobilized CD34 Primary Cells	0.0004
All variants	Roadmap	H3K4me3	CD56 Primary Cells	0.0004

Supplementary Table 11. Temporal comorbidity was determined for the five inflammatory diseases under study in an independent data set covering ICD10 diagnose codes from 6,631,920 diagnoses in the entire Danish population in the period from 1996 to 2014[10].

ICD-10 disease A	ICD-10 disease B	Name disease A	Name disease B	#Patients	P-value	RR	Significance ($P<1.21\times10^{-9}$)
M45	K50	Ankylosing spondylitis	Crohn's disease [regional enteritis]	155	3.39E-243	5.31	significant
M45	L40	Ankylosing spondylitis	Psoriasis	60	1.98E-149	4.75	significant
M45	K83	Ankylosing spondylitis	Other diseases of biliary tract	13	0.0380	1.23	non-significant
M45	K51	Ankylosing spondylitis	Ulcerative colitis	140	4.72E-178	3.74	significant
K50	M45	Crohn's disease [regional enteritis]	Ankylosing spondylitis	178	0	5.84	significant
K50	L40	Crohn's disease [regional enteritis]	Psoriasis	126	4.19E-119	2.28	significant
K50	K83	Crohn's disease [regional enteritis]	Other diseases of biliary tract	145	2.58E-186	2.81	significant
K50	K51	Crohn's disease [regional enteritis]	Ulcerative colitis	2404	0	11.22	significant
L40	M45	Psoriasis	Ankylosing spondylitis	73	3.14E-130	4.37	significant
L40	K50	Psoriasis	Crohn's disease [regional enteritis]	81	4.85E-09	1.32	non-significant
L40	K83	Psoriasis	Other diseases of biliary tract	31	1	0.60	non-significant
L40	K51	Psoriasis	Ulcerative colitis	141	3.76E-05	1.18	non-significant
K83	M45	Other diseases of biliary tract	Ankylosing spondylitis	9	1.68E-06	1.79	non-significant
K83	K50	Other diseases of biliary tract	Crohn's disease [regional enteritis]	79	5.18E-144	3.21	significant
K83	L40	Other diseases of biliary tract	Psoriasis	4	1	0.68	non-significant
K83	K51	Other diseases of biliary tract	Ulcerative colitis	158	0	6.43	significant
K51	M45	Ulcerative colitis	Ankylosing spondylitis	194	1.05E-187	3.54	significant
K51	K50	Ulcerative colitis	Crohn's disease [regional enteritis]	3928	0	13.99	significant
K51	L40	Ulcerative colitis	Psoriasis	127	1.73E-13	1.31	significant
K51	K83	Ulcerative colitis	Other diseases of biliary tract	373	0	4.72	significant

#Patients: Number of pairs of diagnoses with disease A followed by disease B within a 5-year time frame of disease A; **RR:** relative risk, i.e. strength of the correlation between a pair of diagnoses. K83 (Other diseases of biliary tract) includes primary sclerosing cholangitis (PSC).

Supplementary Table 12. Clinical information on comorbidity for individual patients.

Phenotype	Num. Cases	*Found in Annotations (%)	AS			IBD			PS			PSC		
			0	1	2	0	1	2	0	1	2	0	1	2
AS	8,726	8,547	-	-	-	4,900 (57.3)	403 (4.7)	3,244 (38.0)	4,910 (57.5)	508 (5.9)	3,129 (36.6)	8,547 (100)	0 (0)	0 (0)
IBD	34,598	32,586	25,485 (78.2)	330 (1.0)	6,771 (20.8)	-	-	-	26,133 (80.2)	208 (0.6)	6,245 (19.2)	25,828 (79.3)	154 (0.5)	6,604 (20.3)
PS	6,530	3,227	1,964 (60.9)	314 (9.7)	923 (28.6)	1,135 (35.2)	23 (0.7)	2,043 (63.3)	-	-	-	2,322 (72.0)	0 (0)	879 (28.0)
PSC	3,408	3,388	1,038 (30.6)	19 (0.6)	2,314 (68.3)	443 (13.1)	2,114 (62.4)	814 (24.0)	807 (23.8)	41 (1.2)	2,523 (74.5)	-	-	-

***:** Number of samples (from **Supplementary Table 1)** we could ask the corresponding principal investigator for comorbidity information; 0=Unknown, 1=comorbidity present, 2=comorbidity absent; ankylosing spondylitis (AS), Inflammatory bowel disease (IBD), psoriasis (PS) and primary sclerosing cholangitis (PSC).

Supplementary Table 13. BUHMBOX[11] power analysis. For each power simulation 1,000 iterations were performed, each with different proportions of sample heterogeneity (PI). For certain pairs (see N/A values) it is impossible to reach 80% power regardless of PI, given the cohort (disease A)-specific case sample size and the set of specific disease B risk loci (MAF and OR) in **Supplementary Table 14**. Here, the power is maximal at PI~50%. For 10 and 18 out of 20 pairs of diseases, we have >50% power to detect 10% and 20% sample heterogeneity, respectively, suggesting that the GRS association is likely due to pleiotropy for those pairs. To calculate power, we used the real effect sizes and allele frequencies of known loci, and simulated the same number of cases and controls as our sample size. The nominal significance threshold of 0.05 was used.

Cohort	Risk loci	PI (at 50%)	PI (at 80%)
AS	CD	0.07	0.10
AS	PS	0.09	0.14
AS	PSC	0.20	0.39
AS	UC	0.07	0.11
CD	AS	0.12	0.21
CD	PS	0.07	0.10
CD	PSC	0.14	0.25
CD	UC	0.05	0.08
PS	AS	0.21	0.46
PS	CD	0.05	0.08
PS	PSC	0.25	N/A
PS	UC	0.08	0.12
PSC	AS	0.34	N/A
PSC	CD	0.11	0.17
PSC	PS	0.15	0.24
PSC	UC	0.12	0.18
UC	AS	0.15	0.24
UC	CD	0.05	0.08
UC	PS	0.07	0.11
UC	PSC	0.16	0.28

PI: proportion of sample heterogeneity; N/A: Not Available.

Supplementary Table 14. Distinguishing pleiotropy and heterogeneity (BUHMBOX[11] analysis).

Cohort	Cohort size	Risk loci	#Risk loci	#Ichip risk loci	GRS *P*-value	BUHMBOX *P*-value
AS	8232	CD	139	117	3.36e-117	0.74
AS	8575	PS	35	30	8.46e-44	0.19
AS	8710	PSC	15	10	6.19e-21	0.76
AS	8277	UC	133	113	1.63e-91	0.80
CD	18601	AS	30	21	3.70e-80	0.71
CD	18855	PS	35	30	1.66e-24	0.70
CD	19025	PSC	15	10	2.55e-40	0.89
CD	18341	UC	133	113	0	0.87
PS	6509	AS	30	21	1.27e-19	0.75
PS	6451	CD	139	117	7.15e-25	0.61
PS	6511	PSC	15	10	0.0230	0.13
PS	6465	UC	133	113	2.56e-20	0.32
PSC	3377	AS	30	21	1.05e-05	0.13
PSC	3275	CD	139	117	7.01e-36	0.19
PSC	3309	PS	35	30	0.420	0.67
PSC	3283	UC	133	113	2.63e-50	0.14
UC	14173	AS	30	21	3.71e-57	0.77
UC	14020	CD	139	117	0	0.94
UC	14316	PS	35	30	0.00212	0.20
UC	14475	PSC	15	10	3.42e-92	0.48

Cohort: disease cohort; **Cohort size**: number of case samples in disease cohort (see **Methods** section); #**Risk loci:** Number of known disease B associated risk alleles from previous GWAS/Immunochip studies; **#Ichip Risk loci:** Number of known disease B associated risk alleles (from

previous GWAS/Immunochip studies) typed on Immunochip; **#GRS *P*-value:** Genetic risk score *P*-value; **#BUHMBOX *P*-value:** If significant, it indicates excessive positive correlations than expected.

Supplementary Table 15. Immunochip-wide coheritability analysis. Each disease cohort has a disjoint control cohort. Controls were randomly split into two groups (see also **Supplementary Figure 11**).

a) Estimates excluding MHC SNPs from genetic relationship matrix

Trait 1	Trait 2	SNP-h2 trait 1	s.e.	SNP-h2 trait 2	s.e.	C(G)_tr12	s.e.
AS	CD	0.313324	0.010587	0.387648	0.008315	0.038459	0.002039
AS	PS	0.311414	0.010869	0.196479	0.010073	0.013831	0.001788
AS	PSC	0.324823	0.010849	0.200807	0.011054	0.014571	0.001656
AS	UC	0.3136	0.010636	0.305861	0.009123	0.033602	0.002042
CD	PS	0.384341	0.008458	0.203334	0.010214	0.015666	0.00178
CD	PSC	0.376686	0.00841	0.214204	0.011266	0.018139	0.001637
CD	UC	0.384685	0.007959	0.293923	0.008419	0.063766	0.001964
PS	PSC	0.194907	0.010174	0.203223	0.011355	0.005831	0.001376
PS	UC	0.196578	0.010159	0.303892	0.009308	0.008229	0.001766
PSC	UC	0.211393	0.01079	0.305266	0.009091	0.030452	0.001629

Trait 1	Trait 2	rG	s.e.	LIAB_h2 trait 1	s.e.	LIAB_h2 trait 2	s.e.	LIAB_COH	s.e.	CHI_SQR_STAT	PVAL
AS	CD	0.48524	0.022997	0.168731887	0.005701333	0.129351077	0.002774564	0.071686966	0.006659028	445.2160556	7.93E-99
AS	PS	0.280237	0.03505	0.167755904	0.005855032	0.139789697	0.007166677	0.042914293	0.010520117	63.92561364	1.29E-15
AS	PSC	0.32766	0.035322	0.174996268	0.005844828	0.081681343	0.004496385	0.039174121	0.008277081	86.05107129	1.75E-20
AS	UC	0.471562	0.025609	0.169072803	0.005734242	0.108325291	0.003231048	0.063817621	0.006792826	339.0723386	1.02E-75
CD	PS	0.265922	0.029312	0.128263691	0.002822635	0.144601538	0.007263714	0.036215342	0.007824198	82.30337278	1.17E-19
CD	PSC	0.348066	0.029639	0.125712327	0.00280669	0.087116877	0.004581888	0.036425178	0.006079386	137.910112	7.63E-32
CD	UC	0.780559	0.015294	0.12837389	0.002656012	0.104104079	0.002981911	0.09023561	0.003465368	2604.769509	0
PS	PSC	0.181576	0.042088	0.13867126	0.007238536	0.082547511	0.004612308	0.019426907	0.008825912	18.61231147	1.60E-05
PS	UC	0.157911	0.033565	0.13971538	0.007220383	0.107648616	0.003297202	0.019365946	0.008068059	22.1335698	2.54E-06
PSC	UC	0.642348	0.027303	0.085997858	0.004389535	0.108116585	0.003219775	0.061938453	0.00516008	553.5030449	2.18E-122

SNP-h2: SNP-based trait heritability (genetic variation) on the observed scale (estimate and standard error). **C(G)_tr12:** (SNP-based coheritability (genetic covariance) between traits 1 and 2 (estimate and standard error). **rG:** Genetic correlation coefficient; **LIAB_h2**: Proportion of genetic variance in liability (SNP-based heritability; estimate and standard error). **LIAB_COH:** Proportion of genetic covariance in liability between diseases (SNP-based coheritability; estimate and standard error); **CHI_SQR_STAT:** Approximated $\chi 2$ test statistic (estimate/s.e.)[12] was used to test whether estimates were significantly different from zero.

b) Estimates including MHC SNPs from genetic relationship matrix

Trait 1	Trait 2	SNP-h2 trait 1	s.e.	SNP-h2 trait 2	s.e.	C(G)_tr12	s.e.
AS	CD	0.607864	0.008127	0.395896	0.008436	0.018641	0.002003
AS	PS	0.604359	0.00816	0.269043	0.010387	0.008369	0.001826
AS	PSC	0.606925	0.008143	0.243822	0.011304	0.00625	0.001664
AS	UC	0.606463	0.008144	0.330379	0.009255	0.017436	0.002034
CD	PS	0.39212	0.008479	0.27769	0.010443	0.01566	0.001836
CD	PSC	0.386301	0.008431	0.255168	0.011338	0.016333	0.001652
CD	UC	0.393416	0.007996	0.326327	0.008557	0.064567	0.00202
PS	PSC	0.178871	0.001948	0.135062	0.001553	0.00408	0.001428
PS	UC	0.273021	0.010409	0.332998	0.009274	0.006149	0.001839
PSC	UC	0.259351	0.010962	0.329989	0.009092	0.030851	0.001661

Trait 1	Trait 2	rG	s.e.	LIAB_T1_h2	LIAB_T1_h2_se	LIAB_T2_h2	LIAB_T2_h2_se	LIAB_COH	LIAB_COH_SE	CHI_SQR_STAT	PVAL
AS	CD	0.184047	0.019432	0.327348176	0.004376569	0.132103284	0.00281494	0.038272824	0.007920185	89.7062045	2.76E-21
AS	PS	0.116772	0.025335	0.325562726	0.004395718	0.191417096	0.00739008	0.029150527	0.012396089	21.24396709	4.04E-06
AS	PSC	0.104906	0.027794	0.326976876	0.004386988	0.099178358	0.004598076	0.018891537	0.009810115	14.24618401	0.000160386
AS	UC	0.186522	0.021448	0.326965558	0.004390717	0.117008711	0.003277798	0.036482968	0.008222483	75.62868083	3.42E-18
CD	PS	0.228812	0.026154	0.130859728	0.002829643	0.197480014	0.007426568	0.036782681	0.008240599	76.53874831	2.16E-18
CD	PSC	0.289314	0.027931	0.128921165	0.002813698	0.103776957	0.00461117	0.033464322	0.006332207	107.2916514	3.84E-25
CD	UC	0.740193	0.015473	0.131287527	0.002668359	0.115581196	0.003030789	0.091180149	0.00373582	2288.447198	0
PS	PSC	0.100619	0.034934	0.127262063	0.001385951	0.054861074	0.000630816	0.008407398	0.005721185	8.295897199	0.003973474
PS	UC	0.097363	0.028984	0.194046296	0.007398068	0.117958926	0.003285158	0.014730315	0.008594735	11.2842124	0.00078169
PSC	UC	0.576805	0.025402	0.105507895	0.004459507	0.116872772	0.003220129	0.064051332	0.005528701	515.611042	3.81E-114

SNP-h2: SNP-based trait heritability (genetic variation) on the observed scale (estimate and standard error). **C(G)_tr12:** (SNP-based coheritability (genetic covariance) between traits 1 and 2 (estimate and standard error). **rG:** Genetic correlation coefficient; **LIAB_h2**: Proportion of genetic variance in liability (SNP-based heritability; estimate and standard error). **LIAB_COH:** Proportion of genetic covariance in liability between diseases (SNP-based coheritability; estimate and standard error); **CHI_SQR_STAT:** Approximated $\chi 2$ test statistic (estimate/s.e.)[12] was used to test whether estimates were significantly different from zero.

Supplementary Table 16. Tracy-Widom statistics[13] were computed to evaluate the statistical significance of each principal component identified by PCA. The top seven axes of variation are significant ($P<0.05$).

Eigenvector	Eigenvalue	TW p-value
1	71.023013	0
2	34.287195	0
3	16.598979	0
4	12.681529	0
5	12.040553	0
6	9.319227	4.89e-153
7	8.952494	3.75e-56
8	8.135447	1
9	8.083592	1
10	7.858132	1
…	…	…

Supplementary Table 17. Results from Conjunctional False Discovery Rate analysis. The 111 pleiotropic loci for Crohn's diseases(CD) and ulcerative colitis (UC) identified by the conjunction FDR method, with conjFDR ≤ 0.05.

Loci	LeadingSNP	Chr	Pos	Genes	Min conjFDR	P_CD	Z_CD	P_UC	Z_UC
1	rs11804831	1	1194804	*UBE2J2*	1.47E-02	7.66E-03	2.65E+00	1.28E-03	3.19E+00
2	*rs3766606	1	8022197	*PARK7*	4.07E-03	1.83E-03	-3.08E+00	4.70E-05	-4.04E+00
3	rs7523119	1	33766706	*AL513327.1/ZNF362*	1.69E-02	9.55E-04	3.28E+00	1.05E-02	2.53E+00
4	*rs10889669	1	67675728	*IL23R/C1orf141*	6.08E-09	3.20E-37	1.27E+01	4.64E-03	2.81E+00
5	rs12734559	1	101563001	*DPH5/S1PR1*	2.19E-02	8.80E-03	2.57E+00	3.93E-11	6.59E+00
6	*rs4845604	1	151801680	*RORC*	**3.36E-02**	1.87E-02	-2.31E+00	9.59E-03	2.56E+00
7	rs11264305	1	155033572	*ADAM15/EFNA4/EFNA3*	**4.20E-02**	1.16E-04	-3.83E+00	1.26E-21	-9.53E+00
8	*rs201651973	1	161472789	*FCGR2A*	6.07E-04	2.32E-04	3.67E+00	1.04E-05	-4.37E+00
9	rs12740041	1	197814607	*C1orf53/DENND1B*	2.30E-03	7.97E-04	3.33E+00	4.92E-03	2.79E+00
10	*rs55838263	1	200874728	*C1orf106*	8.20E-09	1.13E-09	-6.08E+00	1.47E-02	-2.39E+00
11	rs823096	1	205679887	*AC119673.1/NUCKS1*	**3.55E-02**	6.32E-03	2.70E+00	1.13E-02	2.45E+00
12	*rs3024493	1	206943968	*IL10*	4.30E-07	9.37E-08	5.31E+00	1.66E-04	-3.74E+00
13	rs6752378	2	25150116	*ADCY3/DNAJC27/DNMT3A*	5.66E-03	5.25E-07	4.98E+00	5.62E-14	7.50E+00
14	*rs925255	2	28614794	*FOSL2/AC104695.3/RP11-373D23.2*	**4.20E-02**	3.63E-08	-5.49E+00	4.35E-04	3.49E+00
15	*rs72788875	2	43456430	*THADA/AC010883.5/ZFP36L2*	1.17E-02	7.83E-04	3.34E+00	8.43E-04	-3.30E+00
16	*rs55776317	2	61191995	*PUS10*	3.48E-07	7.57E-08	5.36E+00	5.39E-11	-6.54E+00
17	*rs4671663	2	65661534	*AC074391.1/SPRED2*	1.69E-02	9.34E-04	3.29E+00	7.93E-03	2.61E+00
18	*rs11123902	2	102610642	*IL1R2*	4.07E-03	2.19E-03	-2.40E+00	9.53E-03	2.55E+00
19	rs728700	2	164577569	*FIGN*	**4.36E-02**	2.69E-02	-2.18E+00	4.46E-14	7.52E+00
20	rs74961493	2	185670496	*ZNF804A*	**2.92E-02**	1.11E-03	3.24E+00	4.26E-08	-5.45E+00
21	rs113646228	2	199564311	*AC019330.1*	2.19E-02	7.47E-03	2.64E+00	6.07E-03	2.70E+00
22	rs13023604	2	207413402	*ADAM23*	1.33E-02	3.24E-03	2.90E+00	6.61E-03	-2.67E+00
23	*rs3749171	2	241569692	*GPR35*	1.14E-03	5.58E-04	3.43E+00	1.15E-03	3.21E+00
24	rs265318	3	10180659	*VHL/snoU13*	1.11E-02	3.03E-03	2.93E+00	1.27E-03	3.18E+00
25	rs182867	3	18613387	*AC144521.1*	1.41E-02	5.49E-07	4.98E+00	3.88E-03	2.84E+00

26	rs7646643	3	33046637	*GLB1*	**4.99E-02**	1.76E-02	2.35E+00	1.56E-02	-2.36E+00
27	rs9869542	3	45934588	*LZTFL1/CCR9*	**3.26E-02**	1.74E-02	2.34E+00	3.07E-03	2.94E+00
28	*rs3197999	3	49721532	*APEH/MST1/AC099668.5*	4.33E-08	7.45E-09	5.77E+00	4.70E-03	2.76E+00
29	rs11729849	4	16583148	*LDB2*	**4.94E-02**	2.26E-02	2.26E+00	1.18E-02	-2.47E+00
30	rs2457996	4	74856535	*PPBP/CXCL5*	1.44E-02	7.16E-03	-2.66E+00	1.40E-03	3.17E+00
31	*rs7690997	4	102715549	*BANK1*	1.17E-02	4.47E-05	4.05E+00	8.44E-09	5.74E+00
32	rs35914000	4	123355923	*ADAD1*	1.33E-03	1.34E-06	4.82E+00	1.39E-02	2.41E+00
33	*rs395157	5	38867732	*OSMR*	6.79E-03	2.39E-04	-3.64E+00	1.29E-03	3.14E+00
34	rs7734434	5	40436698	*DAB2/PTGER4*	3.79E-05	7.35E-27	1.07E+01	5.60E-03	2.74E+00
35	rs7445013	5	71697977	*PTCD2/ZNF366*	**3.61E-02**	1.83E-02	-2.33E+00	2.52E-05	-4.19E+00
36	rs304151	5	88125853	*MEF2C*	1.47E-02	7.81E-03	-2.63E+00	4.01E-03	2.84E+00
37	rs12517950	5	131731326	*SLC22A5*	2.75E-03	2.88E-17	8.44E+00	7.64E-03	-2.62E+00
38	*rs6863411	5	141513204	*NDFIP1*	**2.92E-02**	6.66E-05	-3.97E+00	1.86E-03	-3.08E+00
39	*rs12656538	5	150251380	*IRGM*	6.23E-04	3.48E-16	8.15E+00	1.06E-02	2.52E+00
40	rs56167332	5	158827769	*EBF1/IL12B/LOC285627/RNF145*	7.94E-07	1.12E-16	8.28E+00	1.62E-02	-2.37E+00
41	rs17119	6	14719496	*CD83/JARID2*	**3.50E-02**	3.62E-06	-4.60E+00	4.86E-03	2.77E+00
42	*rs4712520	6	20640871	*CDKAL1*	2.03E-02	5.88E-04	-3.39E+00	5.74E-05	-3.98E+00
43	rs7752195	6	25419094	*LRRC16A*	2.50E-02	1.32E-02	-2.44E+00	1.83E-06	4.74E+00
44	rs12214723	6	41993688	*RP11-533O20.2/CCND3*	**4.89E-02**	5.44E-03	2.72E+00	2.65E-03	2.97E+00
45	rs7767178	6	106439072	*PRDM1/PREP*	1.69E-02	2.34E-08	5.57E+00	4.37E-03	2.78E+00
46	rs77086638	6	138000793	*OLIG3/TNFAIP3*	1.55E-02	2.71E-03	-2.96E+00	1.28E-02	2.46E+00
47	*rs111305875	6	167511586	*RP11-517H2.6*	1.41E-02	1.76E-05	-4.27E+00	6.73E-06	4.48E+00
48	*rs12700762	7	26793597	*SKAP2*	1.69E-02	5.67E-05	3.99E+00	6.24E-04	-3.40E+00
49	rs4917131	7	50324652	*C7orf72/IKZF1*	3.94E-03	5.30E-04	-3.44E+00	4.06E-12	6.92E+00
50	rs2395022	7	98750379	*KPNA7/SMURF1*	1.10E-03	2.47E-04	3.63E+00	5.65E-03	2.73E+00
51	rs4730274	7	107479719	*DLD/SLC26A3*	1.44E-02	7.63E-03	-2.61E+00	1.11E-03	-3.22E+00
52	rs73238193	7	128562446	*IRF5/KCP*	1.48E-02	5.63E-03	-2.73E+00	3.08E-03	2.90E+00
53	rs2538470	7	148220448	*C7orf33/CNTNAP2*	9.78E-03	9.46E-04	3.26E+00	7.07E-04	-3.35E+00
54	rs12679874	8	27230819	*PTK2B*	1.88E-02	1.08E-02	-2.53E+00	2.13E-04	3.68E+00
55	rs200219048	8	79240357	*NoGene*	**4.75E-02**	4.27E-03	2.84E+00	1.53E-03	5.46E-01
56	rs60298754	8	89373041	*RP11-586K2.1*	**2.72E-02**	1.57E-02	2.39E+00	1.02E-03	-3.25E+00
57	rs661356	9	244457	*DOCK8*	**2.53E-02**	1.71E-03	3.11E+00	3.51E-06	4.60E+00

58	*rs62541532	9	5017384	*JAK2*	6.08E-09	3.09E-10	6.28E+00	1.27E-03	-3.19E+00
59	*rs11574914	9	34710338	*CCL21*	**2.79E-02**	3.77E-03	2.88E+00	1.37E-02	2.41E+00
60	rs7868736	9	116528183	*RGS3/ZNF618*	**2.71E-02**	3.28E-03	2.92E+00	4.74E-04	3.46E+00
61	*rs4366152	9	117564875	*TNFSF15*	3.79E-05	5.99E-07	-4.96E+00	1.09E-02	-2.51E+00
62	*rs10781499	9	139266405	*CARD9/SNAPC 4*	2.97E-07	1.99E-15	7.93E+00	1.68E-02	2.32E+00
63	rs116874444	10	30711536	*LOC729668/MA P3K8*	**3.87E-02**	2.98E-03	-2.94E+00	1.39E-02	2.42E+00
64	rs66887762	10	35330577	*CUL2*	1.33E-03	2.57E-12	6.98E+00	8.74E-05	3.90E+00
65	rs7072206	10	59925048	*IPMK/MIR3924*	**4.53E-02**	2.57E-03	-2.98E+00	1.60E-03	3.13E+00
66	rs10761659	10	64445564	*ADO/ZNF365*	7.33E-06	1.78E-15	-7.94E+00	7.57E-04	-3.34E+00
67	rs2688607	10	75663736	*C10orf55/CAMK 2G*	**4.20E-02**	2.47E-04	-3.64E+00	5.76E-03	-2.72E+00
68	*rs1892497	10	81043707	*ZMIZ1*	2.43E-02	1.75E-10	-6.37E+00	1.14E-02	-2.49E+00
69	*rs2497318	10	94432000	*EIF2S2P3*	1.33E-03	3.48E-04	-3.53E+00	6.57E-03	-2.65E+00
70	*rs6584281	10	101286480	*RP11-129J12.1/RP11-129J12.2*	6.08E-09	6.63E-13	-7.17E+00	3.93E-03	-2.83E+00
71	rs907611	11	1874072	*LSP1*	2.37E-02	1.39E-02	2.42E+00	1.54E-02	2.35E+00
72	rs10750899	11	58284951	*LPXN/OR5B21*	**4.15E-02**	2.56E-02	2.19E+00	1.44E-02	2.41E+00
73	*rs11230563	11	60776209	*CD6*	1.69E-02	2.86E-05	-4.16E+00	3.68E-03	-2.85E+00
74	rs559928	11	64150370	*PRDX5/RPS6KA4/SLC22A11/TRMT112*	3.94E-03	2.23E-04	-3.66E+00	3.98E-03	-2.83E+00
75	rs559298	11	65998757	*PACS1*	**4.43E-02**	1.94E-02	2.30E+00	7.36E-03	-2.61E+00
76	rs7126418	11	76292573	*C11orf30/LRRC 32*	1.58E-04	1.76E-17	8.49E+00	1.47E-02	2.41E+00
77	*rs56086356	11	128376476	*ETS1*	1.70E-02	5.19E-03	2.77E+00	4.27E-03	-2.81E+00
78	rs7960062	12	40822012	*RP11-115F18.1/MUC1 9*	**4.20E-02**	1.72E-04	3.72E+00	5.03E-03	2.75E+00
79	rs117084250	12	57921866	*DCTN2/MBD6*	2.22E-02	2.76E-03	-2.98E+00	1.45E-04	3.75E+00
80	*rs7969592	12	68579649	*IFNG-AS1*	4.07E-03	2.02E-03	-3.05E+00	8.68E-08	-5.30E+00
81	rs12425244	12	129880928	*TMEM132D*	1.37E-02	3.87E-03	-2.87E+00	3.22E-03	-2.91E+00
82	rs17084983	13	27528301	*GPR12/USP12*	1.41E-03	6.22E-04	3.40E+00	2.52E-03	2.96E+00
83	rs9603611	13	40330105	*COG6*	1.41E-02	9.36E-04	-3.29E+00	1.83E-03	-3.08E+00
84	rs12865253	13	58373697	*DIAPH3/PCDH1 7*	7.78E-03	3.27E-03	2.90E+00	1.47E-02	2.41E+00
85	*rs11624293	14	88488821	*LINC01146/RP1 1-300J18.1*	5.66E-03	1.62E-05	4.29E+00	2.48E-04	3.64E+00
86	rs4984246	15	63758428	*AC007950.1*	2.03E-02	6.67E-04	-3.36E+00	8.89E-03	2.57E+00
87	*rs367569	16	11365500	*TNP2/RMI2/PRM3/PRM2/SNO*	5.66E-03	1.65E-06	-4.76E+00	7.90E-03	2.63E+00

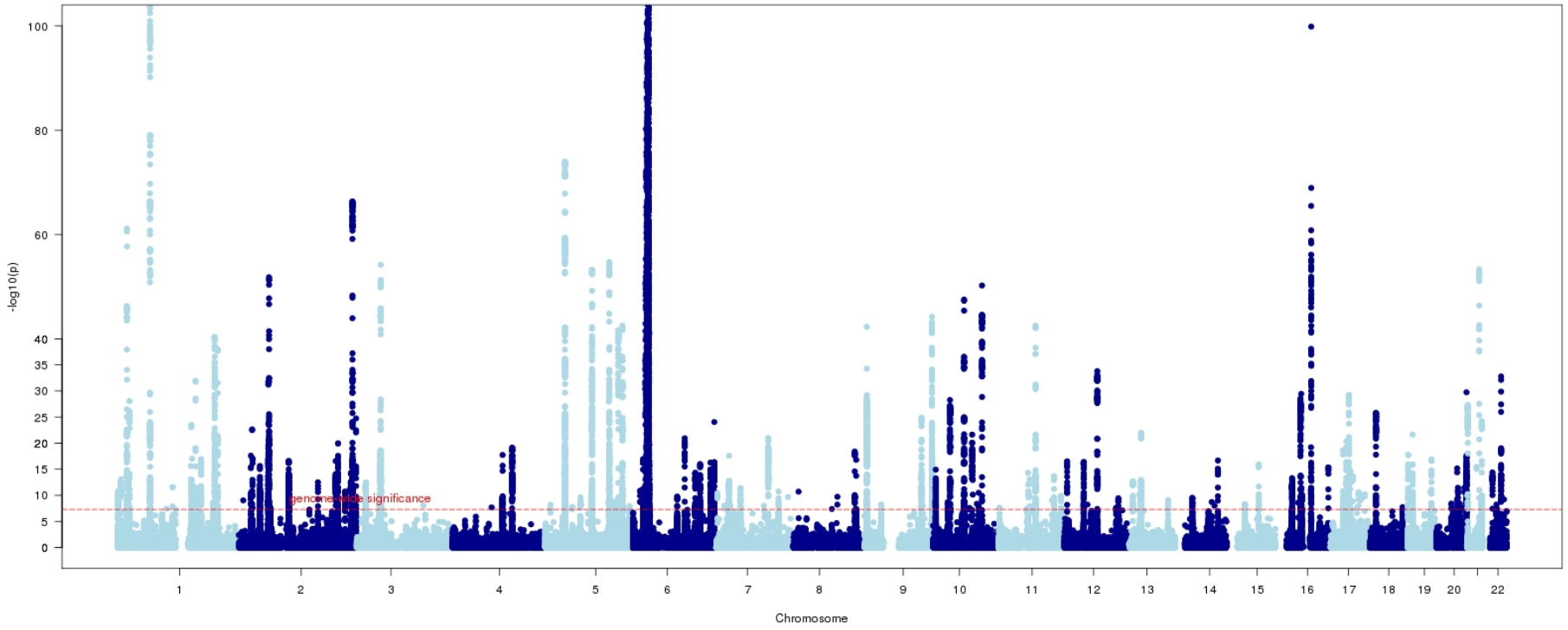
				RA48					
88	*rs7404095	16	23864590	*PRKCB*	5.66E-03	3.95E-04	-3.51E+00	5.56E-11	6.54E+00
89	rs62036620	16	28833097	*ATXN2L/RP11-1348G14.5/RP11-1348G14.4*	5.66E-03	5.52E-08	5.41E+00	8.01E-03	2.62E+00
90	rs1872691	16	50350210	*BRD7/ADCY7*	3.29E-03	3.87E-05	-4.09E+00	8.87E-03	2.57E+00
91	*rs11649485	16	86014455	*RP11-542M13.2*	**4.20E-02**	2.96E-08	-5.53E+00	2.91E-08	-5.52E+00
92	rs11870164	17	32567679	*ACCN1/CCL11/CCL2/CCL8*	4.72E-03	1.36E-07	-5.26E+00	1.38E-08	5.66E+00
93	*rs9907088	17	38035116	*ZPBP2*	2.65E-06	1.13E-08	5.69E+00	8.25E-03	-2.58E+00
94	*rs3816769	17	40498273	*STAT3*	9.10E-04	4.39E-08	-5.45E+00	1.71E-04	3.73E+00
95	*rs35153695	18	12808467	*PTPN2*	1.35E-05	7.44E-11	6.50E+00	1.24E-03	-3.16E+00
96	rs11881821	19	1111895	*SBNO2*	**2.92E-02**	5.39E-05	-4.02E+00	1.18E-02	-2.48E+00
97	*rs12720356	19	10469975	*TYK2*	9.30E-03	3.28E-03	2.91E+00	1.90E-04	3.70E+00
98	rs117755928	19	47225377	*STRN4/PRKD2*	**3.08E-02**	1.56E-02	-2.39E+00	2.63E-03	2.96E+00
99	rs59491394	19	55389375	*FCAR*	2.28E-02	1.24E-02	2.47E+00	7.99E-03	-2.57E+00
100	rs6072275	20	39743905	*TOP1/RP1-1J6.2*	**4.77E-02**	1.27E-02	2.45E+00	2.10E-03	-3.02E+00
101	*rs6031644	20	43156272	*PKIG*	1.41E-03	6.35E-04	3.39E+00	4.80E-07	-5.01E+00
102	*rs259964	20	57824309	*ZNF831*	3.29E-03	7.24E-05	3.94E+00	1.53E-02	-2.36E+00
103	*rs6062496	20	62329099	*RTEL1-TNFRSF6B/ARFRP1/RTEL1/TNFRSF6B*	1.44E-06	3.11E-09	-5.91E+00	1.49E-02	-2.40E+00
104	rs2823286	21	16817938	*NRIP1/USP25*	6.23E-04	3.95E-11	-6.59E+00	7.91E-03	-2.63E+00
105	rs4817988	21	40468838	*ETS2/PSMG1*	1.71E-04	7.03E-05	-3.95E+00	2.10E-04	-3.66E+00
106	rs1893592	21	43855067	*UBASH3A*	5.66E-03	7.54E-04	-3.35E+00	8.06E-03	2.60E+00
107	*rs4456788	21	45616324	*AP001057.1*	1.71E-04	5.99E-05	3.99E+00	8.09E-03	2.61E+00
108	*rs12484550	22	21941915	*UBE2L3*	**2.92E-02**	1.60E-04	3.73E+00	9.47E-13	-7.12E+00
109	rs1076137	22	30223991	*ASCC2*	1.21E-02	5.74E-03	2.74E+00	2.70E-03	2.96E+00
110	*rs2143178	22	39660829	*AL031590.1*	1.35E-05	1.23E-12	-7.09E+00	7.92E-03	2.61E+00
111	rs12172195	22	45813687	*RIBC2/SMC1B*	1.60E-02	7.87E-03	-2.60E+00	2.81E-04	3.59E+00

The locus number (loci), leading SNP (LeadingSNP), chromosome number (Chr), genomic position (Pos), gene symbols (Genes), minimum conjFDR value (Min conjFDR), *P-values* for CD (P_CD), Z scores for CD (Z_CD), *P-values* for UC (P_UC) and Z scores for UC (Z_UC) were listed in columns from left to the right. SNPs in the extended MHC region were removed before the analysis. Loci identified by the subset-based meta-analysis method were

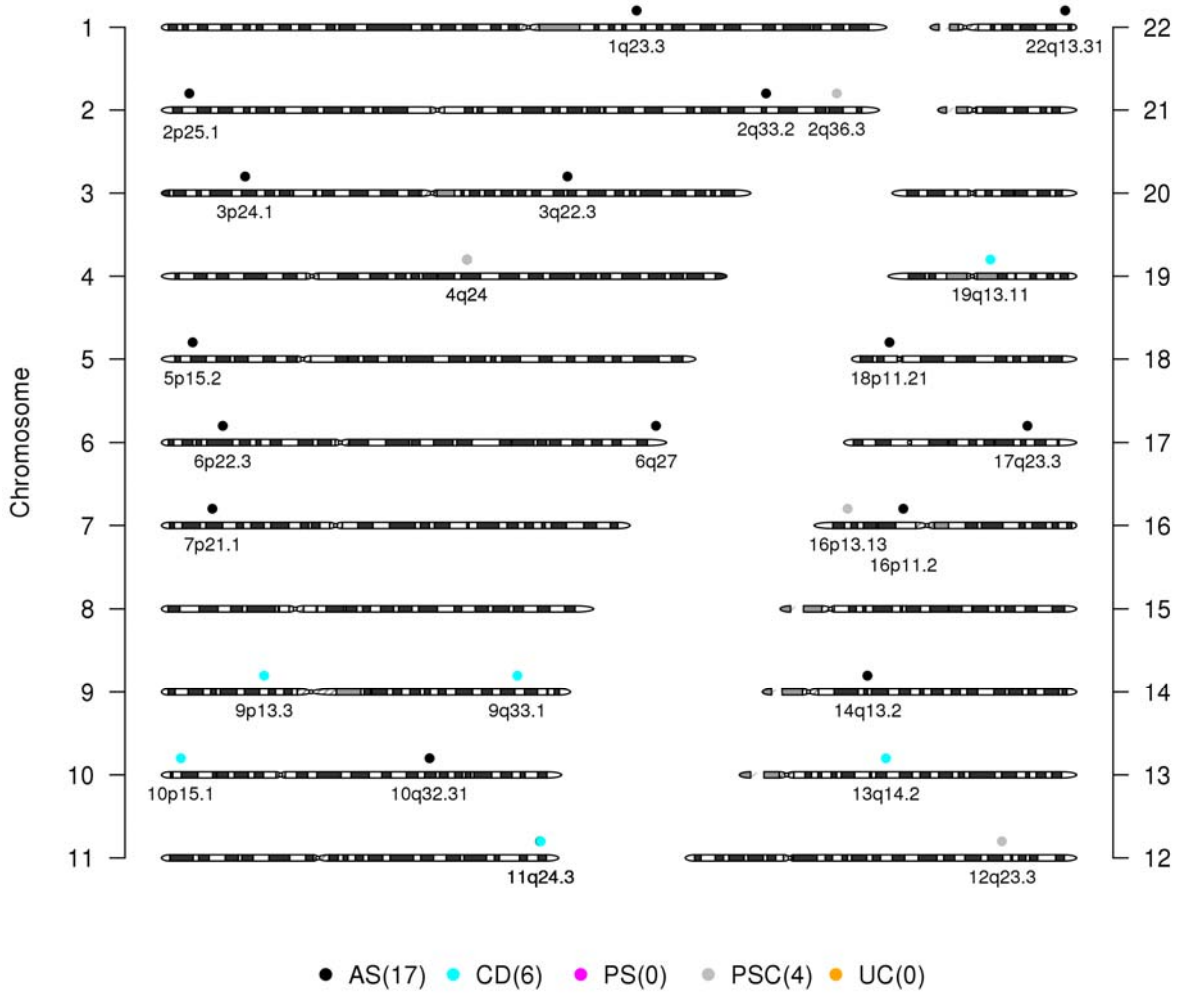
marked by stars to the leading SNPs. The minimum conjFDR value above the expected FDR (0.025) from Liley and Wallace model[14] are marked by bold font.

Supplementary Figures

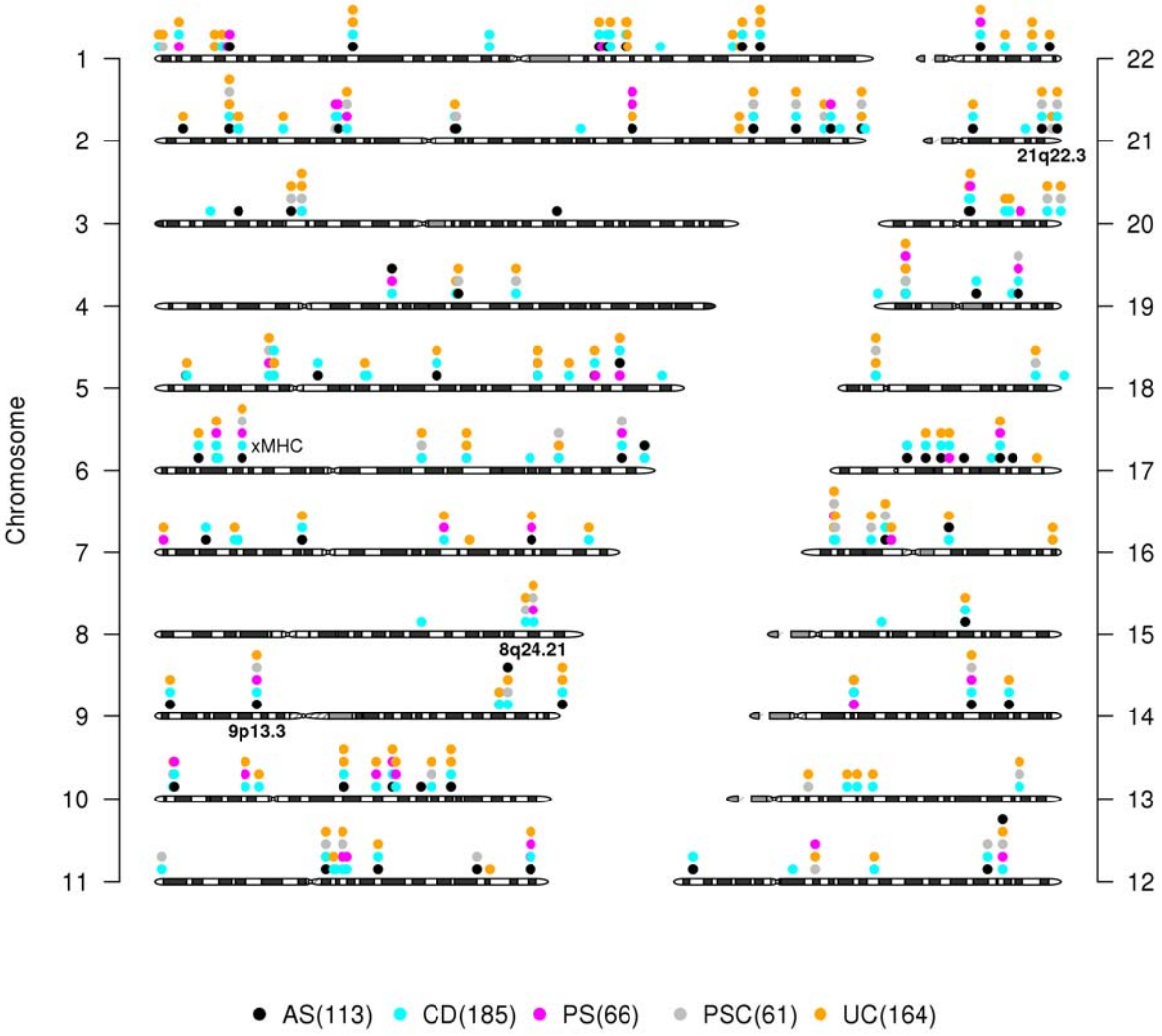
Supplementary Figure 1. Manhattan plot of Immunochip subset-based meta-analysis (SBM) association statistics (P_{SBM}) of 130,052 SNPs. Red horizontal line indicates a genome-wide significance threshold of 5×10^{-8}. SNPs within 166 non-MHC risk loci achieve the genome-wide significance threshold for association in the combined analysis of ankylosing spondylitis (AS), Crohn's disease (CD) psoriasis (PS) and primary sclerosing cholangitis (PSC) and ulcerative colitis (UC) QCed Immunochip data (**Supplementary** Table **1**). Association P_{SBM} values at chr1p31.3 (*IL23R*) and chromosome 6 region at 25–34 Mb, encompassing the HLA region, fall below $P_{SBM}=1\times10^{-100}$.



Supplementary Figure 2. Ideogram summary plot of the 27 newly identified single disease association with genome-wide significance ($P_{disease}<5\times10^{-8}$).



Supplementary Figure 3. Ideogram summary plot of the 169 genome-wide significant non-MHC risk loci from cross-disease subset-based association meta-analysis (SBM) of ankylosing spondylitis (AS), Crohn's disease (CD) psoriasis (PS) and primary sclerosing cholangitis (PSC) and ulcerative colitis (UC). By performing primary SBM analyses, we identified 166 genome-wide significant non-MHC loci ($P_{SBM}<5\times10^{-8}$). 3 out of 166 loci (bold type loci: rs2042011 at 8q24.21; rs2812378 at 9p13.3; rs1893592 at 21q22.3) have not been reported previously for any of the five diseases and thus are new gws shared risk loci. Further by performing single disease analyses on any SNPs that achieved $P_{SBM}<5x10^{-7}$ in the primary SBM analysis, we identified 27 novel genome-wide significant disease associations ($P_{disease}<5\times10^{-8}$; see **Figure 1** and **Supplementary Fig. 2**). 24 out of these 27 associations were also genome-wide significant in the primary SBM analyses ($P_{SBM}<5\times10^{-8}$). The remaining three associations had $5\times10^{-8}<=P_{SBM}<5\times10^{-7}$ and $P_{disease}<5\times10^{-8}$ thus leading to a total of 169 non-MHC risk loci. Using subset-based stepwise regression (see **Methods**), we identified 244 independent association signals within the 169 non-MHC risk loci (for summary statistics see **Supplementary Table 3a**), with 187 signals (not necessarily restricted to genome-wide significance in individual disease cohorts, see **Stepwise subset-based conditional logistic regression**) being shared by at least two diseases. By way of illustration, we added the major histocompatibility complex (MHC, chromosome 6 region at 25–34 Mb) which is a known susceptibility locus for AS, CD, PS, PSC and UC.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xMHC
8q24.21
9p13.3
21q22.3
AS(113)
CD(185)
PS(66)
PSC(61)
UC(164)

Supplementary Figure 4. Regional association plots for 244 independent association signals within 169 gws non-MHC risk loci ($P_{SBM}<5\times10^{-8}$ or ($P_{SBM}<5\times10^{-7}$ and $P_{disease}<5\times10^{-8}$)).

SEE PDF

Blue shaded region corresponds to locus association boundaries (**Supplementary table 3a** and **Methods**). Shown are the -$\log_{10}$ *P*-values from Immunochip analysis (P_{SBM} in **Supplementary table 3a**) with regard to the physical location of markers. **Purple circle:** lead SNP; **Other filled circles:** analyzed SNPs where the fill color corresponds to the strength of linkage disequilibrium (r^2) with the lead SNP (for color coding see legend in the upper left corner of each plot); **line:** recombination intensity (cM/Mb). Positions and gene annotations are according to NCBI's build 37 (hg19). Plots were generate using LocusZoom[15].

Supplementary Figure 5. Synthesis-View[16] plots showing the multi-disease association signals for 244 independent association signals within 169 gws non-MHC risk loci ($P_{SBM}<5\times10^{-8}$ or ($P_{SBM}<5\times10^{-7}$ and $P_{disease}<5\times10^{-8}$)).

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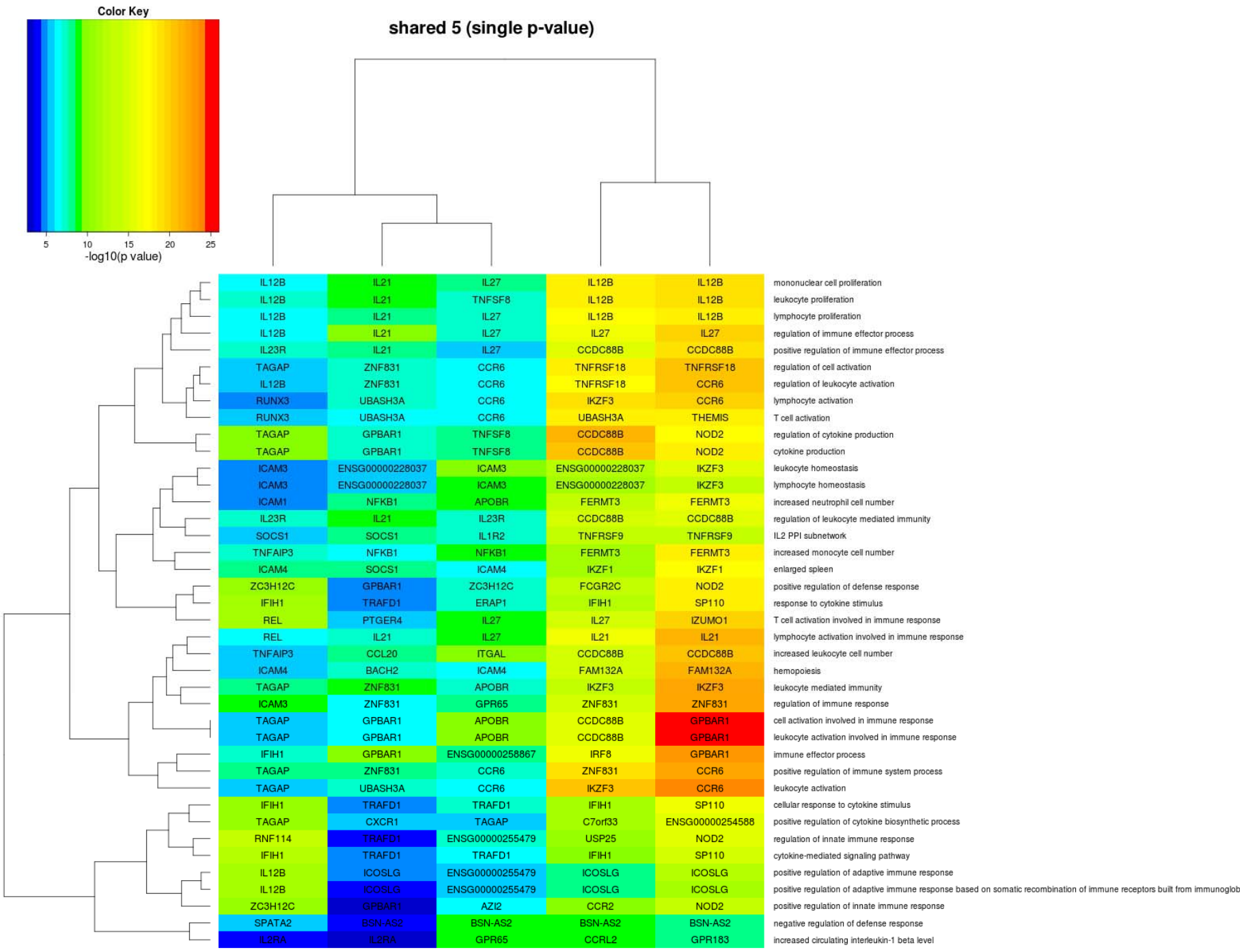
-log$_{10}$ *P*-value: -$\log_{10}$ *P*-values from Immunochip analysis (P_{SBM} in **Supplementary table 3a**) with regard to the physical location of markers; direction of triangle denotes direction of disease-individual effect; **Beta:** effect size from the five single disease vs. control subsearches (natural logarithm of OR(disease) in **Supplementary table 3a**); **OR:** odds ratio from the five single disease vs. control subsearches (OR(disease) in **Supplementary table 3a**). Large circles denote nominal significant disease-individual *P*-values ($P_{disease}<0.05$); **CAF cases/controls:** case/control minor allele frequency.

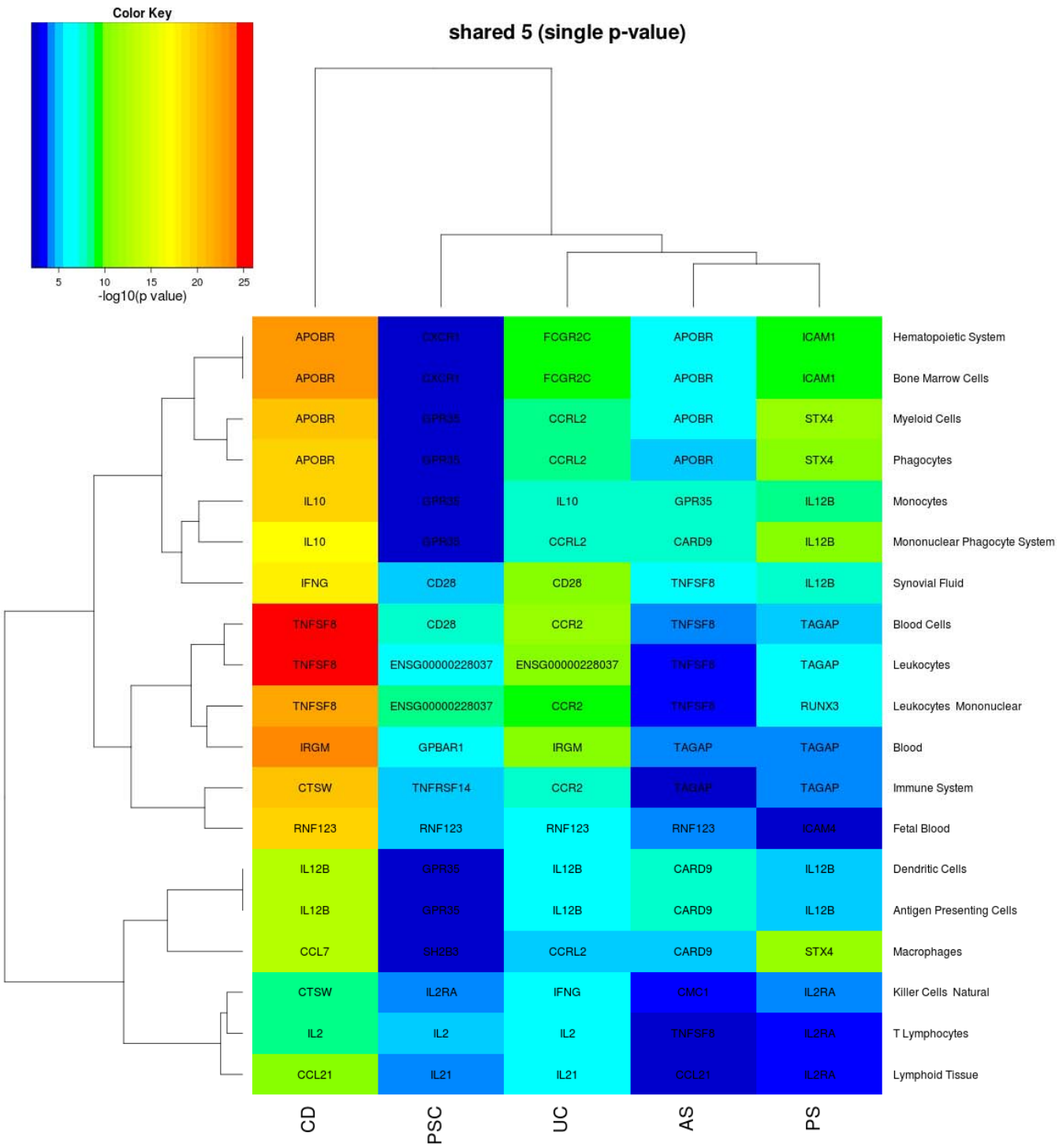
Supplementary Figure 6. Pair-wise comparisons of variance explained per risk variant between ankylosing spondylitis (AS), Crohn's disease (CD) psoriasis (PS) and primary sclerosing cholangitis (PSC) and ulcerative colitis (UC) for a maximum of 244 independent signals from 169 risk loci. Each plot shows the comparison of variance between a pair of diseases (see **Methods**). The disease with the higher explained variance in total in shown on the left side. Each box represents an independently associated SNP for the given disease, if the locus is associated with disease. The size of each box is proportional to the amount of variance explained in disease liability for that variant. Per disease, only SNPs having the disease among the best disease set are included (see columns PHENO_SBM_RISK and PHENO_SBM_PROTECTIVE in **Supplementary Table 3a**). The colors of the boxes denote whether the difference in variance explained is due to different direction of effect (risk versus protective), significant heterogeneity of odds ratios (P<0.01) or both.

SEE PDF

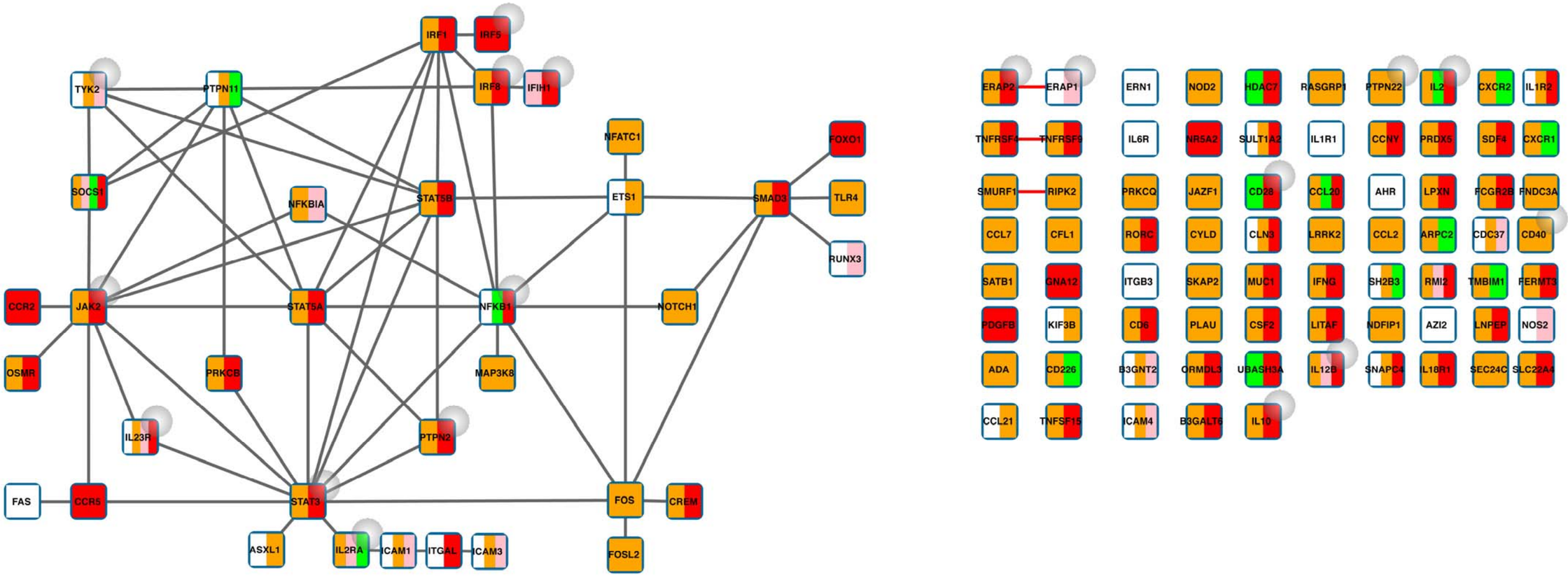
Supplementary Figure 7. Gene set enrichment analyses using precomputed gene sets reconstituted in DEPICT[17]. DEPICT was run on SNP lists of each of the five diseases (**Supplementary Table 14**) separately. DEPICT performs enrichment tests for tissues and gene sets. For every tissue and every gene set we checked how many diseases were significantly enriched for that tissue or geneset. Results were separated into groups based on number of phenotype being involved, i.e. shared5, shared4, shared3, shared2 and non-shared, respectively. Shared5 shows the top 10 gene sets (pathways) or tissue/cell types that are significantly enriched (FDR adjusted *P*-values $P_{FDR}<0.05$) in all 5 diseases (i.e. AS, CD, PS, PSC and UC). The top 10 gene sets ordered by nominal P-value are: (1) positive regulation of immune system process, GO:0002684 (2) increased monocyte cell number, MP:0000220 (3) regulation of cytokine production, GO:0001817 (4) cytokine production, GO:0001816 (5) leukocyte activation, GO:0045321 (6) regulation of defense response, GO:0031347 (7) cytokine metabolic process, GO:0042107 (8) immune effector process, GO:0002252 (9) increased leukocyte cell number, MP:0000218 (10) regulation of immune response, GO:0050776



Supplementary Figure 8. Tissue/cell type enrichment analyses using precomputed gene sets reconstituted in DEPICT[17]. DEPICT was run on SNP lists of each of the five diseases (**Supplementary Table 14**) separately. Results were separated into groups based on number of phenotype being involved, i.e. shared5, shared4, shared3, shared2 and non-shared, respectively. Shared5 shows the top 10 gene sets (pathways) or tissue/cell types that are significantly enriched (FDR adjusted *P*-values P_{FDR}<0.05) in all 5 diseases (i.e. AS, CD, PS, PSC and UC). The top 10 cell types/tissues (MeSH terms) ordered by nominal P-value are: (1) Bone Marrow Cells, A15.378.316 (2) Hematopoietic System, A15.378 (3) Blood Cells, A15.145.229 (4) Leukocytes, A11.118.637 (5) Blood, A15.145 (6) Myeloid Cells, A11.627 (7) Phagocytes, A15.382.680 (8) Synovial Fluid, A02.835.583.443.800.800 (9) Monocytes, A15.378.316.580 (10) Leukocytes Mononuclear, A15.145.229.637.555

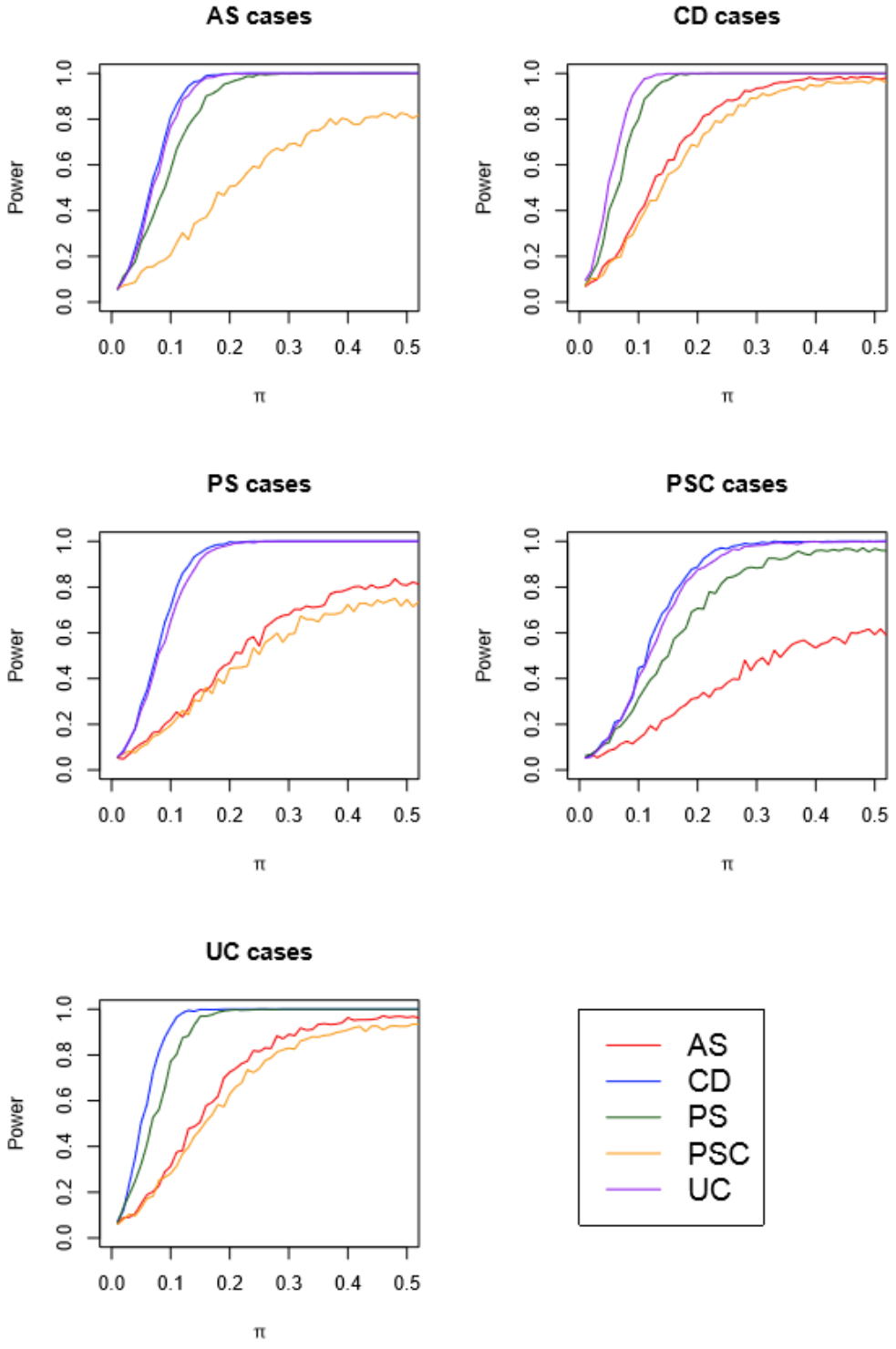


Supplementary Figure 9. Protein-protein-interaction (PPI) network based on five prioritized gene sets from AS, CD, PS, PSC and UC SNP sets, respectively, from DEPICT analyses. DEPICT performs gene prioritization and gene set enrichment based on these reconstituted gene sets (see **Methods**). The PPI reference database ConsensusPathDB (CPDB)[18] was filtered for interactions with >95% confidence and prioritized genes from DEPICT analyses on AS, CD, PS, PSC SNP sets (see **Methods**). This resulted in a network of 111 nodes and 65 edges.

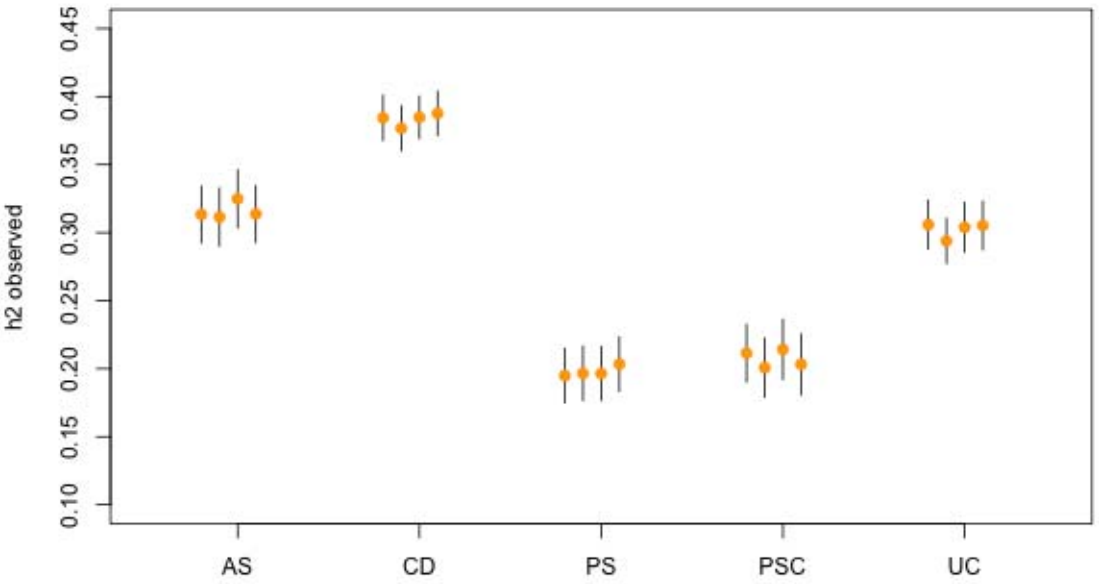


White: AS; Orange: CD; Pink: PS; Green: PSC; Red: UC; grey circles: Genes listed in Parkes *et al.* [19]

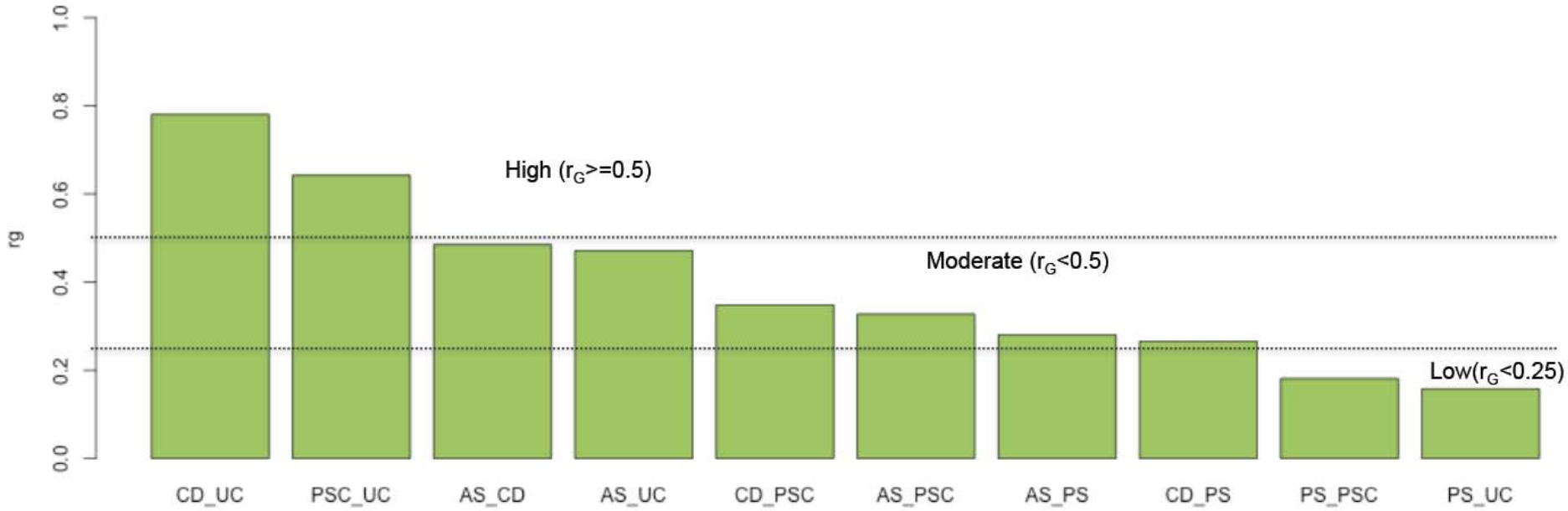
Supplementary Figure 10. Statistical power analysis of BUHMBOX[11]. For each power simulation 1,000 iterations were performed. To calculate power, we used the real effect sizes and allele frequencies of known loci, and simulated the same number of cases and controls as our sample size. The nominal significance threshold of 0.05 was used. Pi(π) indicates the heterogeneity proportion (proportion of disease A cases that has genetic characteristics of disease B).



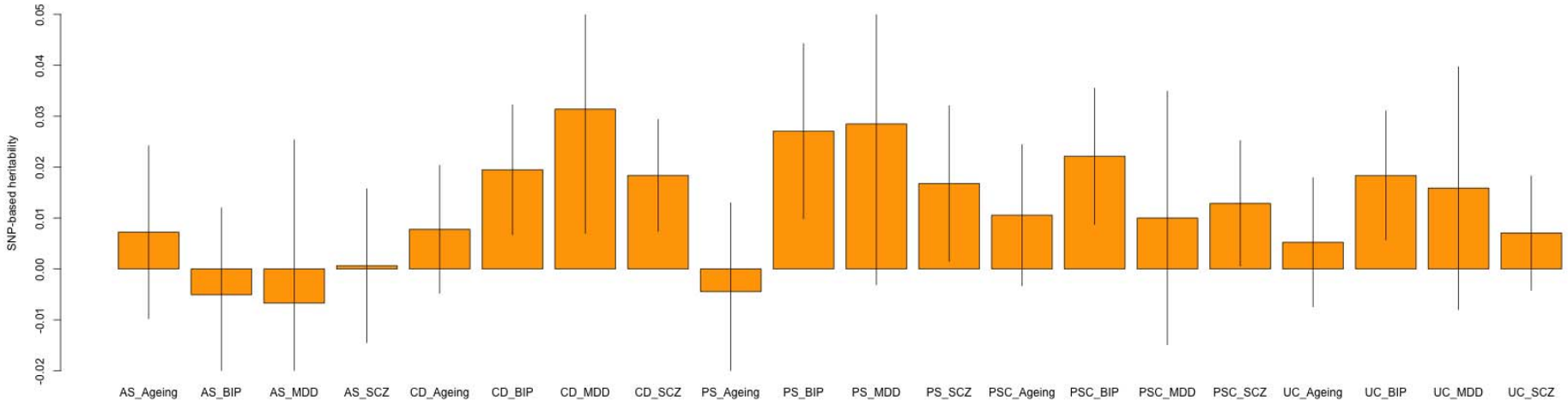
Supplementary Figure 11. Estimates of SNP-h^2 in the observed scale for different control splits. For each bivariate analysis controls were split into two groups at random.



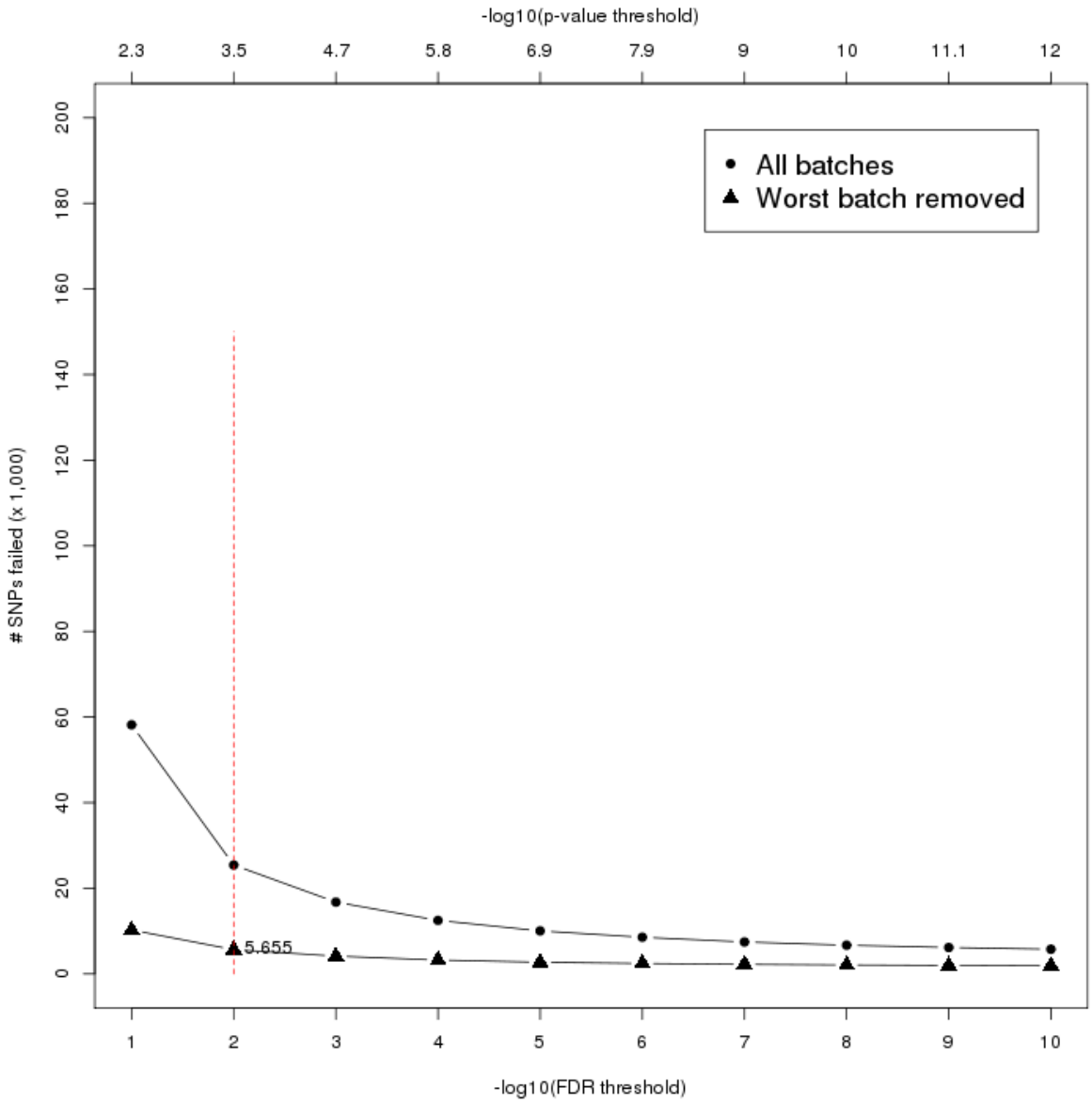
Supplementary Figure 12. Estimation of Immunochip-wide pleiotropy excluding the MHC region. Genetic and residual variances for the traits were estimated as well as the genetic covariance and the genetic correlation rG (see **Supplementary Table 15**).



Supplementary Figure 13. Negative control coheritability analysis (on liability scale with 95% error bars) between each disease under study and longevity, Bipolar disease, Major depressive disorder and Schizophrenia Immunochip studies. For longevity (ageing), bipolar disorder (BIP), major depressive disorder (MDD) and schizophrenia (SCZ) studies we assumed prevalences of 0.01, 0.01, 0.15 and 0.01[12].



Supplementary Figure 14. Test for difference in the mean allele frequencies (after correcting for population stratification) across different batches from a particular disease or the control group. Allele dosages were regressed against top 7 principle components from principle component analyses (PCA) (see **Methods**) and residuals were obtained. *P* values were calculated from the ANOVA between the residuals of the genotypes and the batches. The null hypothesis is that all groups from a particular disease or from the group are simply random samples of the same population. Variants that had significantly different allele frequencies across the batches within phenotypic sets with a false discovery rate (FDR) threshold of 0.01 were removed. Variants that only failed one quality control criterion in a single batch were set to missing in the failed batch.



Supplementary Figure 15. Variants that failure the Hardy-Weinberg equilibrium test in unaffected individuals at a false discovery rate (FDR) threshold of 10^{-5} we removed. (a) Number of variants that failed the Hardy-Weinberg test, for the sample of as a whole, with at most one batch being removed. **(b)** Number of variants that failed the Hardy-Weinberg test, within 40 individual batches, falling below the individual batch FDR threshold in two single batches. Variants that only failed one quality control criterion in a single batch were set to missing in the failed batch.

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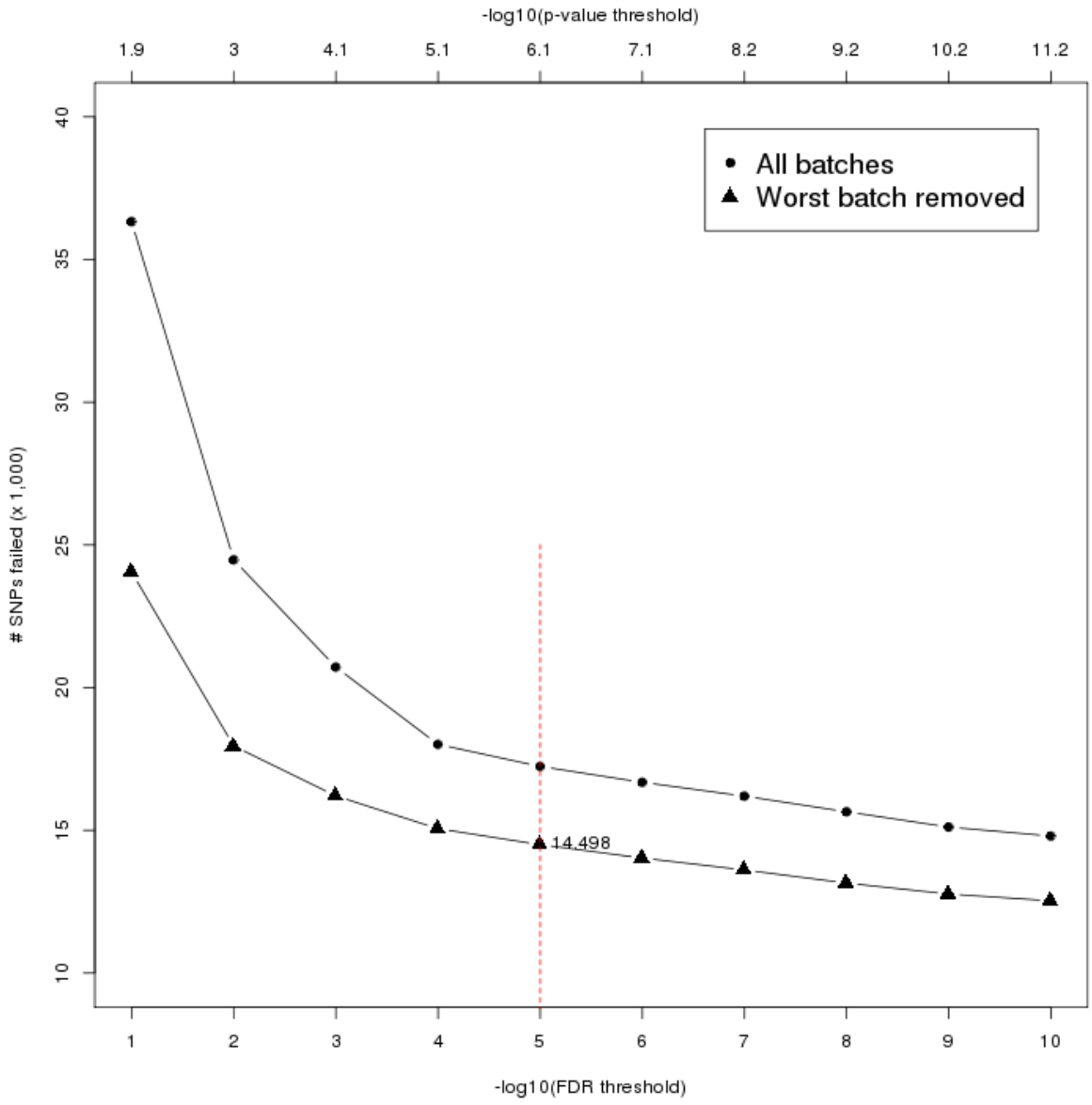

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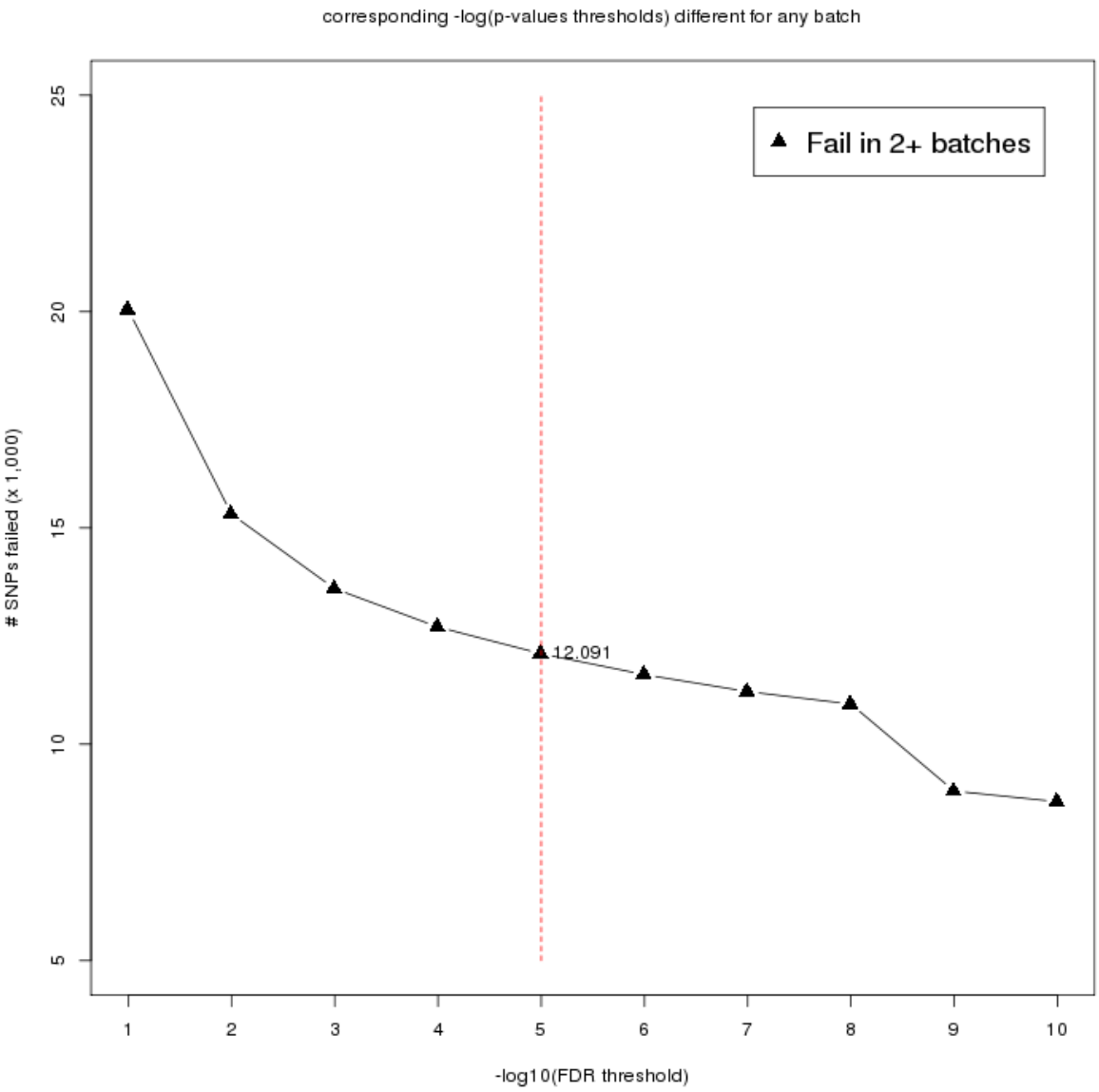
corresponding -log(p-values thresholds) different for any batch
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SNPs failed (x 1,000)
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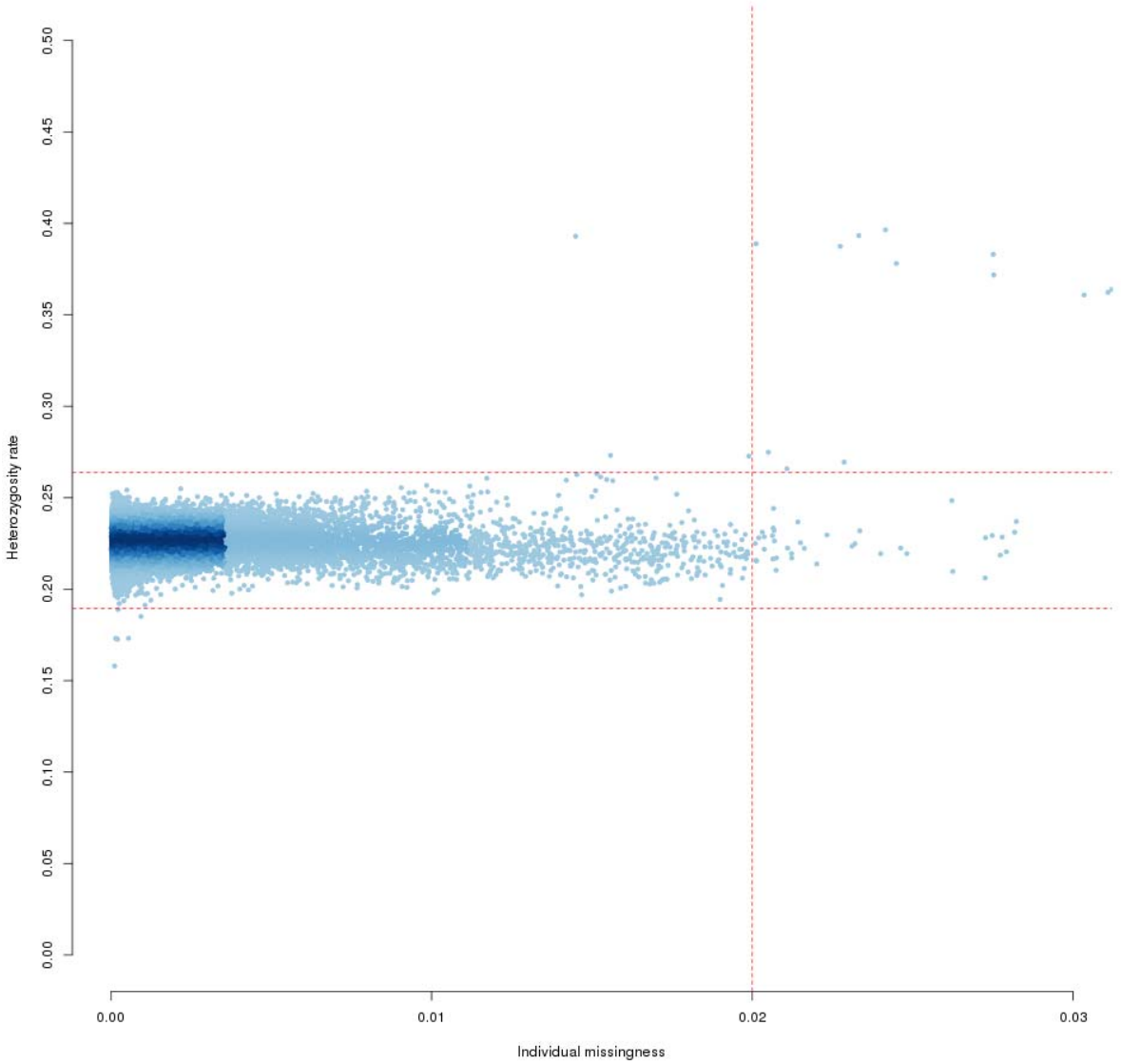
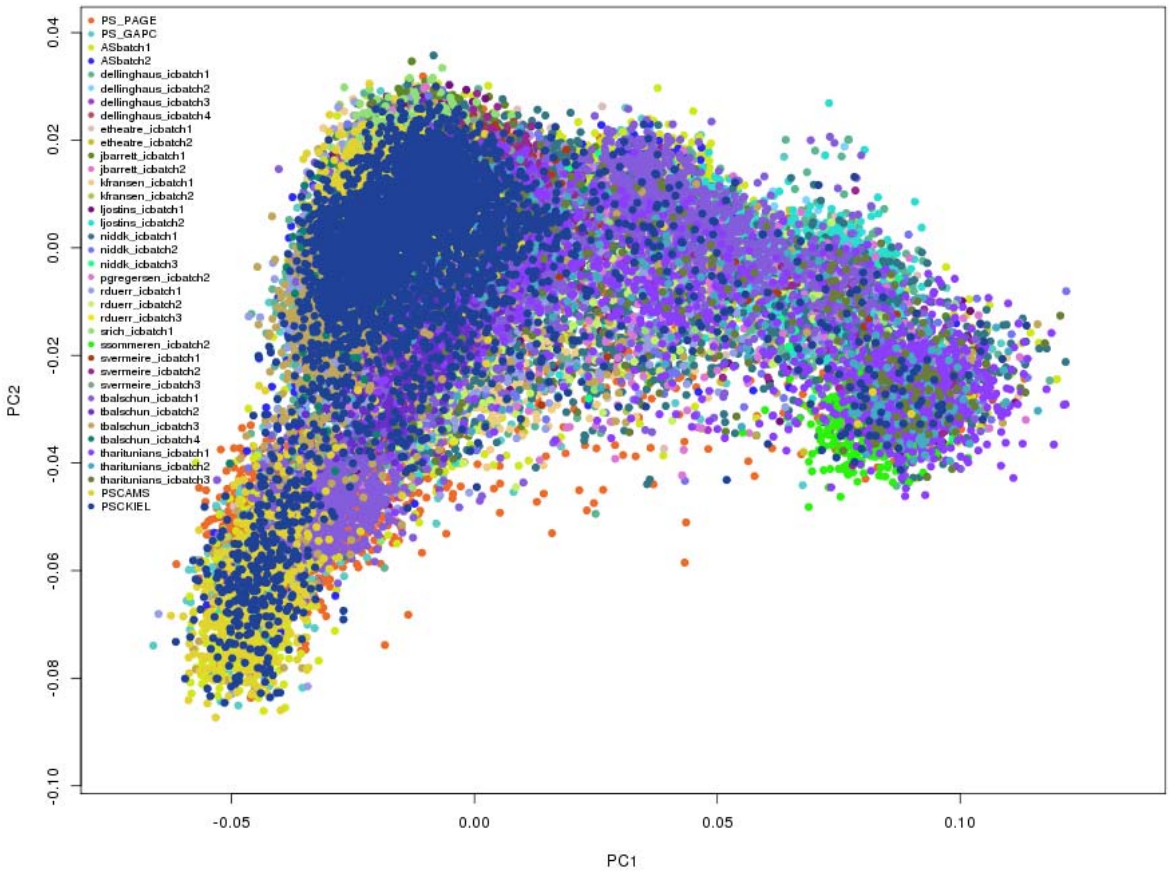
Supplementary Figure 16. Individual missing data and heterozygosity. Scatter plot of the proportion called missing (x-axis) against the proportion of SNPs called heterozygote (y-axis) for each individual in the study. 1,676 samples with >2% missing data and 51 outlier samples with an average marker heterozygosity of ±5 s.d. away from the sample mean were excluded.



Supplementary Figure 17. Principal component analysis of QCed Immunochip data. (a) All Immunochip samples are plotted on the first two principal components colored by batch code. (b) Principal component pairs for the first four PCs. (c) Distribution of cases and controls along the first ten principal component stratified by phenotype. For the psoriasis data set (the blue curve), there is an overrepresenation of Estonian individuals which cluster a bit far from usual Western European individuals. Tracy-Widom statistics revealed that top seven axes of variation are significant and should be used as covariates in regression analyses (see **Supplementary table 16**). AS: ankylosing spondylitis; CD: Crohns's disease; PS: psoriasis; PSC: primary sclerosing cholangitis; UC: ulcerative colitis

(a)



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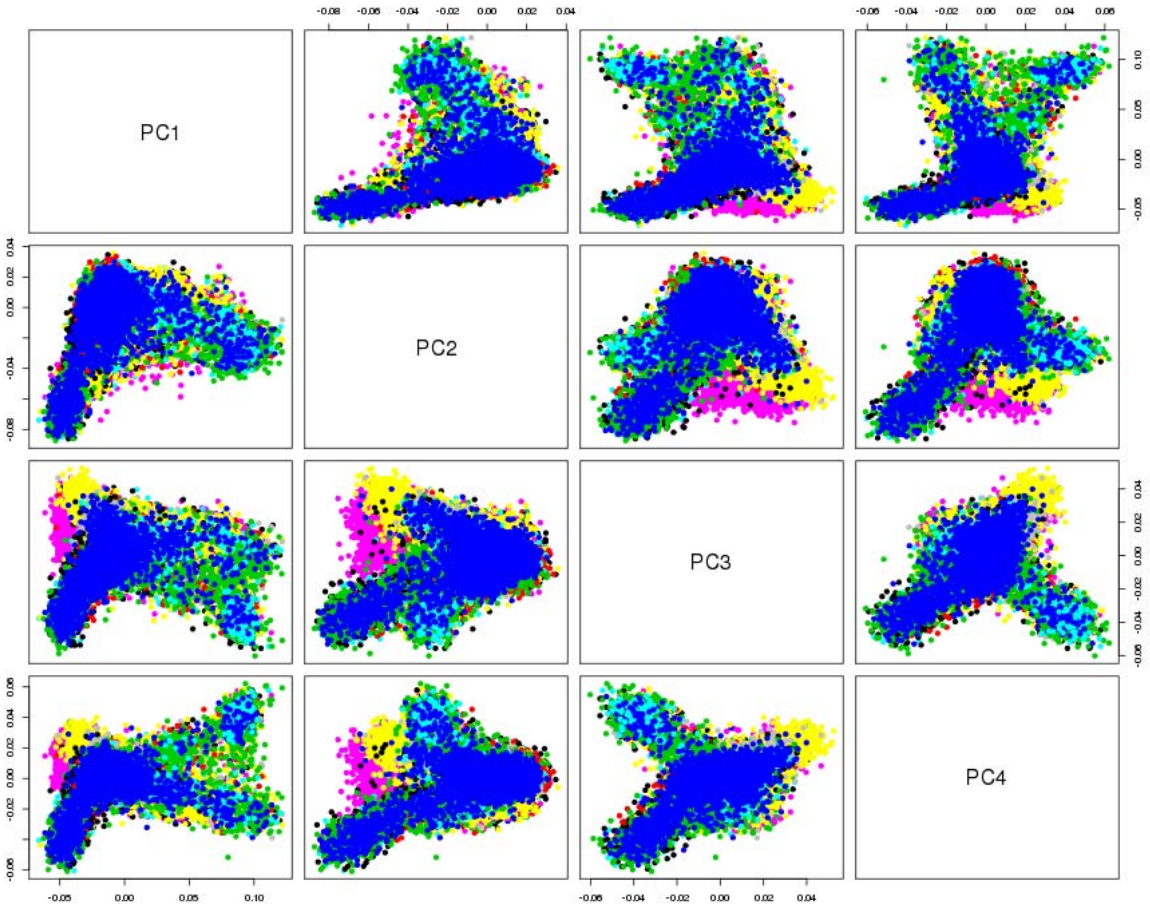

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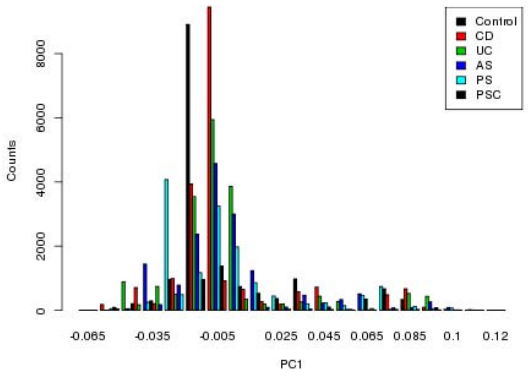
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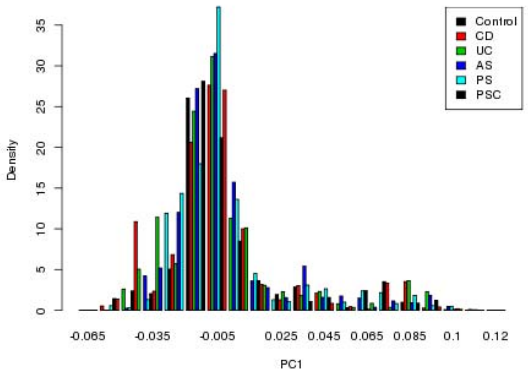
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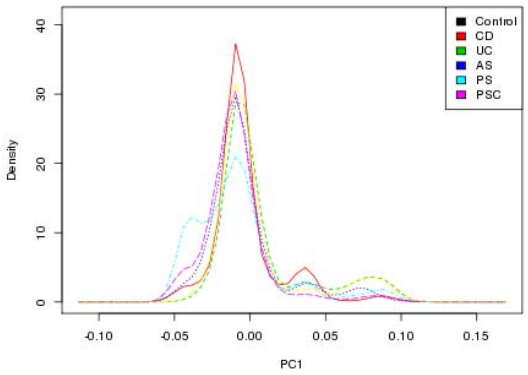
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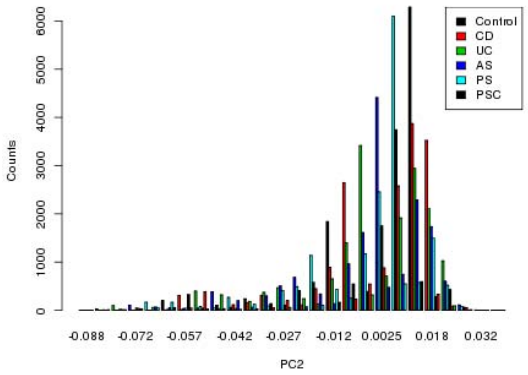
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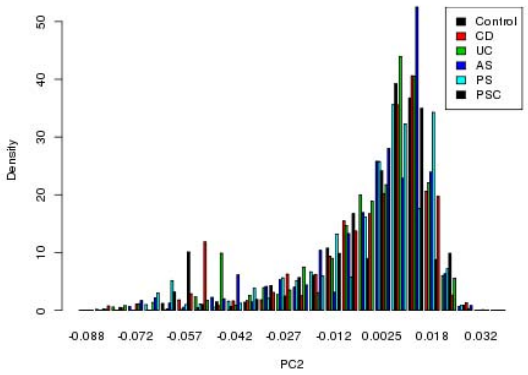
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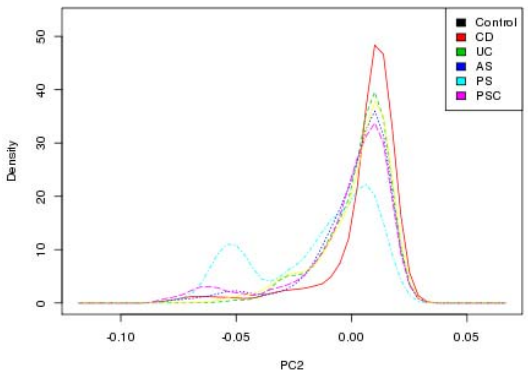
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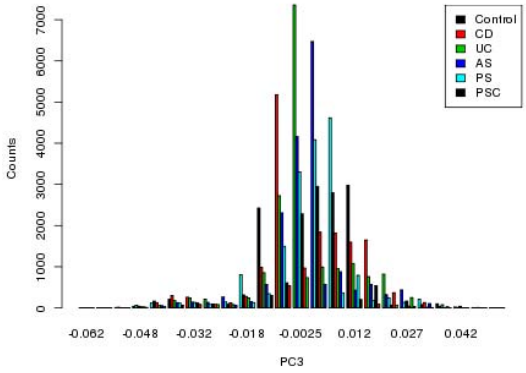
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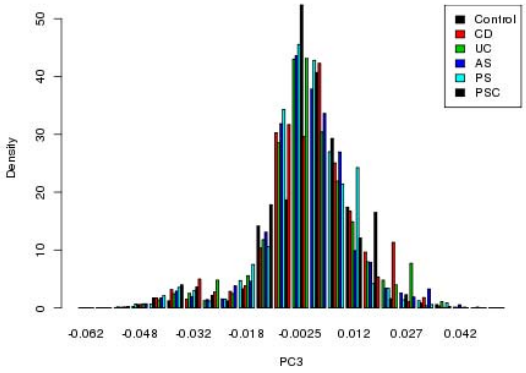
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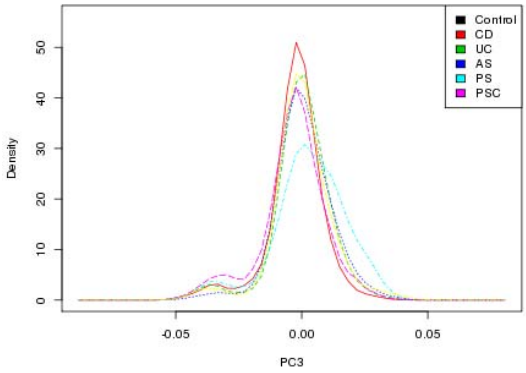
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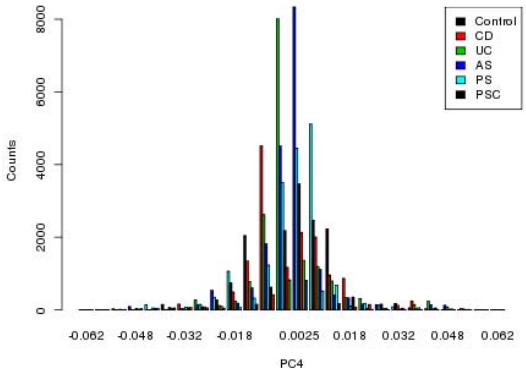
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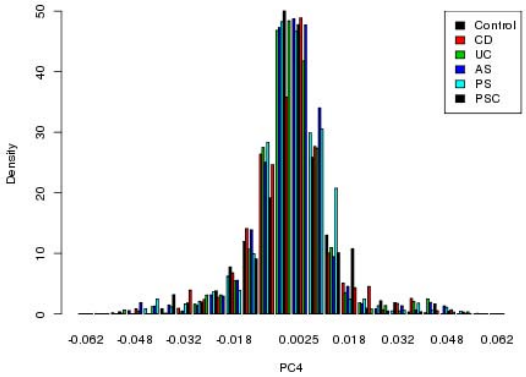
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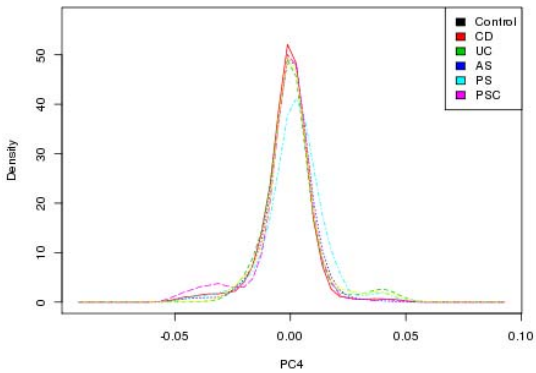
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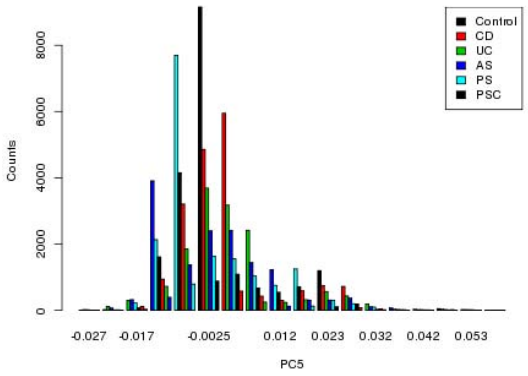
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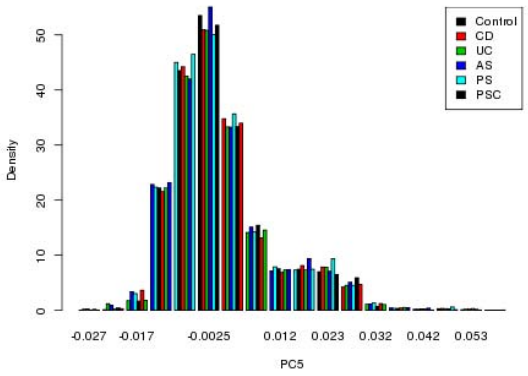
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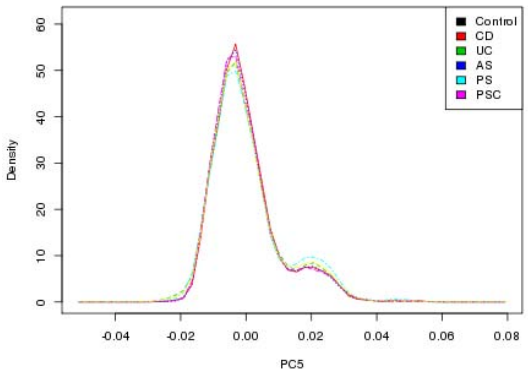
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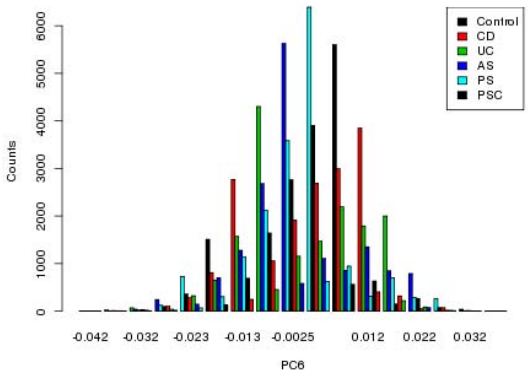
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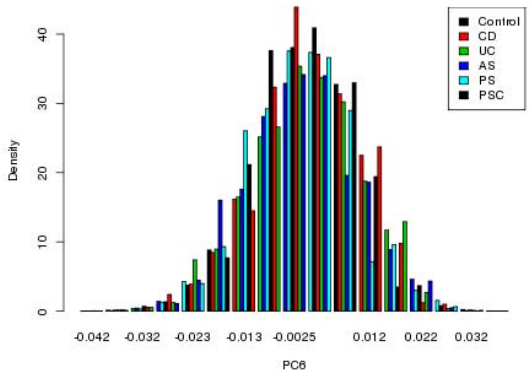
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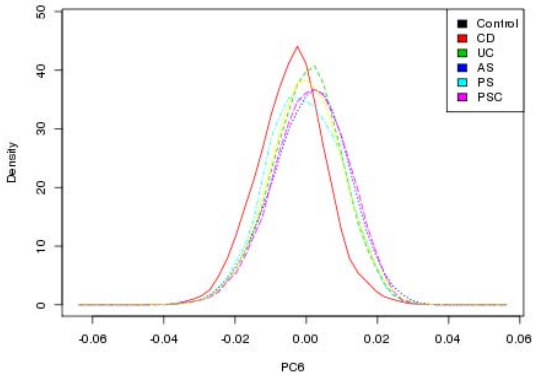
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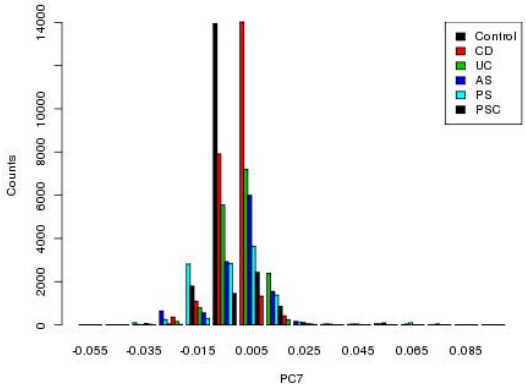
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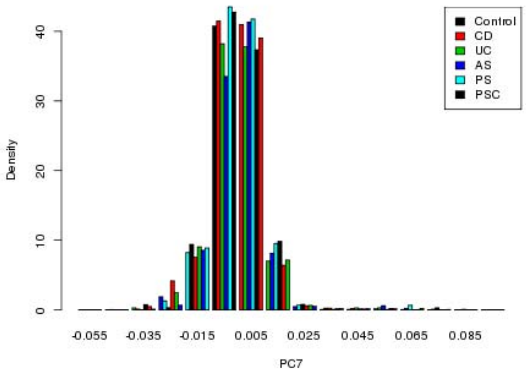
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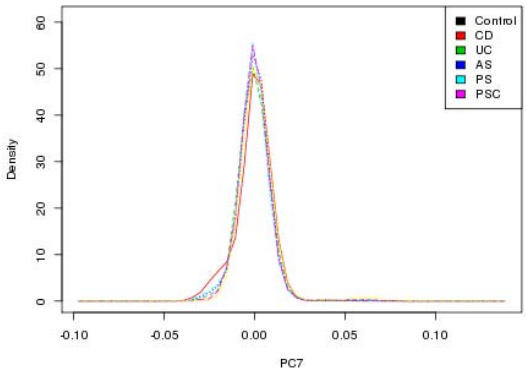
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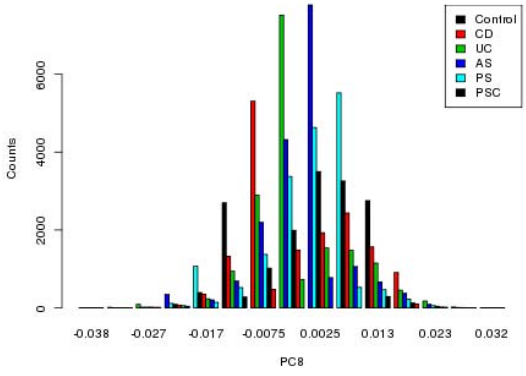
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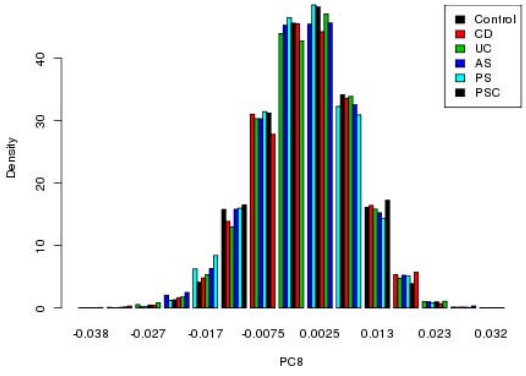
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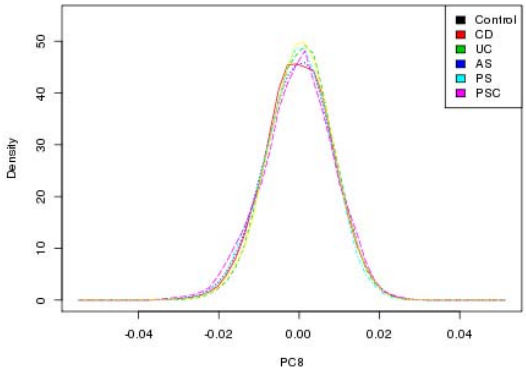
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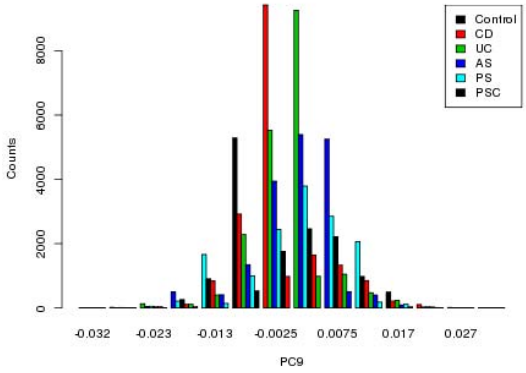
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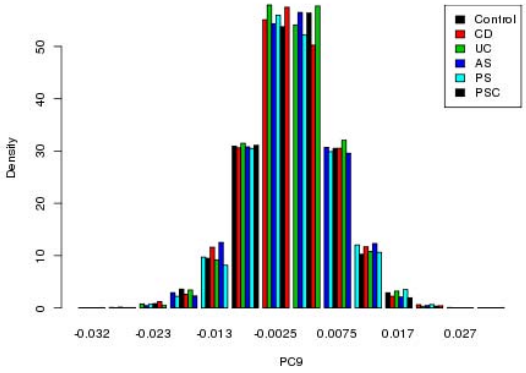
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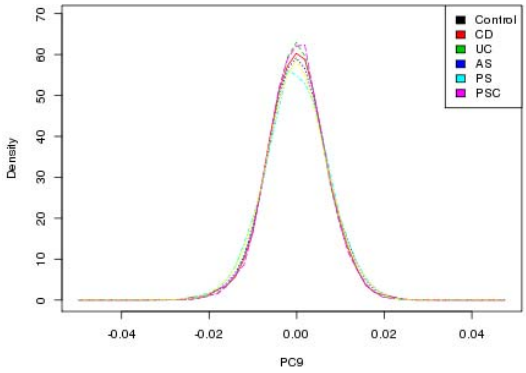
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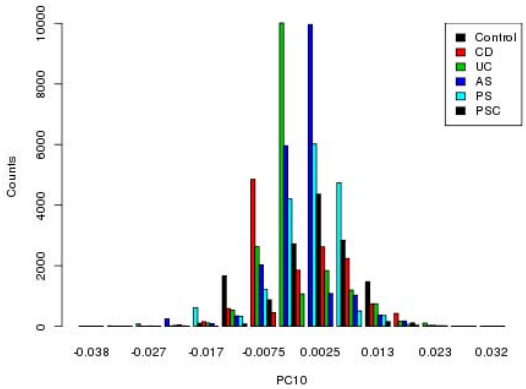
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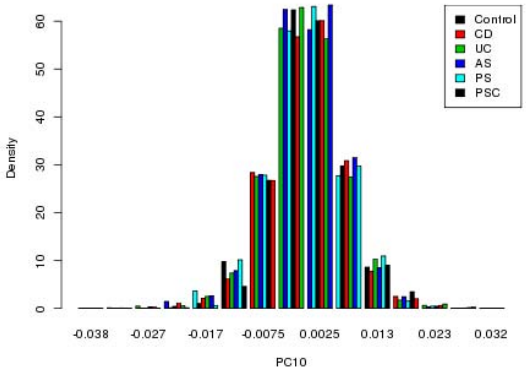
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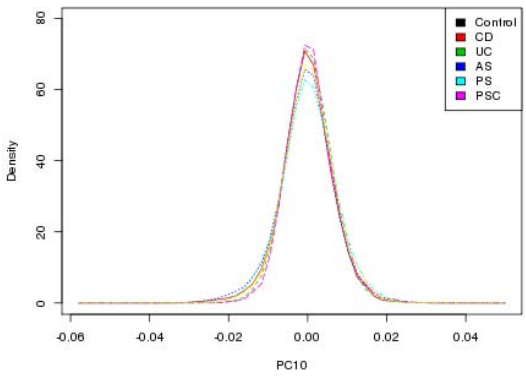
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Supplementary Note

eQTL analysis in peripheral blood

We used *cis*-eQTL data from a total of 2,360 unrelated individuals obtained from three datasets with gene expression data measured from whole peripheral blood (1,240 individuals from Fehrmann-HT12v3, 229 individuals from Fehrmann-H8v2[6] and 891 individuals from the EGCUT study[7]) as described in a previous study[20]. In summary, quality controlled genotype data was imputed using the 1000 Genomes Phase 3 (March 2013 version) cosmopolitan reference panel[21] and imputation dosage values were used for analysis. A more detailed overview of the quality control has been published elsewhere[20]. To detect cis-eQTLs, we assessed only those combinations of SNPs and probes where the distance between SNP and the midpoint of the probe was smaller than 1 megabase (Mb). Individual datasets were meta-analyzed using a Z-score method, weighted for the sample size of each dataset. The sample labels were permuted (repeated 100 times) in order to obtain the *P*-value distribution used to control the FDR at 5%. Since SNPs can be highly correlated due to LD, *cis*-eQTL effects are often caused by SNPs in high LD with the disease-associated query SNP. In order to determine whether our disease-associated SNPs have independent *cis*-eQTL effects with respect to other SNPs in their locus, we performed conditional analysis. Using the procedure described above, we first determined which SNPs show the strongest *cis*-eQTL (eSNP) effect for each of the probes associated with the 244 disease-associated SNPs (gSNP). Then, we adjusted the gene expression data for these effects using linear regression, and repeated the *cis*-eQTL analysis on the disease-associated SNPs (and vice-versa). This analysis allowed us to identify disease-associated variants that were also the best *cis*-eQTL SNP.

Gene prioritization, pathway analysis and tissue/cell type enrichment analysis

We used the analysis framework called Data-driven Expression Prioritized Integration for Complex Traits (DEPICT)[17] to determine most likely affected genes, pathways and tissue/cell types from associated loci. Based on 77,840 microarrays from two human, one rat and one mouse Affymetrix gene expression, DEPICT reconstituted 14,461 existing various pathways and gene sets[22]: 737 Reactome pathways[23], 5,083 Gene Ontology terms[24], 184 KEGG pathways[25], and 2,473 phenotypic gene sets (based on 211,882 gene-phenotype pairs from the Mouse Genetics Initiative[26]) and 5,984 molecular pathways (based on 169,810 high-confidence experimentally-derived protein-protein interactions[27]). DEPICT performs gene prioritization and gene set enrichment based on these reconstituted gene sets and three major

steps: Quantification of similarity of a given gene to genes from other associated loci across all 14,461 gene sets (gene scoring step), adjustment for inflation in gene scores caused by gene length and structure in underlying expression data through 200 pre-permuted null Immunochip GWAS (bias adjustment step), and estimation of Immunochip-wide false discovery rates (FDRs) by repeating step 1 and 2 based (20 randomized runs) based on top SNPs from precomputed null Immunochip studies. Tissue/cell type enrichment analysis utilizes 37,427 human Affymetrix HGU133a2.0 platform microarrays to examine whether genes in associated loci are highly expressed in any of 209 Medical Subject Heading (MeSH) tissue and cell type annotations[17,22].

DEPICT was run on each of the five diseases separately. The results were separated into groups based on number of phenotype being involved, i.e. shared5, shared4, shared3, shared2 and non-shared, respectively. For example, shared5 includes the top 10 gene sets (pathways) or tissue/cell types that are significantly enriched (FDR adjusted *P*-values $P_{FDR}<0.05$) in all 5 diseases (i.e. AS, CD, PS, PSC and UC) (**Supplementary Figure 7 and 8**). The "Non-shared" results depicts top 10 gene sets (pathways) or tissue/cell types significantly enriched in one disease ($P_{FDR}<0.05$) but in no other disease, thus showing disease-specific enrichments.

Enrichment analysis using GoShifter

We used the Genome Annotation Shifter (GoShifter)[28] package to test for enrichment between SNPs in associated loci and genomic annotations. Specifically, we used annotations from the Fantom5[8] and NIH Roadmap Epigenomics[9] projects to look for enrichment of expressed enhancers and histone modifications, respectively. For the Fantom5 data, groups of samples (facets) were created based on ontology terms that were mutually exclusive and cover a broad range of functional annotations. Enhancers (regions of the genome that can be bound by transcription factors to activate transcription of a gene) were identified from cap analysis of gene expression (CAGE) across samples using single molecule sequencing[8]. Facet expressed annotations are robustly expressed enhancers that were significantly expressed in each contained sample within a facet. Facet differentially expressed annotations are expressed enhancers that significantly deviate in expression between facets (Bonferroni corrected $P<0.05$)[29]. For Fantom5 data, where cell/tissue id begins 'CL' these are cell types, those beginning ' UBERON' are tissues. Cell/tissue types, enhancer types and number of facets that were tested are shown in **Supplementary Table 7.** For Roadmap annotations, we used the peak regions for the histone modifications H3K27ac, H3K4me3, H3K4me1, H3K9me3, and

H3K9ac. These marks are enriched at active promoters and enhancers or transcriptionally silent or repressed regions. Number of annotation cell types, modification type and suggested function are depicted in **Supplementary Table 8.**

The results from the association analysis where separated into groups based on phenotype (**Supplementary Table 9**). These groups were: "Shared3+" (variants that were associated with 3 or more phenotypes), variants associated with a phenotype, but not specific to that phenotype (IBD (variants associated with CD or UC), CD, UC, PSC, PS and AS) and "All variants" (all variants identified in the study regardless of phenotype). The PSC only group was not included owing to the small number of variants in this group.

GoShifter was run using default parameters, except, the number of permutations to perform was set to '10,000' and the –no-ld flag was set to 'False' in order to extend the analysis to variants in high LD with the lead variants. Peaks were called using MACS software (v2) with default parameters. For each annotation, the peak regions were used, which were called using q-value<0.001. The 1000 genomes v3 project haplotypes were used to generate LD estimates between variants in the dataset and variants in 1000 genomes, therefore SNPs that were not present in the 1000 genomes dataset were removed from this analysis.

Annotation of association boundaries

Linkage disequilibrium regions (association boundaries) around independently associated SNPs were defined by extending in both directions a distance of 0.1 centimorgans (cM).

Variance explained and heritability of single SNPs.

The proportion of variance explained by each associated association signal per population was calculated using a liability threshold model[30] assuming a disease prevalence of 0.0055, 0.001, 0.012, 0.000039, 0.001 for ankylosing spondylitis, Crohn's disease, psoriasis, primary sclerosing cholangitis and ulcerative colitis, respectively, and log-additive disease risk.

Immunochip-wide co-heritability analysis

SNP-heritabilities and SNP-coheritabilities between the five immune-mediated diseases were estimated by fitting a bivariate linear mixed model[31] as implemented in the Genome-wide Complex Trait Analysis (GCTA) tool[32]. The genetic relationship between individuals was estimated using all SNPs passing quality control and excluding SNPs located within the MHC (chr6:2800000-33000000) and having MAF<1%. Variance components were estimated correcting for population structure by fitting the top seven principal components (PCs) as fixed effects. As the bivariate analysis requires disjoint control cohorts for each of the two

diseases, these were randomly allocated to two proportions of equal size (see **Supplementary Fig. 11**). The bivariate analysis gives a simultaneous estimate of the SNP-heritability to both diseases and an estimate of the SNP-genetic correlation (single disease SNP-heritability estimates were robust to the different control partitions **Supplementary Fig. 11**). Estimates of variance components in the observed scale, case-control risk scale, were transformed to the scale of liability as described previously[32,33], for a range of assumed disease prevalence (0.0055, 0.0007, 0.012, 0.000039, 0.001 for ankylosing spondylitis, Crohn's disease, psoriasis, primary sclerosing cholangitis and ulcerative colitis, respectively).

Identification of drugs targeting genes within the core network

The Drugbank (www.drugbank.ca) is the largest publicly available database containing 7737 drugs, their protein targets and the genes encoding these protein targets[34]. First genes that have been identified within the core network (**Supplementary Fig. 9)** were linked to drugs by using an R-script, which checks synonyms of gene names by using the R package "org.Hs.eg.db" and extracts the drugs that target the proteins encoded by the candidate genes. Since the nature and effect of the interaction between the drug and the encoded protein is mostly unknown (e.g some drugs we identified have effects opposite to the what we aim for) we performed a manual literature search to assess which of the identified drugs show evidence or could potentially be promising for any of the disease under study by using PubMed (www.pubmed.gov, last search July 1st 2015) and ClinicalTrials.gov (www.clinicaltrials.gov). All drugs were selected based on evidence from phase I/II/III randomized clinical trials (RCTs) or published animal studies. We grouped the registered drugs in three ways. 1) Known drugs for any of the diseases under study : a drug is already used or has been investigated showing evidence of effect in phase 2 or 3 randomized clinical trials in the treatment of AS, PSC, PS, CD or UC . 2) Efficacy in other immune mediated diseases then AS, PSC, PS, CD or UC: a drug was investigated or used for treatment in other immune mediated disorders. 3) No published clinical evidence for efficacy in immune mediated disease but the identified drug could potentially be suited for treating AS, PSC, PS, CD or UC.

Conjunctional False Discovery Rate analysis

Conjunctional FDR: The FDR is the posterior probability of SNP association with the phenotype being null given that its *P*-value is as small or smaller than the observed one. Specifically, for a given p-value cutoff, the FDR is defined as

$$FDR(p) = \pi_0 F_0(p) / F(p), [1]$$

where π_0 is the proportion of null SNPs, F_0 is the null cdf, and F is the cdf of all SNPs, both null and non-null. Under the null hypothesis, F_0 is the cdf of the uniform distribution on the unit interval [0,1], so that Eq. [1] reduces to

$$FDR(p) = \pi_0 p / F(p), [2]$$

The cdf F can be estimated by the empirical cdf $q = \pi_p / \pi$, where π_p is the number of SNPs with p-values less than or equal to p, and N is the total number of SNPs. Replacing F by q in Eq. [2], we get

$$\text{Estimated } FDR(p) = \pi_0 p / q, [3]$$

which is biased upwards as an estimate of the FDR. Replacing π_0 in Equation [3] with unity gives an estimated FDR that is further biased upward;

$$q^* = p/q [4]$$

If π_0 is close to one, as is likely true for most GWAS, the increase in bias from Eq. [3] is minimal. The quantity 1 – p/q, is therefore biased downward, and hence is a conservative estimate of the TDR.

Conditional FDR analysis (described in detail previously [35,36]) is defined as the posterior probability that a given SNP is null for the first phenotype given that the *P*-values for the other phenotype are as small as or smaller than the observed *P*-values. We assign a conditional FDR value for the first trait (Trait1) given the *P*-values of the second trait (Trait2) (denoted by condFDRTrait1|Trait2) to each SNP by computing conditional FDR estimates on a grid and interpolating these estimates into a two-dimensional look-up table. Vice versa, we assign a conditional FDR value for the second trait given the P-values of the first trait to each SNP (denoted by condFDRTrait2|Trait1).

To identify SNPs significantly associated with both phenotypes, we used a genetic epidemiology framework based on the conjunction false discovery rate (conjFDR). We assigned the conjFDR values by interpolation into a bi-directional two-dimensional look-up table. ConjFDR, is defined as the posterior probability that a SNP is null for either phenotype or both simultaneously, given the *P*-values for both traits are as small or smaller than the observed *P*-value. A conservative estimate of the conjunction FDR is given by the maximum

statistic, i.e. the maximum of $FDR_{Trait1|Trait2}$ and $FDR_{Trait2|Trait1}$. While the condFDR can be used to reorder association of SNPs to one trait based on the additional information provided by the co-morbid secondary traits, the conjFDR pinpoints pleiotropic loci, since a low conjFDR is only possible if there is an association with the two traits of interest jointly.

Conjunctional analysis between pairs of diseases: We randomly divided the controls into each disease in a pair 10 times, proportionally to the number of cases for the disease in the pair. The program PLINK [37]was used to compute the *P-values* for associations of SNPs with each disease in each iteration, including the first 10 principal components and ethnicity as covariates. We, then, computed the bi-directional look-up table of the conjFDR for each pair of diseases and for each iteration. The averaged look-up table across 10 iterations was used to assign conjFDR to each SNP. SNPs in the extended MHC region (chr6: 25652429–33368333) were removed before analysis for all pairs.

Annotation SNPs to Genes: SNPs having conjFDR ≤ 0.05 were considered as signals of association with both diseases (pleiotropic with two diseases). We defined the genomic loci tagged by the identified SNPs by using LD $r^2 \leq 0.1$ (two SNPs having LD $r^2 > 0.1$ are considered as within one loci) and by distance 1Mb (two consecutive loci with genomic distance closer than 1Mb, were merged in one). The SNP with the lowest conjFDR value in each locus was taken as the leading SNP of the locus. Genes closest to or in the each locus were identified by the online Ensembl variant effect predictor tool based on the GRCH37 build.

Pleiotropy between pair of diseases: Since the power of the conjunctional FDR method depends on the sample sizes and the similarity of genetic architecture (mainly, polygenicity) of both diseases in a pair. We didn't find pleiotropic signals outside of the MHC region between other pairs of diseases except for CD and UC. We identified 111 independent loci pleiotropic to the CD and UC with conjFDR ≤ 0.05, which include 179 unique genes (**Supplementary Table 17**). Among the 111 independent loci, 44 overlap with the loci identified by the primary subset-based meta-analysis. There are 29 loci above the estimated expected FDR (0.025) using the recently described method[14] of which 6 overlaps with the loci identified by the primary subset-based meta-analysis.

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