Association analysis identifies 38 susceptibility loci for inflammatory bowel disease and shows pervasive sharing of genetic risk across diverse populations

Supplementary Materials

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Members of the International IBD Genetics Consortium

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Supplementary Table 4. Overlap with other diseases or traits for 38 novel loci. For each of the 38 newly identified IBD loci, this table shows whether it overlaps known GWAS loci of other diseases and phenotypes, obtained from the NHGRI GWAS Catalog.

SNP	CHR	BP_HG19/n27	Associations all other traits
rs1748195	1	63049593	Total cholesterol, LDL cholesterol, Lipid metabolism phenotypes, Triglycerides
rs34856868	1	92554283	Total cholesterol, Height, Multiple sclerosis
rs11583043	1	101466054	
rs6025	1	169519049	Activated partial thromboplastin time, D-dimer levels, Hemostatic factors and hematological phenotypes, Hippocampal atrophy, QT interval, Soluble levels of adhesion molecules, Venous thromboembolism
rs10798069	1	186875459	
rs7555082	1	198598663	Mean corpuscular hemoglobin, Red blood cell traits
rs11681525	2	145492382	Common traits (Other)
rs4664304	2	160794008	Educational attainment, Type 2 diabetes
rs3116494	2	204592021	
rs111781203	2	228660112	Pulmonary function (interaction)
rs35320439	2	242737341	
rs113010081	3	46457412	Behcets disease, Celiac disease, Monocyte chemoattractant protein-1, Obesity-related traits
rs616597	3	101569726	Multiple sclerosis
rs724016	3	141105570	Height, Prostate cancer, Red blood cell traits
rs2073505	4	3444503	Total cholesterol, Fibrinogen, LDL cholesterol, Triglycerides
rs4692386	4	26132361	Rheumatoid arthritis, Type 1 diabetes
rs6856616	4	38325036	Allergic sensitization, Helicobacter pylori serologic status, Self-reported allergy
rs2189234	4	106075498	Pulmonary function, Pulmonary function (interaction)
rs395157	5	38867732	
rs4703855	5	71693899	
rs564349	5	172324978	
rs7773324	6	382559	Basal cell carcinoma, Black vs. blond hair color, Black vs. red hair color, Chronic lymphocytic leukemia, Eye color, Freckles, Freckling, Hair color, Non-melanoma skin cancer, Progressive supranuclear palsy, Tanning
rs13204048	6	3420406	Crohns disease
rs7758080	6	149577079	Alopecia areata, Breast cancer
rs1077773	7	17442679	Caffeine consumption, Coffee consumption, HDL cholesterol, Metabolic traits
rs2538470	7	148220448	

rs17057051	8	27227554	Alzheimers disease, Alzheimers disease (late onset)
rs7011507	8	49129242	
rs3740415	10	104232716	Cardiac hypertrophy, Interstitial lung disease, Telomere length, Uterine fibroids
rs7954567	12	6491125	Ankylosing spondylitis, Coagulation factor levels, Mean platelet volume, Multiple sclerosis, Platelet counts, Primary biliary cirrhosis
rs653178	12	112007756	Alcohol consumption, Alcohol consumption Biomedical quantitative traits, Blood pressure, Celiac disease, Celiac disease and Rheumatoid arthritis, Total cholesterol, Chronic kidney disease, Coronary heart disease, Diastolic blood pressure, Drinking behavior, Esophageal cancer, Gamma glutamyl transpeptidase, Glycemic traits, HDL cholesterol, Hematocrit, Hematological and biochemical traits, Hematological parameters, Hemoglobin, LDL cholesterol, Mean platelet volume, Metabolite levels, Renal function-related traits (BUN),Renal function-related traits (sCR), Response to alcohol consumption (flushing response),Tetralogy of Fallot, Type 1 diabetes, Upper aerodigestive tract cancers, Urate levels, mean corpuscular hemoglobin concentration
rs11064881	12	120146925	
rs9525625	13	43018030	Bone mineral density, Cortical thickness, End-stage coagulation
rs3853824	17	54880993	Breast cancer, Urate levels
rs17736589	17	76737118	Retinal arteriolar caliber
rs9319943	18	56879827	
rs7236492	18	77220616	
rs727563	22	41867377	

Supplementary Table 8. Functional annotation of 38 Novel SNPs – Non-synonymous coding SNPs. Non-synonymous coding SNPs in high LD ($R^2 > 0.8$ in either European (CEU+FIN+GBR+IBS+TSI) or East Asian (CHB+CHD+JPT) 1000 Genomes Phase I samples) with a novel associated variant were identified. Functional consequences (polyPhen, PhastCons and GERP scores) were identified using functionGVS (http://snp.gs.washington.edu/SeattleSeqAnnotation134/)

	Position (hg19/GRCh37)	SNP	cSNP	R^2 Eur	R^2 Eas	Type	Gene	polyPhen score	PhastCons score	GERP score	Amino acid change	Protein position	DNA position
1	92326871	rs34856868	rs34856868	1	1	missense	BTBD8	benign	0.859	3.42	VAL,ILE	60/379	178
2	160502254	rs4664304	rs3828323	0.78	0.84	missense	PLA2R1	benign	0	-3	GLY,SER	1106/1325	3316
4	3414301	rs2073505	rs16844401	0.25	0.8	missense	HGFAC	benign	1	4.02	ARG,HIS	509/656	1526

Supplementary Table 10. Pairwise genetic correlation (r_G) between European and non-European cohorts tagged by Immunochip SNPs. r_G and SE were estimated using the bivariate linear mix model implemented in GCTA.

Phenotype	European vs.	r_G	SE	P-value (H_1: $r_G > 0$)	P-value (H_1: $r_G < 1$)
Crohn's disease	East Asian	0.76	0.04	<2.22E-16	4.47E-14
	Indian	0.56	0.09	6.58E-10	0.000343
	Iranian	0.82	0.34	0.000000506	0.357
Ulcerative colitis	East Asian	0.79	0.04	<2.22E-16	6.61E-09
	Indian	0.84	0.05	<2.22E-16	0.000823
	Iranian	0.67	0.08	2.61E-15	0.000675

Supplementary table 11a. Disease demographics in European and non-European IBD patients. Complete data available: [a]77%; [b]81%; [c]72%; [d]52%.

	CD (N=21281)			UC (N=18533)		
	European (N=19290)	**Non-European (N=1991)**	**P value**	**European (N=15838)**	**Non-European (N=2695)**	**P value**
Gender, male, n (%)	8467 (45.1%)	1325 (67.1%)	7.091E-78	7870 (52.1%)	1319 (50.4%)	0.09808
Age of diagnosis, mean (±SD)	28.39 (±14.156)	27.58 (±12.192)	0.013	34.10 (±15.776)	35.76 (±13.685)	6.203E-08
Smoking history[a], n (%)						
Never	8737 (57.3%)	376 (77.8%)		7174 (59.8%)	2102 (87.0%)	
Ex	2359 (15.5%)	49 (10.1%)	7.23E-19	3448 (28.7%)	47 (1.9%)	2.15E-180
Current	4159 (27.3%)	58 (12.0%)		1382 (11.5%)	267 (11.1%)	
Family history of IBD[b]	4438 (28.3%)	88 (5.6%)	4.783E-85	2763 (21.8%)	151 (6.2%)	2.328E-70
Primary Sclerosing Cholangitis[c]	152 (1.1%)	12 (0.8%)	0.205	374 (3.2%)	34 (1.4%)	2.84E-06
Ankylosing Spondylitis[d]	1006 (9.6%)	14 (0.9%)	1.081E-30	535 (7.0%)	12 (0.5%)	1.771E-34

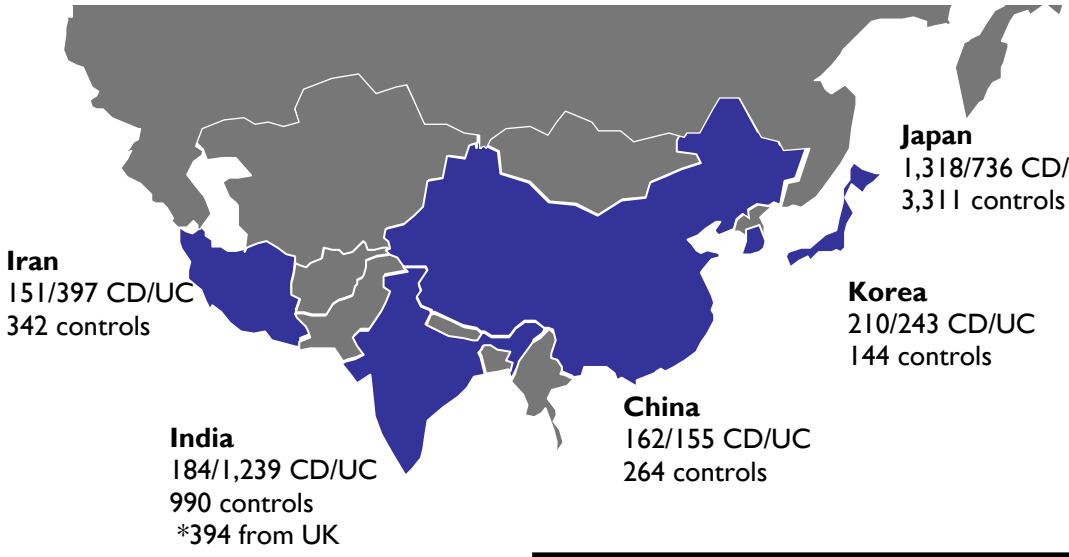
Supplementary Table 11b. Disease phenotype of IBD in European and non-European patients. Complete data available: a86%; b83% (not mutually exclusive); [c]84%; [d]84%; [e]85%; [f]82%.

Demographics	European	non-European	P value
CD location[a], n (%)			
L1 (ileal)	4,916 (29.6%)	498 (34.8%)	3.93E-05
L2 (colon)	3,921 (23.6%)	269 (18.8%)	3.47E-05
L3 (ileocolon)	7,778 (46.8%)	665 (46.4%)	0.7852
Upper gastrointestinal	1,738 (46.8%)	113 (7.3%)	8.693E-10
CD behavior[b], n (%)			
B1 (Inflammatory)	7,478 (46.4%)	408 (29.9%)	4.279E-32
B2 (Stricturing)	4,453 (27.6%)	587 (43.0%)	2.738E-33
B3 (Penetrating)	4,174 (25.9%)	393 (28.8%)	0.02034
B1p (Perianal) [c]	4,516 (27.8%)	663 (42.1%)	5.355E-33
UC location[d], n (%)			
E1 (Proctitis)	1,726 (12.9%)	285 (14.2%)	0.11
E2 (Left sided)	5,097 (38.2%)	1,033 (51.6%)	4.655E-30
E3 (Extensive)	6.526 (48.9%)	686(34.2%)	1.522E-34
Surgery, n (%)			
CD (abdominal surgery)[e]	8,656 (52.8%)	728 (48.1%)	5.42E-04
UC (colectomy)[f]	2,385 (18.5%)	100 (4.1%)	1.229E-69

Supplementary Table 12. Per-population Immunochip cohorts

Per-population Immunochip cohorts				
Population	**CD**	**UC**	**Controls**	**Total**
European	17897	13768	33977	65642
East Asian	1690	1134	3719	6543
Indian	184	1239	990	2413
Iranian	151	397	342	890

Supplementary Figure 1: Map depicting the origin of the samples in the non-European cohort



Total non European 9,846
2,025 Crohn's Disease
2,770 Ulcerative colitis
5,051 Healthy controls

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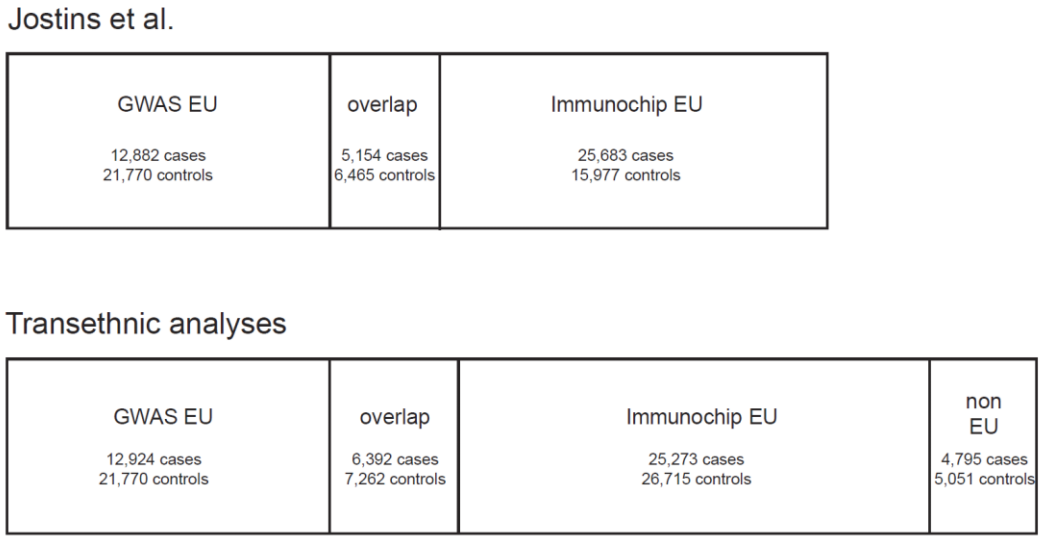
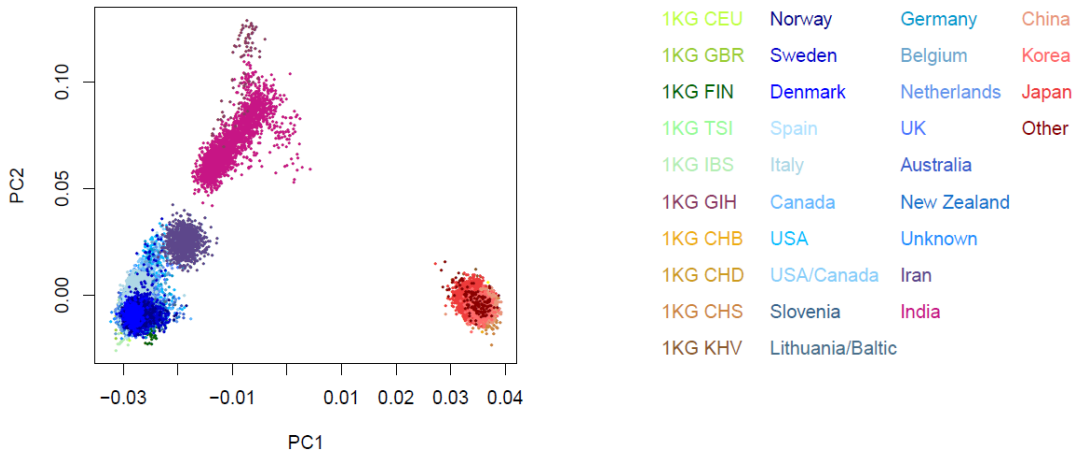
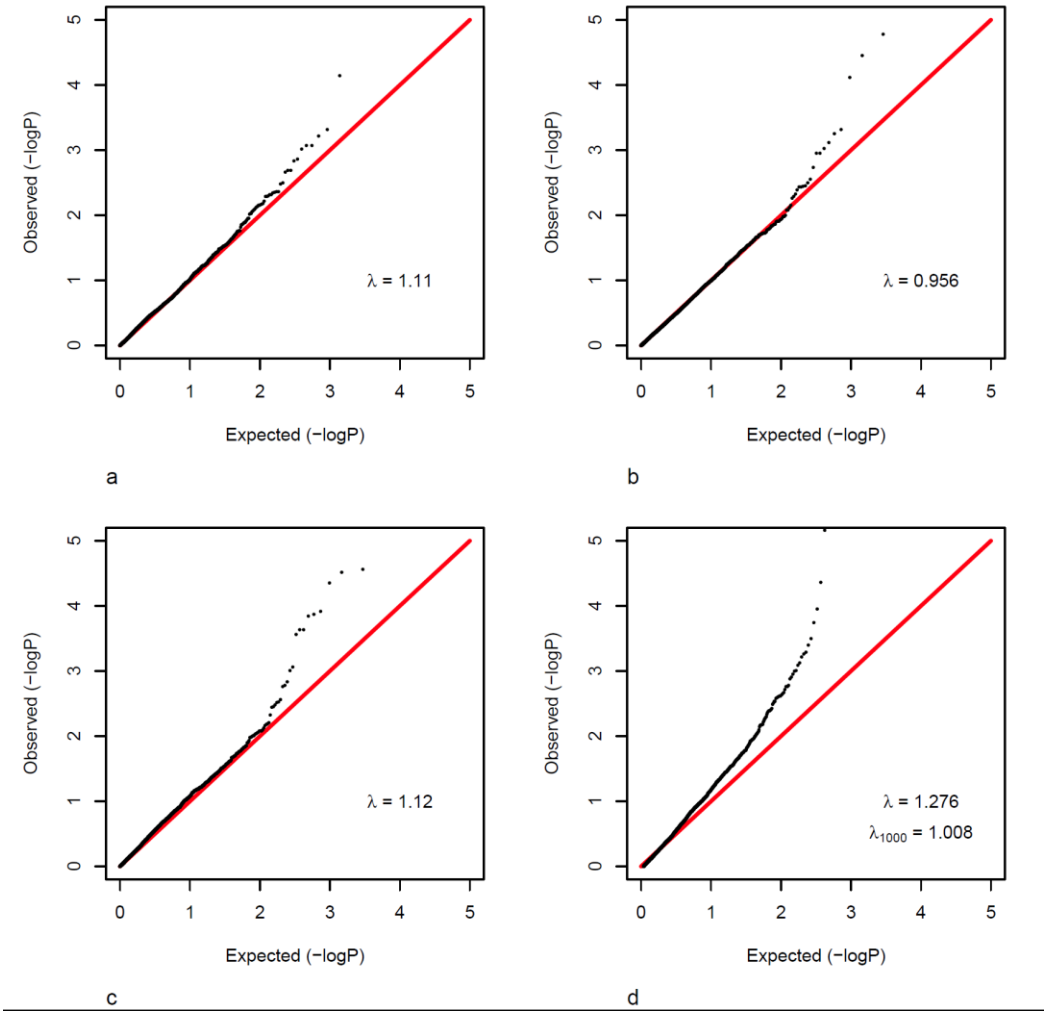
***Supplementary Figure 2**:* Comparison of cohorts of the current trans-ethnic association analysis to the previous IIBDGC GWAS-Immunochip analysis [6]



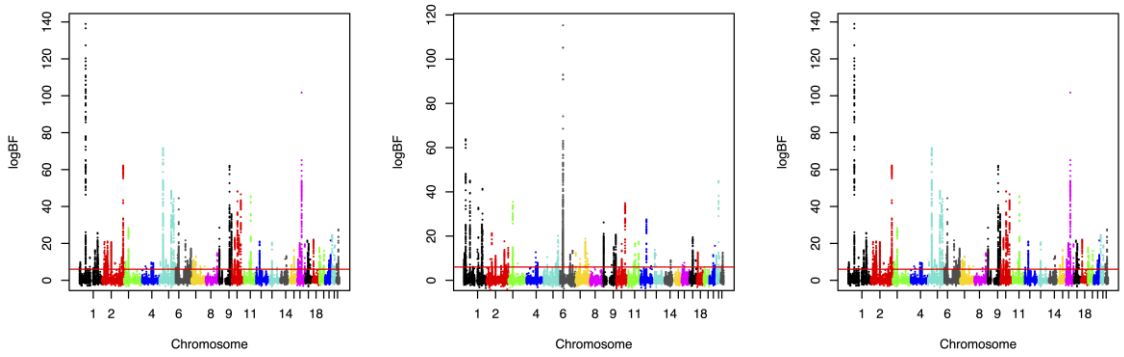
Supplementary Figure 3: Principal Component Analysis all included cohorts.
Principal components analysis (PCA) was performed with the first two PCs estimated from 1000 Genomes Phase I samples and projected onto each of the European and non-European samples



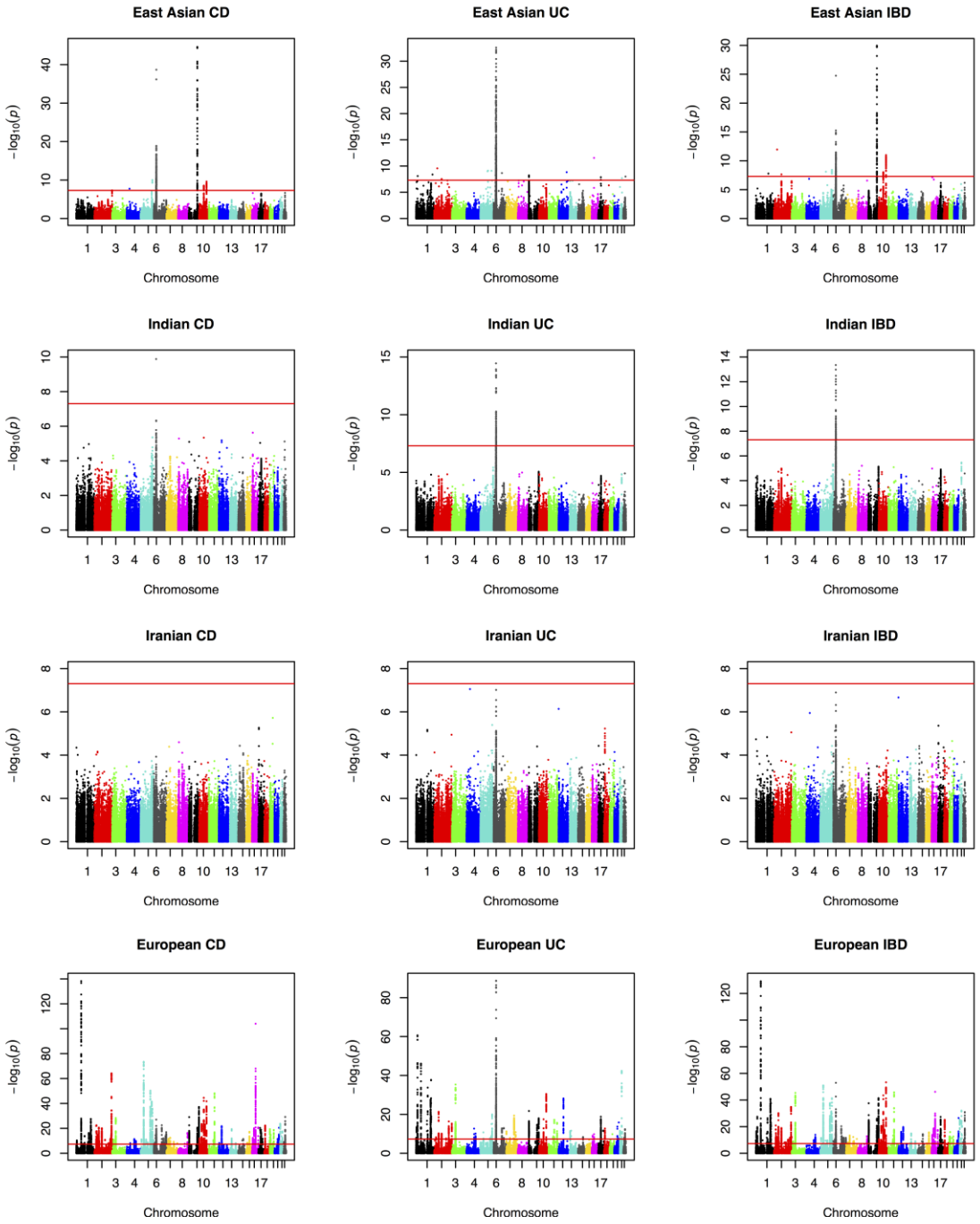
Supplementary Figure 4: Quantile–quantile plots for the p-values of each individual ancestral group - MMM analysis.The x-axis indicates the expected distribution of -log10(P values). The y-axis indicates the observed distribution of -log10 (P values). The overall inflation of the observed distribution of association test statistics is reflected by the lambda (λ). Considering the size of the European cohort a lambda equivalent for 1000 cases and 1000 controls is also provided. a. East Asian b. Indian c. Iranian d. European



Supplementary Figure 5: Manhattan plots for transethnic association analysis. MANTRA association results are plotted for Crohn's disease (CD), ulcerative colitis (UC) and combined inflammatory bowel disease (IBD). The x-axis indicates the position of all tested SNPs per chromosome. The y-axis shows the strength of association (log_{10} Bayes factor)



Supplementary Figure 6: Manhattan for each separate ancestral cohort. MMM association results are plotted for each ancestral cohort. The x-axis of each plot indicates the position of all tested SNPs per chromosome. The y-axis shows the strength of association ($-\log_{10}$ P-value). In rows from top to bottom: East Asian, Indian, Iranian and European. In columns from left to right: Crohn's disease (CD), ulcerative colitis (UC) and combined inflammatory bowel disease (IBD).



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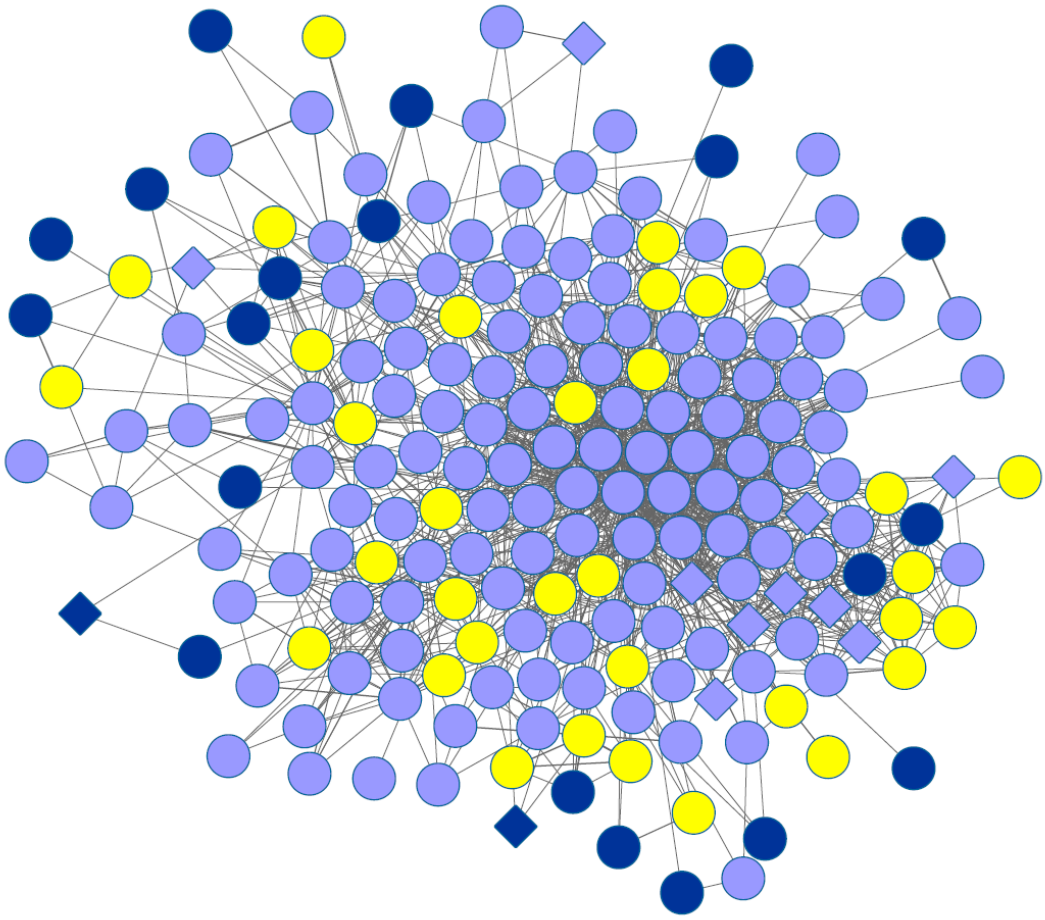
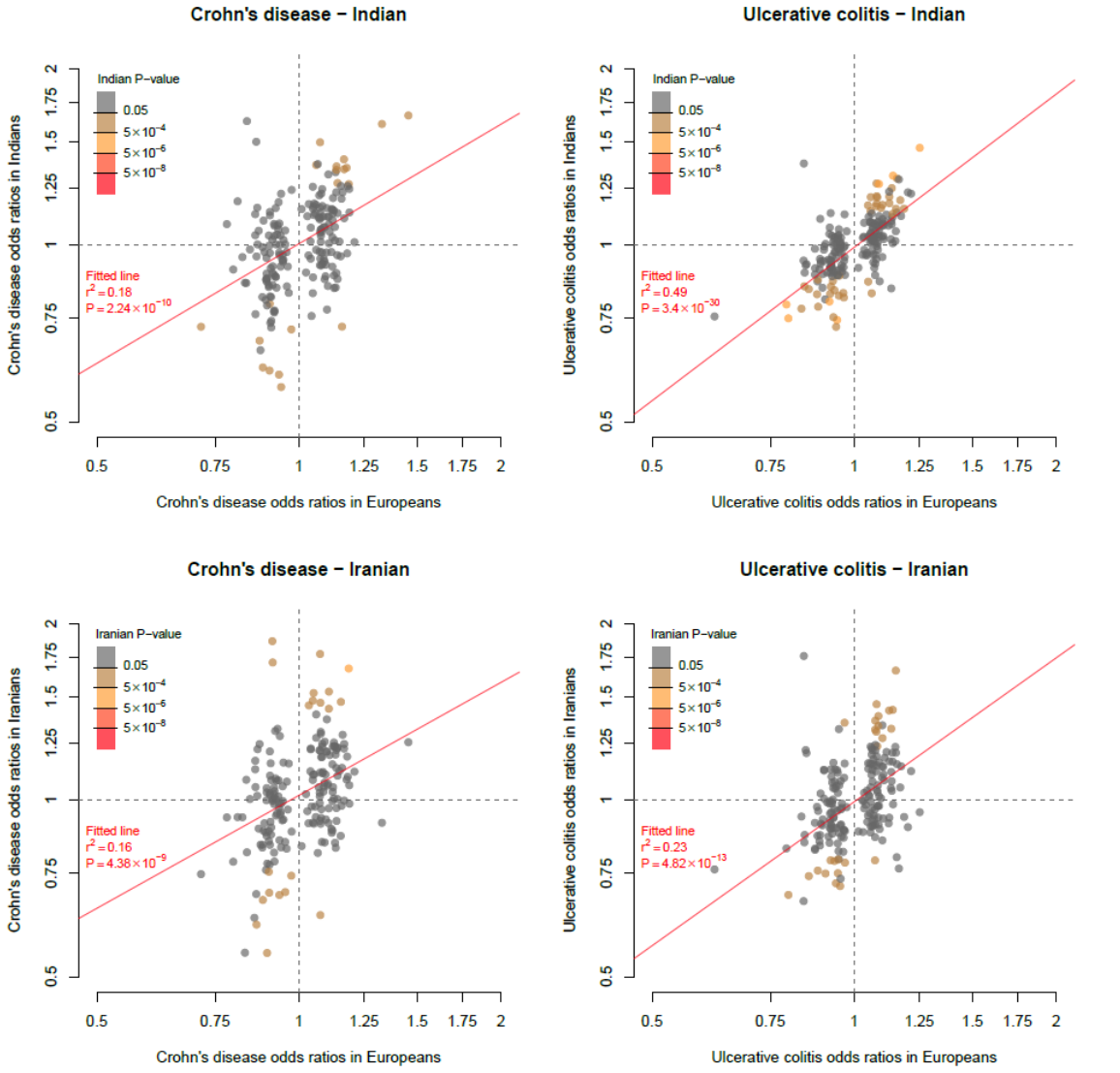
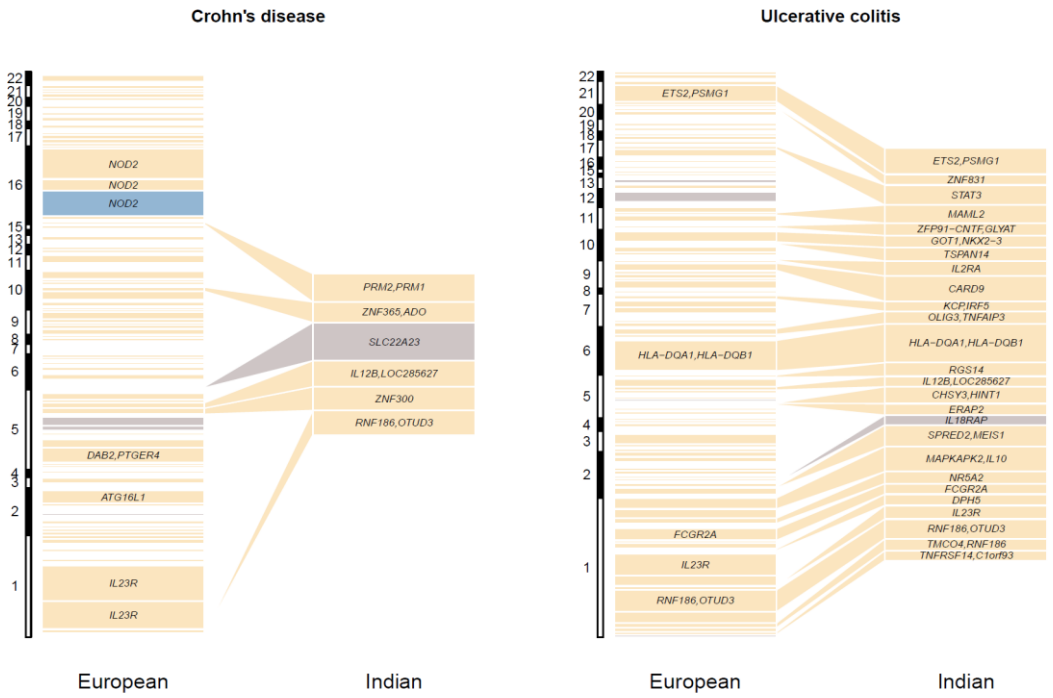
Supplementary Figure 8: GRAIL Connectivity Network.
The GRAIL network includes all genes that reside in loci associated with IBD, have a GRAIL p-value<0.05 and interact with at least one other GRAIL gene. The edge weights are proportional to the connection scores and we only plotted edges with scores ≥ 0.5. We colored the previous GRAIL genes in light blue, newly connected genes in previously identified loci in dark blue, and genes from newly associated loci in gold. Genes in loci that have BF<6 are shown as diamonds. As in the previous publication, only the main cluster was shown in this figure. [6]

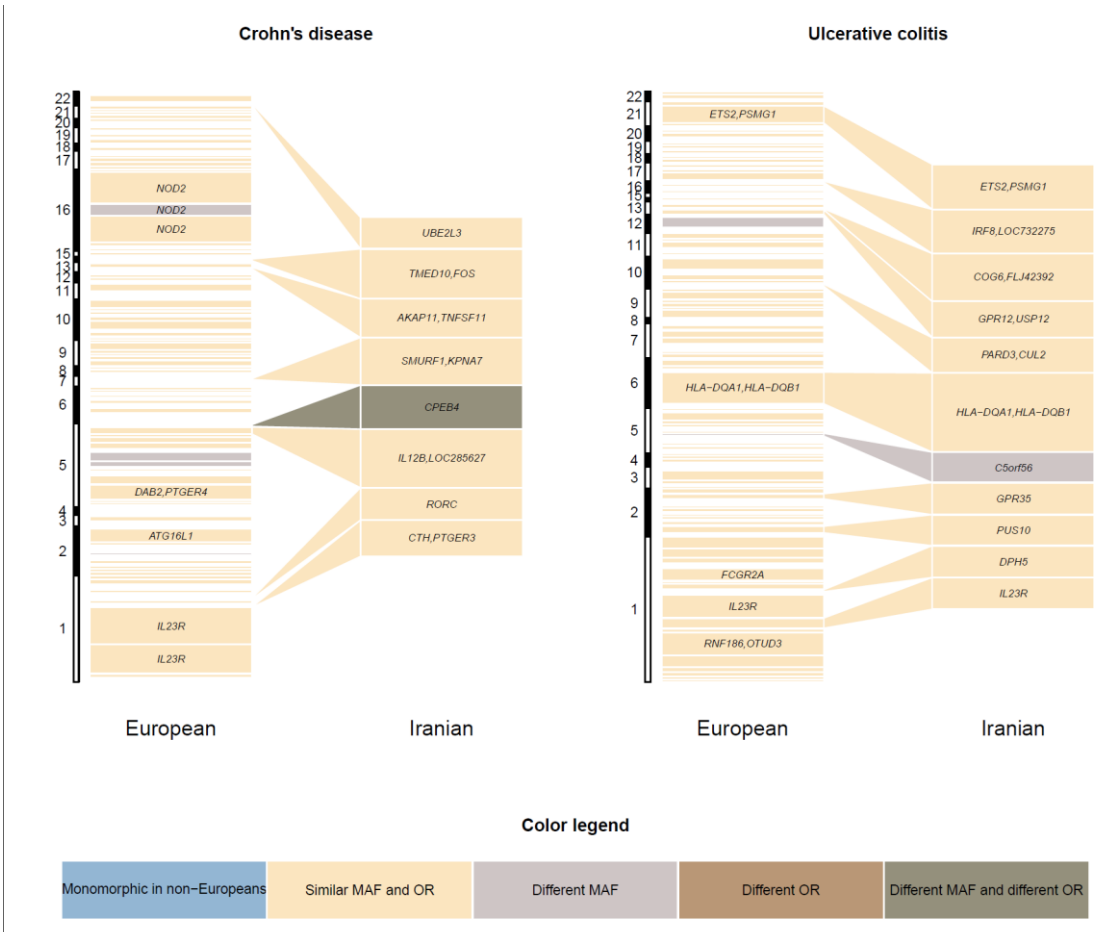


Supplementary Figure 9: Odds ratio comparison between European and non-European populations at SNPs associated with CD or UC or IBD (both). For each SNP, ORs (on log-scale) were estimated within each population for each phenotype. The colour of each point denotes the association P-value for that phenotype in the non-European population. The red line indicates the best fitting linear regression line, weighted by the inverse of the variance of the log ORs in the non-European population. The regression coefficient, significance and goodness of fit are listed in red.

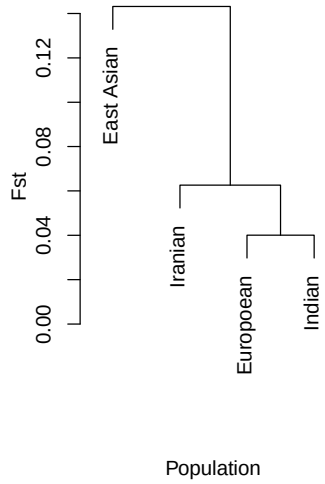


Supplementary Figure 10: Comparison of Variance explained per risk variant between Non-European and European Populations. Each box represents an independently associated SNP with that disease. Only SNPs with an association P-value < 0.01 are included in the non-European panel. The size of each box is proportional to the amount of variance explained in disease liability for that variant. The colours of the boxes denote whether the difference in variance explained is due to differences in allele frequencies (F_{st} > 0.1/monomorphic in the non-European population), significant heterogeneity of odds ratios ($P < 2.5\times10^{-4}$) or both.




Crohn's disease
Ulcerative colitis
NOD2
NOD2
NOD2
DAB2,PTGER4
ATG16L1
IL23R
IL23R
UBE2L3
TMED10,FOS
AKAP11,TNFSF11
SMURF1,KPNA7
CPEB4
IL12B,LOC285627
RORC
CTH,PTGER3
ETS2,PSMG1
HLA-DQA1,HLA-DQB1
FCGR2A
IL23R
RNF186,OTUD3
ETS2,PSMG1
IRF8,LOC732275
COG6,FLJ42392
GPR12,USP12
PARD3,CUL2
HLA-DQA1,HLA-DQB1
C5orf56
GPR35
PUS10
DPH5
IL23R
European
Iranian
European
Iranian
Color legend
Monomorphic in non−Europeans
Similar MAF and OR
Different MAF
Different OR
Different MAF and different OR

Supplementary Figure 11: Dendogram, generated from the data used in the MANTRA analysis, showing the clustering of the populations included in our study.



Supplementary Note

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