Supplemental Materials

Genetic Variation in the Inflammation and Innate Immunity Pathways and Colorectal Cancer Risk

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Quality control (QC) for Stage 1 genotypes

A total of 724 SNPs were successfully genotyped for 7,086 subjects (82% whites) at the Translational Genomics Research Institute (TGen, Phoenix, AZ) using Illumina GoldenGate bead-based genotyping technology. Duplicate samples of study subjects (2%) and 90 HapMap CEU (European) subjects were also genotyped for QC purposes. Mean concordance rates were 99.8% (all ≥97%) for both intra- and inter-plate replicates. 50 SNPs with concordance rates <99% were manually reviewed and one was removed due to poor clustering. SNPs were then excluded (n=107) based on the following criteria: 1) call rate <95%; 2) >1 Mendelian error among the 22 HapMap CEU trios; 3) p-value from Hardy-Weinberg Equilibrium (HWE) test among unrelated CEU subjects < 0.001; or 4) ≤2 counts of minor alleles. Subjects were removed if call rates were <90%, key covariates (age, gender, race or parents) were missing, or if no discordant sib pair was available after previous filtering. In the end, 6,450 subjects on 616 SNPs were retained for analysis.

Risk factors considered in Stage 1 in CCFR

The following colorectal cancer risk factors did not substantially change the ORs and were not included as covariates in the final model: pack-years of smoking (0, ≤20, >20), aspirin intake (ever/never taken aspirin regularly, i.e. ≥ twice per week for more than a month), BMI (2 years before interview), education, whether subjects participated in rigorous physical activity in the nearest age decade, history of irritable bowel syndrome, diabetes, and Crohn's disease, and hormone replacement therapy (men were assigned zero).

Quality control (QC) for Stage 2 genotypes

We excluded 13 SNPs based on the following criteria: 1) call rates <95%; 2) any Mendelian errors in HapMap trios; 3) concordance rates among replicates <99% and of poor clustering quality; 4) p-value from HWE test <0.0001 in European American controls and of poor clustering quality; or 5) MAF < 0.005 in MEC data. The average concordance rate was 99.5% among replicate pairs and 99.6% among 56 HapMap subjects for the 333 overlapping SNPs genotyped both here and in the HapMap database. Subjects were excluded (n=151) if call rates were < 90% or if the principal components (PCs) based on 93 ancestry informative markers indicated inconsistencies with their self-reported ethnicity (ancestry informative markers and therefore PCs were not available for 144 subjects).

SNP-set enrichment analysis in Stage 1 (in CCFR data)

For SNP-set based analyses, SNPs were associated with the closest gene based on distance (within ≤ 25kb on both sides, as shown in Table 1). Genes within 25kb of each other were grouped into one region. We restricted analysis to the 28 gene regions (400 SNPs) that contained ≥5 SNPs with minor allele frequency 0.01 or higher. The 28 gene regions were: *IL15, TLR1/TLR6, TLR2, TLR4, TLR5*, *TIRAP*, *TLR7/TLR8*, *CRP*, *IL1A*, *IL1B*, *IL1RN*, *IL6*, *IL10*, *ILR23, LTA /TNF*, *PPARG, NOD1(CARD4), NOD2(CARD15*), *ALOX5*, *ALOX12*, *PGDH*, *PGIS*, *TBXAS* 1, *PTGES*, and PGE2 receptors *EP1 - EP4*. The number of variants was from 5 to 48 per gene region.

To test whether any gene is over-represented among the top associated SNPs – an indicator of the collective effect of all SNPs in that gene, a Kolmogorov-Smirnov-like running sum based on the ranked single-variant χ^2 statistics, as proposed before [Wang, et al. 2007].

Let $r_{(j)}$ be the decreasingly ordered χ^2 association statistics of SNP *j* and G_j be the gene that SNP *j* is mapped to. For each gene *S* that contains multiple SNPs, a weighted Kolmogorov-Smirnov-like running sum score *SG* was calculated as,

$$SG = \max_{1\le j\le N}\left\{\sum_{j^*\le j, G_{j^*}\in S}\frac{r_{(j^*)}}{\sum_{G_{j^*}\in S} r_{(j^*)}} - \sum_{j^*\le j, G_{j^*}\notin S}\frac{1}{N-N_S}\right\}$$

where *N* is the number of total SNPs and N_S is the number of SNPs for gene *S*.

To get a p-value for a gene *S*, case-control status was permutated 2500 times within each sibship. Larger genes tend to result in larger scores (by chance). To make the scores comparable across genes, we calculated a normalized observed score

$$ZG = \frac{SG - mean(SG(\pi))}{SE(SG(\pi))}$$

where *mean* and *SE* were from all "permuted" scores for the same gene, denoted by $SG(\pi)$. The P-value for the observed score was the fraction among all permutations where the *permuted* scores were greater than the observed.

Reference

Wang K, Li M, Bucan M. 2007. Pathway-Based Approaches for Analysis of Genomewide Association Studies. Am J Hum Genet 81(6):1278-1283.

Supplementary Table 1. Genes in the inflammation and innate immunity pathways this study

Gene Symbol	Gene Name	CHR	Number of genotyped	Number of analyzed
CRP	C-reactive protein	1	7	5
IL10	Interleukin 10	1	8	8
PHGDH	phosphoglycerate dehydrogenase	1	22	14
PTGER3	prostaglandin E receptor 3 (subtype EP3)	1	44	36
TLR5	Toll-like receptor 5	1	22	17
IL1A	Interleukin 1-alpha	2	9	6
IL1B	Interleukin 1-beta	2	7	6
IL1RN	Interleukin 1 receptor antagonist	2	12	11
IL12A	Interleukin-12A	3	7	2
PPARG	peroxisome proliferative activated receptor, gamma	3	68	60
TLR9	Toll-like receptor 9	3	15	8
IL15	Interleukin 15	4	12	11
IL8	Interleukin 8	4	1	1
TLR1/TLR6	Toll-like receptor 1 and 6	4	26	19
TLR2	Toll-like receptor 2	4	21	14
TLR3	Toll-like receptor 3	4	13	10
PTGER4	prostaglandin E receptor 4 (subtype EP4)	5	9	6
LTA/TNF	lymphotoxin alpha (TNF superfamily, member 1) & Tumor necrosis factor (TNF superfamily, member 2)	6	19	15
CARD4	caspase recruitment domain family, member 4	7	21	18
IL6	Interleukin 6 (interferon, beta 2)	7	8	7
TBXAS1	thromboxane A synthase 1	7	75	65
PTGES	prostaglandin E synthase	9	11	9
TLR4	Toll-like receptor 4	9	28	22
ALOX5	arachidonate 5-lipoxygenase	10	31	21
TIRAP	Toll-interleukin 1 receptor (TIR) domain containing adaptor protein	11	18	15
IL23A	Interleukin 23, alpha subunit p19	12	10	7
KLRK1	killer cell lectin-like receptor subfamily K, member 1	12	12	10
PTGER2	prostaglandin E receptor 2 (subtype EP2), 53kDa	14	10	10
CARD15	caspase recruitment domain family, member 15	16	21	17
ALOX12	arachidonate 12-lipoxygenase	17	11	9
GDF15	Growth differentiation factor 15	19	7	3
PTGER1	prostaglandin E receptor 1 (subtype EP1), 42kDa	19	16	15
PTGIS	prostaglandin I2 (prostacyclin) synthase	20	48	31
TLR7/TLR8	Toll-like receptor 7 and 8	23	36	29
	Total	34	685	537

Supplementary Table 2. GxE interaction effects in CCFR analysis that were promoted to Stage 2, all with pack-years of smoking (0, ≤20, >20) ($P_{interaction}$ < 0.001).

rs ID	Chr	Position (HG18)	Gene	Minor	Major	$P_{interaction}$
12487012	3	12331196	PPARG	G	A	0.0007
4684101	3	12336295	PPARG	G	A	0.0006
560976	20	47604010	PTGIS	A	G	$5x10^{-5}$
4147584	9	131542720	PTGES	G	C	0.0004
4837403	9	131545447	PTGES	A	G	0.0004

Analysis was adjusted for age and gender based on 2,322 discordant sibships. Sample size may vary due to sporadic missing genotypes. All SNPs were genotyped.

Supplementary Table 3. Important main effects [a] in CCFR analysis

CHR	BP (GRCh37)	SNP	Minor (Tested)	Major	OR (95% CI)	P	Type	Gene[b]
1	71328234	rs7533733	G	A	0.91 (0.82, 1.01)	0.09	Genotyped	PTGER3
	71334273	rs1409985	A	T	1.11 (1.00, 1.23)	0.05	Imputed	PTGER3
	120256713	rs636101	G	A	1.10 (0.98, 1.23)	0.10	Genotyped	PHGDH
	120262112	rs41276626	A	G	0.80 (0.69, 0.93)	0.004	Imputed	PHGDH
	120262848	rs12139860	G	T	1.25 (1.07, 1.44)	0.004	Imputed	PHGDH
	120267431	rs55899400	A	G	0.81 (0.70, 0.93)	0.004	Imputed	PHGDH
	120271077	rs6668589	C	T	0.89 (0.80, 1.00)	0.05	Imputed	PHGDH
	120272726	rs3828090	A	G	0.89 (0.80, 1.00)	0.05	Imputed	PHGDH
	120273204	rs11589332	G	A	0.89 (0.80, 1.00)	0.04	Genotyped	PHGDH
	120274455	rs2246410	A	G	0.88 (0.79, 0.99)	0.03	Genotyped	PHGDH
	206944233	rs1554286	A	G	1.15 (1.01, 1.31)	0.03	Genotyped	IL10
	206944645	rs1518111	A	G	1.15 (1.02, 1.3)	0.02	Genotyped	IL10
	206944861	rs1518110	A	C	1.16 (1.03, 1.31)	0.02	Imputed	IL10
	206946407	rs1800872	A	C	1.18 (1.04, 1.32)	0.007	Genotyped	IL10
	206946634	rs1800871	A	G	1.18 (1.05, 1.32)	0.007	Genotyped	IL10
2	113885269	rs55860727	A	G	11.0 (2.57, 47.3)	0.001	Genotyped	IL1RN
	241530750	rs2975758	G	A	1.14 (0.99, 1.30)	0.07	Genotyped	CAPN10
3	12340925	rs17036188	C	T	0.73 (0.55, 0.97)	0.03	Imputed	PPARG
	12376427	chr3_12376427	A	G	1.38 (1.04, 1.82)	0.02	Imputed	PPARG
	12463176	rs709158	A	G	1.12 (1.01, 1.25)	0.03	Imputed	PPARG
	12465243	rs1175540	A	C	0.89 (0.80, 1.00)	0.04	Imputed	PPARG
	12465488	rs1175541	A	C	0.90 (0.80, 1.00)	0.04	Imputed	PPARG
	12466433	rs1175543	A	G	1.12 (1.01, 1.25)	0.04	Imputed	PPARG
	12466490	rs1177809	A	G	1.13 (1.01, 1.26)	0.03	Imputed	PPARG
	12470239	rs1797912	C	A	0.91 (0.82, 1.01)	0.07	Genotyped	PPARG
	12475994	rs4135300	A	G	0.85 (0.70, 1.02)	0.08	Genotyped	PPARG
	52247110	rs352163	A	G	0.88 (0.79, 0.98)	0.02	Imputed	ALAS1
	52247314	rs164640	C	T	1.14 (1.02, 1.26)	0.02	Imputed	ALAS1
	52252969	rs352162	A	G	1.13 (1.02, 1.25)	0.02	Genotyped	TLR9
	52256697	rs352140	C	T	1.14 (1.02, 1.26)	0.02	Imputed	TLR9
	52258372	rs352139	C	T	0.88 (0.79, 0.98)	0.02	Imputed	TLR9
	52261031	rs187084	G	A	0.91 (0.82, 1.01)	0.07	Genotyped	TLR9
	99873317	rs2130369	C	T	0.89 (0.80, 0.99)	0.03	Imputed	CMSS1
	99880569	rs720688	G	A	1.12 (1.01, 1.23)	0.04	Genotyped	CMSS1
	159713846	rs640039	G	A	0.88 (0.76, 1.02)	0.10	Genotyped	IL12A
4	175429808	rs3775977	A	G	1.15 (1.03, 1.28)	0.02	Genotyped	PGDH
5	40681710	rs34902673	G	A	1.95 (0.95, 4.00)	0.07	Genotyped	PTGER4
	78830778	rs6859424	C	G	0.88 (0.79, 0.98)	0.02	Imputed	
	78837556	rs736201	T	A	1.12 (1.01, 1.24)	0.03	Genotyped	
6	31543672	rs3179060	A	C	9.05 (1.03, 79.29)	0.05	Genotyped	LTA/TNF
	31544591	rs1800620	A	G	6.94 (0.76, 63.1)	0.09	Genotyped	LTA/TNF
7	22771038	rs2069860	T	A	1.56 (0.92, 2.63)	0.10	Genotyped	IL6
	139542268	rs6952056	G	T	1.15 (1.03, 1.28)	0.01	Imputed	TBXAS1
	139542515	rs6974960	A	G	1.15 (1.03, 1.28)	0.010	Imputed	TBXAS1
	139543904	rs4725857	C	T	0.87 (0.78, 0.96)	0.009	Imputed	TBXAS1
	139544552	rs7796073	C	G	0.87 (0.78, 0.97)	0.010	Imputed	TBXAS1
	139544674	rs7810415	G	A	1.13 (1.02, 1.25)	0.02	Genotyped	TBXAS1
	139545370	rs2267682	G	T	0.88 (0.79, 0.97)	0.01	Imputed	TBXAS1
	139565916	rs17161190	G	A	0.63 (0.38, 1.03)	0.06	Genotyped	TBXAS1

	139572123	rs6138	A	G	0.15 (0.02, 1.21)	0.08	Genotyped	TBXAS1
	139654256	rs4725563	G	A	0.90 (0.80, 1.01)	0.07	Genotyped	TBXAS1
	139669877	chr7_139669877	C	G	0.44 (0.20, 1.00)	0.05	Imputed	TBXAS1
	139672739	rs2267701	C	G	0.84 (0.72, 0.96)	0.01	Genotyped	TBXAS1
	139680969	rs2299896	C	T	1.2 (1.04, 1.39)	0.01	Imputed	TBXAS1
	139681566	chr7_139681566	C	T	2.25 (1.00, 5.05)	0.05	Imputed	TBXAS1
	139681614	chr7_139681614	C	T	2.25 (1.00, 5.05)	0.05	Imputed	TBXAS1
	139683640	chr7_139683640	G	T	2.25 (1.00, 5.05)	0.05	Imputed	TBXAS1
	139684043	rs10487667	C	A	1.13 (1.01, 1.27)	0.03	Genotyped	TBXAS1
9	120478936	rs7873784	G	C	0.87 (0.75, 1.00)	0.05	Genotyped	TLR4
	120485215	rs2183016	C	A	0.86 (0.75, 1.00)	0.04	Genotyped	TLR4
	120485795	rs7045953	G	A	0.87 (0.75, 1.00)	0.05	Genotyped	TLR4
	120488996	rs10759934	A	T	0.91 (0.82, 1.01)	0.07	Genotyped	TLR4
	132496676	rs12001465	G	A	1.12 (0.98, 1.29)	0.10	Genotyped	PTGES
	132498957	rs36022765	A	G	1.68 (0.92, 3.09)	0.09	Genotyped	PTGES
10	45920506	rs2228065	A	G	3.38 (1.00, 11.5)	0.05	Genotyped	ALOX5
11	35156500	rs353560	C	A	0.82 (0.66, 1.03)	0.10	Genotyped	LOC100507144
	126147003	rs7116126	G	A	3.96 (0.89, 17.5)	0.07	Genotyped	TIRAP
16	48173381	rs8046826	G	A	0.88 (0.79, 0.99)	0.03	Genotyped	ABCC12
	50744688	rs5743271	G	A	0.55 (0.30, 1.02)	0.06	Genotyped	CARD15
	50756540	rs2066845	G	C	0.70 (0.46, 1.07)	0.10	Genotyped	CARD15
	56980908	rs173537	G	A	1.30 (1.02, 1.66)	0.03	Genotyped	HERPUD1
19	14573654	rs2420538	G	A	1.09 (0.98, 1.21)	0.09	Genotyped	PTGER1
20	48113300	rs6095543	G	A	1.14 (1.00, 1.31)	0.05	Genotyped	PTGIS
	48119430	rs491025	C	T	1.15 (1.03, 1.27)	0.009	Imputed	PTGIS
	48121978	rs5602	A	G	0.88 (0.80, 0.98)	0.02	Genotyped	PTGIS
	48166050	rs7274270	A	T	0.26 (0.07, 0.92)	0.04	Genotyped	PTGIS
	48175598	rs6125671	A	G	1.12 (1.00, 1.25)	0.04	Genotyped	PTGIS
	48180058	rs477627	A	G	1.14 (0.99, 1.3)	0.06	Genotyped	PTGIS
22	44666676	rs1807715	G	A	0.90 (0.81, 1.00)	0.06	Genotyped	KIAA1644
23	12865224	rs3827469	G	A	1.09 (0.98, 1.21)	0.10	Genotyped	TLR7/TLR8

Analysis was adjusted for age and gender based on 2,322 discordant sibships. Sample size may vary due to sporadic missing genotypes. Allele frequencies are not shown because this is a sib-pair design and allele frequencies may not represent the general population.

[a] P < 0.1 if a marker is genotyped (n=49) and P< 0.05 if imputed (n=31)

[b] Blank if the variant is not within a gene region.

Supplementary Table 4. 31 SNPs with P<0.05 from analysis in the Multi-ethnic Cohort

					All Subjects		MAFs in Controls					OR (95% CI)					In All Subjects		
SNP	CHR	BP (HG19)	Gene	Loc	Mi	Ma	EA	AA	JA	LA	NH	EA	AA	JA	LA	NH	OR (95% CI)	P_{het} [1]	P [2]
rs541503	1	120208297	PHGDH/ZNF697	Inter	C	T	.37	.19	.05	.32	.12	1.06(0.86, 1.3)	1.21(0.98, 1.49)	1.31(0.95, 1.79)	1.15(0.94, 1.39)	1.59(0.98, 2.59)	1.15(1.03, 1.28)	.58	0.01
rs6768587	3	12338115	PPARG	Intr	G	A	.26	.28	.50	.38	.54	0.93(0.74, 1.17)	0.97(0.8, 1.18)	0.85(0.73, 0.98)	0.94(0.78, 1.14)	0.84(0.6, 1.17)	0.9(0.83, 0.98)	.91	0.02
rs17036188	3	12340925	PPARG	Intr	C	T	.03	.04	.29	.02	.28	1.17(0.64, 2.14)	0.87(0.55, 1.38)	0.83(0.71, 0.98)	0.89(0.47, 1.68)	0.84(0.57, 1.23)	0.84(0.74, 0.96)	.79	0.01
rs12636461	3	12341830	PPARG	Intr	G	A	.26	.27	.49	.38	.54	0.93(0.74, 1.17)	0.99(0.81, 1.2)	0.86(0.74, 0.99)	0.94(0.78, 1.13)	0.82(0.59, 1.15)	0.91(0.83, 0.99)	.93	0.03
rs17036242	3	12349490	PPARG	Intr	A	G	.25	.31	.28	.37	.40	0.96(0.77, 1.21)	0.98(0.81, 1.18)	0.75(0.63, 0.89)	0.96(0.79, 1.16)	0.72(0.5, 1.04)	0.88(0.8, 0.96)	.21	0.005
rs13061415	3	12349924	PPARG	Intr	C	T	.25	.31	.28	.36	.40	0.97(0.77, 1.22)	1.00 (0.83, 1.2)	0.75(0.64, 0.89)	0.96(0.79, 1.16)	0.7(0.49, 1.02)	0.88(0.81, 0.97)	.20	0.007
rs9310401	3	12352468	PPARG	Intr	C	T	.25	.31	.28	.36	.40	0.97(0.77, 1.22)	0.86(0.71, 1.04)	0.76(0.64, 0.9)	0.97(0.8, 1.18)	0.72(0.5, 1.03)	0.85(0.78, 0.94)	.20	7.1E-04
rs12487012	3	12356196	PPARG	Intr	C	T	.25	.24	.28	.36	.40	0.99(0.78, 1.24)	0.85(0.69, 1.04)	0.75(0.64, 0.89)	0.97(0.8, 1.17)	0.72(0.5, 1.04)	0.86(0.78, 0.94)	.18	0.001
rs4684101	3	12361295	PPARG	Intr	C	T	.26	.24	.29	.36	.41	0.99(0.79, 1.25)	0.86(0.7, 1.06)	0.75(0.63, 0.89)	0.95(0.78, 1.16)	0.72(0.5, 1.04)	0.86(0.78, 0.94)	.17	0.001
rs12493718	3	12363637	PPARG	Intr	T	G	.25	.24	.28	.36	.40	0.98(0.77, 1.23)	0.85(0.69, 1.04)	0.75(0.64, 0.89)	0.97(0.8, 1.18)	0.73(0.5, 1.05)	0.85(0.78, 0.94)	.19	9.1E-04
rs79644791	3	12376427	PPARG	Intr	G	A	.02	.01	.25	.02	.22	1.2(0.64, 2.25)	0.92(0.46, 1.86)	0.77(0.65, 0.92)	0.76(0.37, 1.55)	0.84(0.56, 1.26)	0.81(0.7, 0.94)	.64	0.004
rs12497191	3	12390135	PPARG	Intr	G	A	.13	.08	.26	.26	.26	1.08(0.81, 1.45)	0.71(0.5, 1.01)	0.77(0.65, 0.92)	0.87(0.7, 1.08)	0.75(0.5, 1.12)	0.83(0.74, 0.92)	.30	6.3E-04
rs4135304	3	12394601	PPARG	Intr	A	G	.00	.35	.00	.03	.00	0.59(0.1, 3.61)	1.34(1.14, 1.59)	NA	1.3(0.75, 2.25)	2.68(0.16, 45.2)	1.33(1.14, 1.56)	1	2.9E-04
rs6788489	3	12397838	PPARG	Intr	A	T	.00	.10	.00	.00	.00	NA	1.43(1.1, 1.87)	NA	1.98(0.6, 6.51)	2.65(0.16, 44.7)	1.47(1.15, 1.88)	1	0.002
rs6778740	3	12398636	PPARG	Intr	T	C	.00	.31	.00	.03	.00	0.31(0.03, 3.05)	1.35(1.14, 1.61)	NA	1.26(0.72, 2.21)	2.65(0.16, 44.7)	1.35(1.15, 1.58)	1	2.5E-04
rs9858822	3	12411238	PPARG	Intr	C	A	.00	.31	.00	.03	.00	0.31(0.03, 3.05)	1.36(1.15, 1.62)	NA	1.26(0.72, 2.2)	2.65(0.16, 44.7)	1.36(1.16, 1.6)	.99	1.5E-04
rs9842021	3	12411727	PPARG	Intr	G	T	.00	.10	.00	.01	.00	NA	0.74(0.55, 1)	NA	1.1(0.42, 2.85)	NA	0.74(0.56, 0.98)	.36	0.04
rs17036753	3	12479552	TSEN2/PPARG	Inter	T	C	.00	.19	.00	.02	.10	0.34(0.03, 3.31)	1.36(1.11, 1.66)	NA	0.8(0.41, 1.56)	0.93(0.53, 1.64)	1.24(1.04, 1.48)	.42	0.02
rs2115176	3	159716107	IL12A	Inter	C	A	.37	.55	.16	.41	.22	1.08(0.88, 1.32)	1.08(0.91, 1.28)	1.11(0.91, 1.34)	1.2(1, 1.45)	1.12(0.75, 1.67)	1.1(1.01, 1.21)	.94	0.03
rs4679867	3	159723903	IL12A	Inter	A	T	.40	.35	.09	.29	.18	0.83(0.68, 1.03)	0.8(0.66, 0.96)	0.91(0.7, 1.17)	0.95(0.77, 1.17)	0.76(0.47, 1.22)	0.85(0.77, 0.94)	.83	0.002
rs11746854	5	78829154	PAPD4/HOMER1	Inter	G	A	.18	.27	.24	.17	.21	1.25(0.97, 1.62)	0.97(0.8, 1.17)	1.1(0.93, 1.3)	1.24(0.97, 1.59)	1.55(1, 2.39)	1.12(1.02, 1.24)	.54	0.02
rs10942894	5	78831995	HOMER1/PAPD4	Inter	A	G	.15	.36	.19	.40	.18	0.96(0.73, 1.27)	1.05(0.88, 1.26)	0.98(0.81, 1.18)	0.67(0.56, 0.82)	0.8(0.49, 1.31)	0.9(0.82, 0.99)	.07	0.03
rs41527045	5	78832082	PAPD4/HOMER1	Inter	A	G	.17	.39	.47	.42	.29	0.9(0.69, 1.17)	1(0.84, 1.19)	0.98(0.85, 1.13)	0.7(0.57, 0.84)	0.66(0.44, 0.99)	0.89(0.81, 0.97)	.05	0.006
rs7037117	9	120483663	TLR4	Inter	G	A	.25	.67	.20	.23	.36	1.05(0.84, 1.32)	1.17(0.97, 1.4)	1.04(0.88, 1.25)	1.12(0.9, 1.4)	1.23(0.85, 1.77)	1.11(1.01, 1.22)	.92	0.03
rs4147584	9	132502899	PTGES	Intr	C	G	.08	.03	.23	.12	.25	0.9(0.62, 1.31)	1.3(0.84, 2.01)	0.84(0.71, 1.01)	0.86(0.64, 1.15)	0.56(0.36, 0.88)	0.86(0.76, 0.98)	.70	0.02
rs12553596	9	132504668	PTGES	Intr	C	T	.09	.03	.23	.12	.26	0.85(0.59, 1.23)	1.45(0.95, 2.22)	0.87(0.73, 1.04)	0.84(0.62, 1.14)	0.55(0.35, 0.86)	0.87(0.77, 0.99)	.65	0.04
rs3780906	10	45921982	ALOX5	Intr	A	G	.27	.34	.23	.23	.19	1.05(0.84, 1.32)	1.14(0.96, 1.37)	1.12(0.94, 1.33)	1.11(0.9, 1.37)	0.79(0.5, 1.23)	1.1(1, 1.21)	.77	0.05
rs702366	10	45934372	ALOX5	Intr	G	A	.47	.51	.42	.38	.34	1(0.81, 1.22)	1.12(0.95, 1.34)	1.17(1.01, 1.35)	1.01(0.83, 1.23)	0.89(0.63, 1.25)	1.09(1, 1.19)	.50	0.04
rs353560	11	35156500	CD44/PDHX	Inter	G	T	.06	.36	.09	.04	.06	0.82(0.52, 1.31)	1.14(0.95, 1.37)	1.14(0.9, 1.46)	1.45(0.94, 2.25)	1.37(0.68, 2.73)	1.13(1, 1.28)	.45	0.05
rs2553809	11	35163486	CD44	Intr	C	T	.30	.16	.23	.20	.16	1.24(1, 1.54)	1(0.79, 1.26)	1.23(1.04, 1.45)	0.94(0.74, 1.19)	1.04(0.66, 1.65)	1.12(1.02, 1.24)	.40	0.02
rs11700258	20	48153744	PTGIS	Intr	G	A	.11	.05	.04	.08	.05	0.84(0.6, 1.18)	0.71(0.46, 1.11)	0.89(0.63, 1.28)	0.76(0.53, 1.1)	0.79(0.33, 1.88)	0.81(0.68, 0.96)	.99	0.02

Intr=Intron; Inter=intergenic; EA=European Americans; AA=African Americans; JA=Japanese Americans; LA=Latinos; NH=Native Hawaiians; Mi=Minor; Ma=Major; MAF=Minor Allele Frequency. All analyses were adjusting for age, gender and race. 2153 cases and 2630 controls were included in analysis. However, sample size may vary due to sporadic missing genotypes.

[1] P-value from tests of heterogeneity across racial groups

[2] P-value from single-marker analysis

Supplementary Table 5. Association results for rs1801282 in *PPARG* (Pro12Ala)

SNP	CHR	BP (HG19)	Minor /Major	Study[$]	Group	MAF[¶] (controls)	MAF[¶] (cases)	OR (95% CI)	P
rs1801282 (Pro12Ala)	3	12393125	G/C	CCFR		0.12	0.12	1.06 (0.91, 1.25)	0.44
				MEC*				0.95 (0.80, 1.12)	0.54 [#]
					LA	0.09	0.11	1.19 (0.87, 1.64)	0.27
					JA	0.034	0.025	0.69 (0.44, 1.07)	0.099
					AA	0.050	0.050	0.93 (0.60, 1.43)	0.73
					EA	0.13	0.12	0.89 (0.65, 1.22)	0.47
					NH	0.14	0.12	0.84 (0.50, 1.41)	0.51
				Combined[+]				1.01 (0.90, 1.13)	0.89

CCFR: Colorectal Cancer Family Registry; MEC: Multiethnic Cohort; EA: European Americans; AA: African Americans; JA: Japanese Americans; LA: Latinos; NH: Native Hawaiians.

[¶] MAF: minor allele frequency. MAFs from cases and controls in CCFR were without adjustment for relatedness.

[$] Analysis in CCFR (2322 sibships) was adjusted for age and sex and that in the MEC (2153 cases, 2630 controls) was adjusted additionally for ethnic groups.

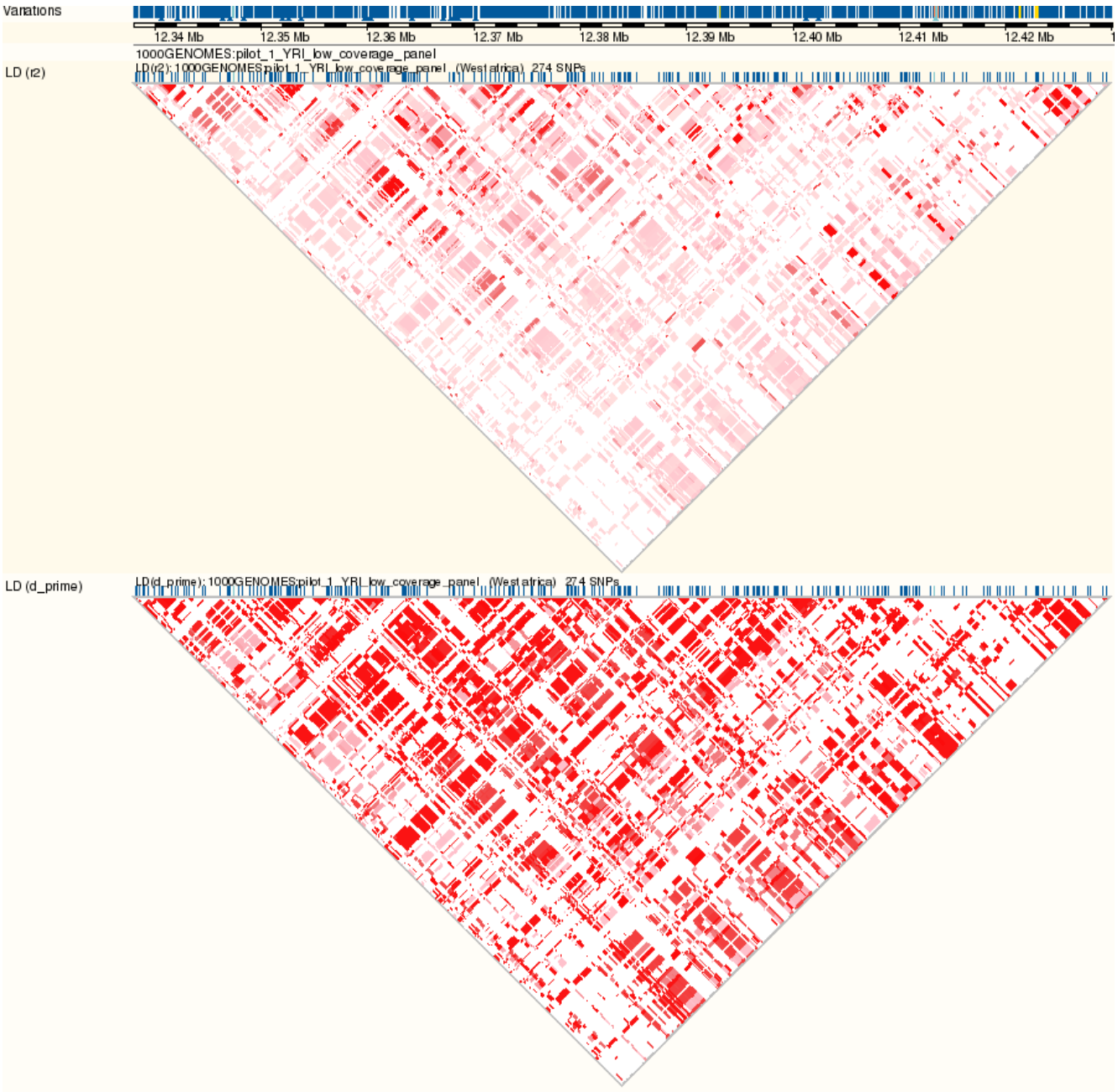
[#] P-values from tests of heterogeneity across ethnic groups in the MEC were > 0.3

+ I^2 for heterogeneity was zero.

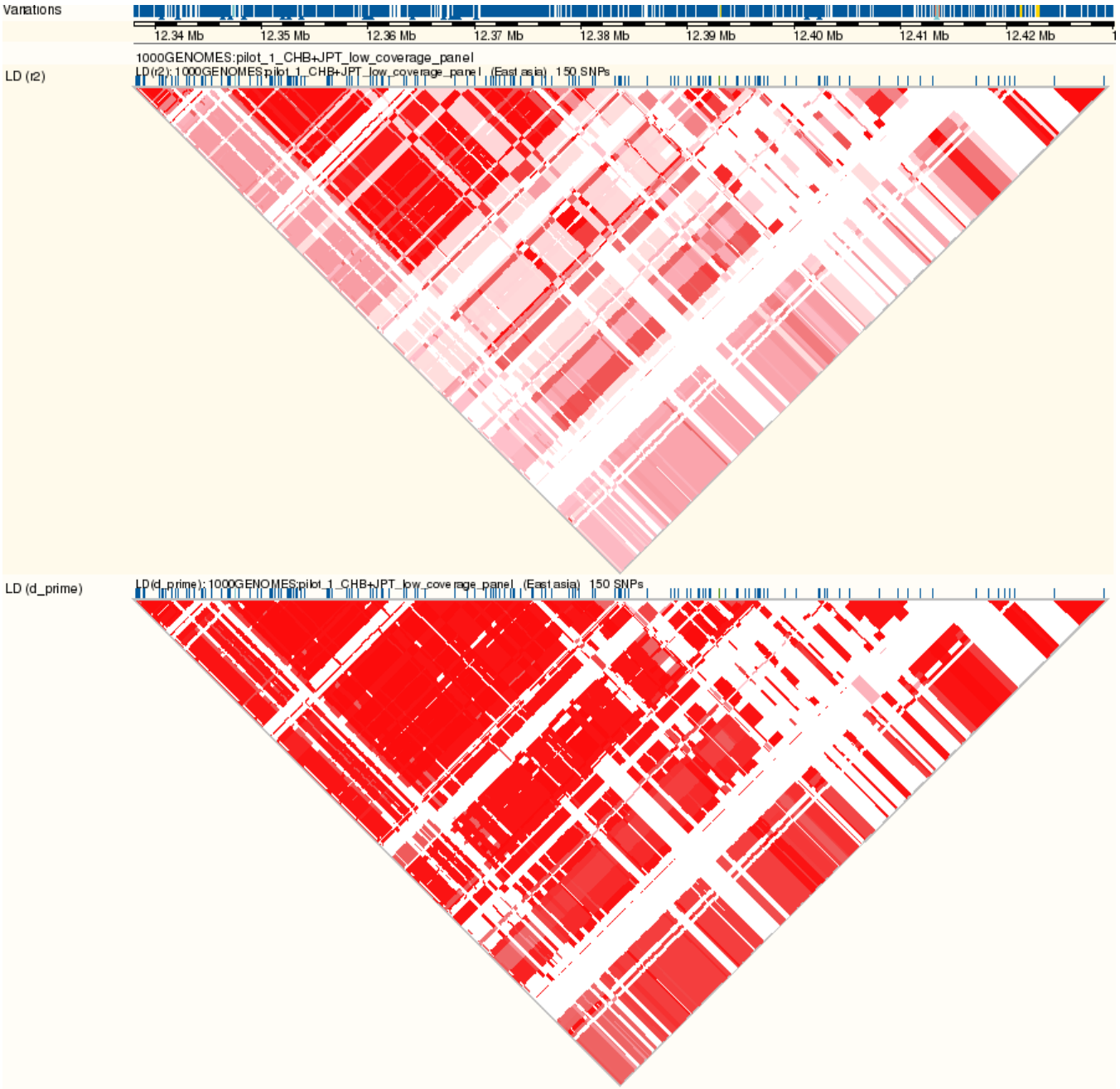
* rs1801282 was imputed in the MEC with R^2 = 1 in EA and NH, 0.96 in LA, 0.99 in JA, 0.80 in AA.

Supplementary Table 6. SNPs (n=79) with published evidence of association with colorectal cancer that were included in CCFR analysis

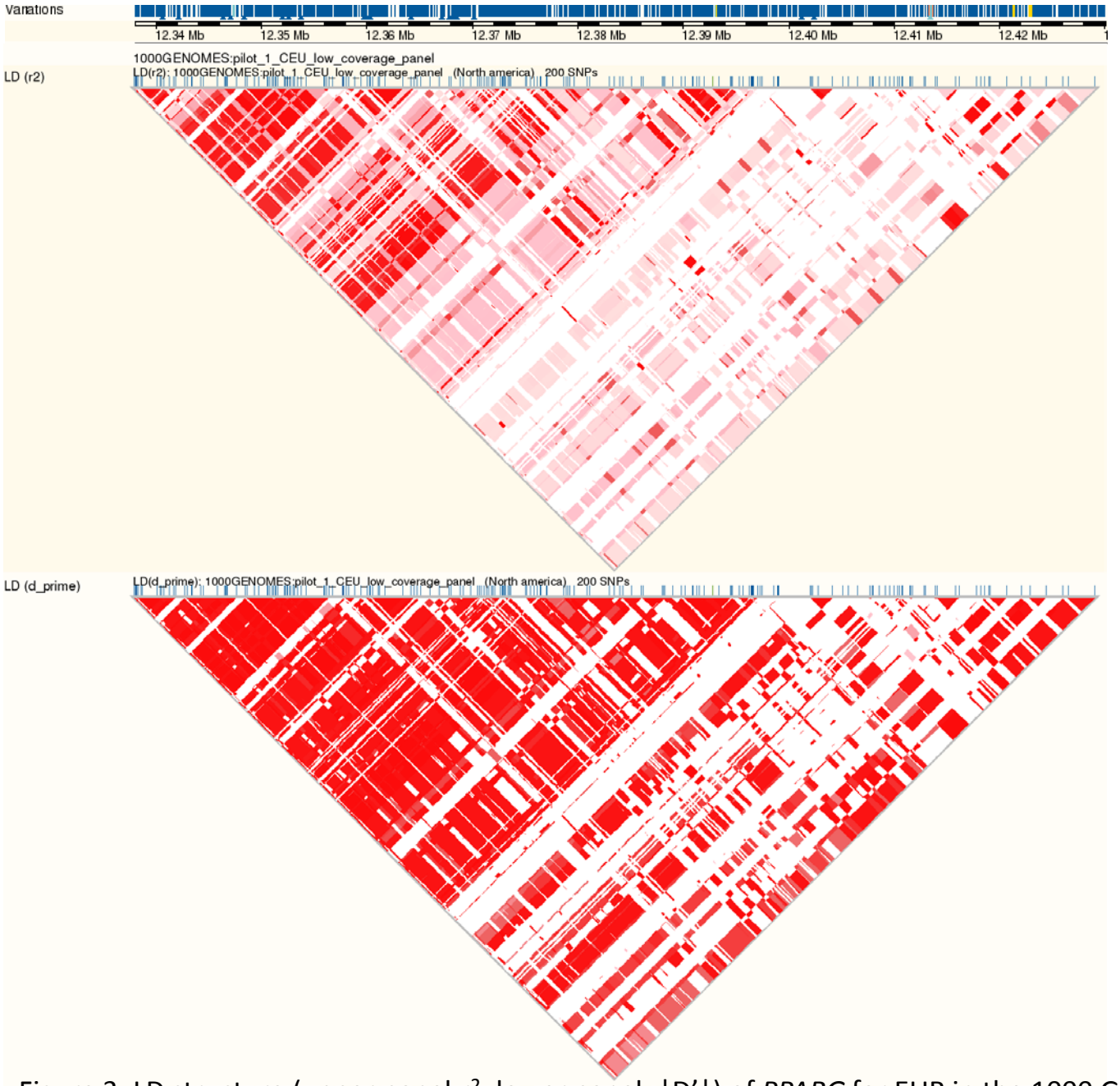
SNP	CHR	BP (HG18)	Gene (inside or nearby)
rs4659426	1	26516801	CD52
rs1326390	1	101031613	
rs4648268	1	184913761	PTGS2
rs10735510	1	210852083	ATF3
rs12070345	1	210856958	ATF3
rs1966813	2	45951401	PRKCE
rs11903923	2	46112445	PRKCE
rs12474258	2	102183127	IL1RL2
rs11692230	2	102221497	IL1RL2
rs4988235	2	136325116	MCM6
rs2066804	2	191550004	STAT1
rs13029247	2	191574903	STAT1
rs13389408	2	191641528	STAT4
rs2975758	2	241179423	CAPN10
rs6764111	3	53182441	PRKCD
rs6778964	3	53183822	PRKCD
rs720688	3	101363259	CMSS1
rs2053211	3	145257282	
rs231983	3	173719134	TNFSF10
rs17453783	4	87827881	PTPN13
rs3775977	4	175666383	PGDH
rs1863642	4	175670488	PGDH
rs12500316	4	175676599	PGDH
rs1877730	4	187842470	FAT
rs7722221	5	7783872	ADCY2
rs30168	5	13772089	DNAH5
rs1862610	5	52163637	ITGA1
rs736201	5	78873312	
rs31517	5	135314928	LECT2
rs1368375	5	139582578	CYSTM1
rs2569193	5	139995679	CD14
rs25856	5	156556482	ITK
rs4361609	6	31348614	
rs2524082	6	31349740	
rs723725	7	17652870	
rs3752651	7	55197037	EGFR
rs2740764	7	55234952	EGFR
rs1104666	8	56391240	XKR4
rs7820484	8	56968031	LYN
rs884115	9	129927677	PTGES2
rs2801499	10	12436016	CAMK1D
rs2768367	10	12537776	CAMK1D
rs8177029	10	30788504	MAP3K8
rs2776937	10	33646195	NRP1
rs768395	10	79879516	
rs7895217	10	88578719	BMPR1A
rs2883420	10	88601102	BMPR1A
rs10749542	10	88621608	BMPR1A
rs353560	11	35113076	CD44
rs567075	11	85507805	
rs2286600	12	6353047	SCNN1A
rs16907705	12	12128996	BCL2L14
rs697212	12	102624747	STAB2
rs3809240	12	105519399	LOC100287944
rs5637	12	119247148	PLA2G1B
rs17222919	13	30206329	ALOX5AP
rs9315048	13	30225840	ALOX5AP
rs8046826	16	46730882	ABCC12
rs173537	16	55538409	HERPUD1
rs3785275	16	88369530	
rs2227321	17	35424820	MED24, CSF3
rs1481280	18	16909449	ROCK1
rs891282	18	19793058	LAMA3
rs953786	18	19859785	TTC39C
rs9963281	18	54550898	MALT1
rs874299	18	73185272	
rs8108253	19	4607466	C19orf10
rs8112182	19	4619417	C19orf10
rs2312586	19	40525246	CD22
rs3928916	19	46899465	CEACAM5
rs10211789	20	8485044	PLCB1
rs6055995	20	8610222	PLCB1
rs926668	20	49594865	NFATC2
rs2426512	20	52493666	
rs17241025	21	15254794	NRIP1
rs2298560	21	39107845	EST2
rs760456	21	45153843	ITGB2
rs8141011	22	30671790	YWHAH
rs1807715	22	42998009	KIAA1644



Supplementary Figure 1. LD structure (upper panel:r^2, lower panel: |D'|) of *PPARG* for YRI in the 1000 Genomes project



Supplementary Figure 2. LD structure (upper panel:r^2, lower panel: |D'|) of *PPARG* for ASN in the 1000 Genomes project



Supplementary Figure 3. LD structure (upper panel:r^2, lower panel: |D'|) of *PPARG* for EUR in the 1000 Genomes project