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IL1B genetic variation and plasma C-reactive protein level among young adults: The CARDIA study

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Abstract

Objective—Interleukin-1B (IL1B) modulates C-reactive protein (CRP) expression. However, whether *IL1B* genetic variation is associated with CRP level is unknown. Further, obesity, a state of low-grade inflammation that influences cellular IL-1 functions may modify this association.

Methods and results—Study participants ($N = 3289$), 48% blacks and 52% whites, had CRP level measurements at year 7 and year 15 examinations as part of the CARDIA study. Ten tag single nucleotide polymorphisms (SNPs) that characterize common *IL1B* gene variation were genotyped. In SNP analysis, no significant associations with either level or change in time CRP were observed after multiple testing adjustments. However, global *ILIB* gene variation was associated with year 7 to year 15 change in CRP (global nominal $p = 0.004$, multiple testing corrected $p = 0.048$) among obese blacks. Compared to the commonest haplotype, a common haplotype that includes the SNP rs1143642 was associated with greater increases in CRP from year 7 to year 15 among obese blacks and whites while another common haplotype that includes the SNP rs3917356 was associated with decreased change in CRP from year 7 to year 15 among obese blacks. The rare alleles of *ILIB* SNPs, SNP 7114 (rs1143642) and SNP 3298 (rs3917356), were associated with greater increases and decreases in CRP from year 7 to year 15 among blacks, respectively, compared to their common variants.

Conclusion—*IL1B* genetic variation may have a role in CRP level regulation and this association may be modified by obesity.

Keywords

Interleukin-1B; Plasma C-reactive protein; Obesity; Genetic variation; Young adults

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1. Introduction

Inflammation is related to the development and progression of atherosclerosis [1]. Candidate genes (and their variations) regulating C-reactive protein (CRP), a marker of systemic inflammation associated with cardiovascular diseases have not been fully described [2]. Interleukin-1Beta (*IL1B*) gene, part of a cluster of genes on chromosome 2 coding for a family of IL-1 proteins, has been shown to be an important modulator of inflammatory pathways, with potential involvement in the pathogenesis of atherosclerosis and other cardiovascular diseases [3].

Associations of *IL1B* gene single nucleotide polymor-phisms (SNP) with IL1beta levels [4] and cardiovascular diseases [5,6] have been documented. IL1B levels regulate plasma CRP directly through CRP gene regulation and indirectly through the production of inflammatory mediators such as IL-6 [7–13]. Findings from previous association studies of *IL1B* SNPs and CRP levels have been inconsistent [6,12–15]. These studies did not evaluate the associations of whole gene common *IL1B* variation with CRP levels, using multiple SNPs and haplotype analyses, and the study populations were typically clinically ill patients, rather than healthy individuals. Further, while the effect of IL1B on some cellular functions appears to depend on obesity [11], and obesity is strongly related to CRP levels [16], the effect of obesity on the association between *IL1B* genetic variation and CRP levels has not been examined. We evaluated the associations of common *IL1B* genetic variation with CRP levels and with 8-year change in CRP levels in a population of black and white young adults participating in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Further, we examined whether these associations are modified by obesity.

2. Materials and methods

2.1. Study population

This study was conducted as part of an ancillary study to CARDIA, an NHLBI-funded multi-center cohort study. The Inflammation Genomics and Atherosclerosis Prevention (IGAP) ancillary study was initially designed to investigate associations of common patterns of variations in genes involved in inflammation and thrombosis with variations in CRP and fibrinogen levels. CARDIA study participants were 18–30-year-old black and white men and women recruited from four geographic locations by community-based sampling (Birmingham, AL, Chicago, IL, and Minneapolis, MN) and from a prepaid health plan (Oakland, CA) in 1985–1986. 5115 (51% of eligible) were enrolled in the study. Participants were contacted every 6 months and were re-examined at five follow-up examinations at year 2 (1987–1988), year 5 (1990–1991), year 7 (1992–1993), year 10 (1995–1996) and year 15 (2000–2001) [17]. A subset of CARDIA participants provided DNA samples at year 10 examinations (N = 3950) and 3600 attended both year 7 and year 15 examinations. Information on *IL1B* tag SNP genotypes was available for 3289 participants who attended both examinations.

2.2. Data collection

Information on socio-demographic characteristics, lifestyle, physiologic and metabolic risk factors, including body mass index (BMI), was assessed at each examination (Table 1). BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). CRP levels were measured in stored blood obtained from CARDIA participants during the year 7 and year 15 examinations using the Latex method, which used particle enhanced technology (BN II nephelometer, Dade Behring, Deerfield, Illinois).

2.3. SNP selection

TagSNPs were selected based on publicly available data generated by the SeattleSNPs Variation Discovery Resource (http://pga.gs.washington.edu). Briefly, SeattleSNPs performed resequencing of the *IL1B* gene region on 47 unrelated individuals; 24 of African American ancestry (from the Coriell AA100 panel) and 23 of European American ancestry (from the CEPH pedigrees) [17]. Detailed protocols for PCR and sequencing are available at the SeattleSNPs web site. Bins of common SNPs (minor allele frequency > 10%) were determined by grouping SNPs in linkage disequilibrium (LD) ($r^2 > 0.64$) separately in each population using LDselect v1.0 [18]. One tagSNP from each bin was selected to capture the genetic variation in the two populations (Table 2).

2.4. Genotyping and haplotype inference

Genotyping of ten selected tagSNPs, 302 (rs1143625), 2143 (rs1143629), 3298 (rs3917356), 4006 (rs1143630), 5277 (rs1143634), 7114 (rs1143642), 8234 (rs1071676), 8546 (rs3917363), 12885 (rs3917368) and 15235 (rs3917375) was performed using TaqMan Assays By Design (ABI). SNP IDs represent locations of each tagSNP with respect to nucleotide position in GenBank accession AY137079. An algorithm based on a Bayesian method of inferring haplotypes was used to estimate haplotype frequencies in the sample, using *Phase* (*v2.0*) [19]. In subsequent regression models, uncertainty in haplotype estimation was handled by including probability estimates [20].

2.5. Data analysis

Allele frequencies were estimated by direct gene counting. Hardy Weinberg equilibrium was assessed, using a chi-square test. Raw CRP levels were right skewed, so log-transformed values were used. We examined the associations of genetic variation in *IL1B* with CRP, both cross-sectional year 7 and year 15 and year 7 to year 15 change in CRP. In addition, potential interaction of *IL1B* genetic variation and obesity on CRP levels and change were examined. In SNP analysis, separate models for whites and blacks were fit for each outcome variable (cross-sectional and change in ln(CRP)) that included terms for each SNP (additive effect of SNPs coded 0, 1 and 2 for none, one or two copies of the rare allele, respectively), sex, age, recruitment center, BMI change between year 7 and year 15 and year 7 ln(CRP) (the latter two covariates for the analysis of change in ln(CRP)). For each outcome, in race stratified models that included terms for sex, age and recruitment center, each haplotype was represented by an indicator variable marking whether a person had or did not have one or more copies. Indicators for eight haplotypes (haplotypes 2–9) among blacks and four haplotypes (haplotypes 2, 3, 4, and 5) among whites were included in each model along with an indicator for haplotype O, representing rare haplotypes (frequencies < 4.5%). Haplotype 1, the most common haplotype overall, was used as the referent. Effect modification by BMI (at the year 15 examination) was assessed using stratified analysis where the strata were defined by race and BMI in the non-obese range (BMI < 30 kg/m^2) and obese range (BMI ≥ 30 kg/m^2) and tests of interaction [21].

Exponentiated coefficients and their 95% confidence intervals from GEE models (for year 7 and year 15 ln(CRP) levels and log linear regression models (for the change from year 7 to year 15 ln(CRP) levels), denotes the contrast between presence of one copy of the rare allele (in SNP analysis) or one or more copy of each haplotype (in haplotype analysis) to the referent; the common allele or haplotype 1, respectively. These values correspond to percent decreases or increases in CRP associated with each copy of the rare allele or presence of one or more copy of each haplotype, compared to the referent group. *p*-Values of global tests of association correspond to associations of any haplotype with level or change in CRP. Statistical analyses were performed using STATA software *version 8.0* (STATA, College Station, TX). Confidence intervals were calculated at the 1-alpha = 95% level. Adjustment for multiple

testing was performed using the conservative Bonferroni correction of *p*-values. At the SNP level, adjustments were made using number of tests conducted (20) assessing each outcome. At the haplotype level, adjustments were made using the total number of all global haplotype tests (12).

3. Results

Characteristics of the study population at the year 15 examinations are presented in Table 1. Fifty-six percent were female and 46% were black. Blacks tended to have both higher BMI and mean CRP levels at year 7 and year 15, compared with whites. Female participants had generally higher CRP levels compared with their male counterparts.

All tag-SNPs selected were synonymous (Table 2). No significant departures from HWE were observed. Overall, minor allele frequency (MAF) differences were observed for various SNPs between blacks and whites. For example, MAF for SNPs 7114 (rs1143642), 15235 (rs3917375) and 8546 (rs3917363) were two- to fivefold higher among blacks compared to whites. Considerable genetic variation was observed among blacks, where nine haplotypes (inferred from tagSNPs) with frequencies above 4.5% accounted for 75% of the observed haplotypes. Among whites, only five haplotypes with frequencies above 4.5% accounted for 88% of the observed haplotypes. Although haplotype 4 was the most frequent among blacks, for consistency, haplotype 1, the most frequent haplotype overall and among whites, was chosen as a referent in subsequent analyses.

Results of race-specific GEE models fit to evaluate associations between specific *IL1B* SNPs and CRP (year 7 and year 15 ln(CRP)) as well as race specific regression models fit to evaluate associations between specific *IL1B* SNPs and change in years 7–15 ln(CRP) level are presented in Table 3. None of the SNPs were associated cross-sectionally with CRP levels in either race group. Among blacks, the rare allele of SNP 7114 (rs1143642) was associated with 13% increase in ln(CRP) levels between year 7 and year 15 (nominal *p*-value; 0.010) and the rare variant of SNP 3298 (rs3917356) was associated with a 9% decrease in CRP levels from year 7 to year 15 (nominal *p*-value = 0.030). However, these associations were not statistically significant, after correction for multiple testing. No significant associations were seen among whites.

The associations of *IL1B* gene haplotypes with CRP levels and change are presented in Tables 4 and 5, respectively. Overall, among both black and white participants, there was little evidence of global or haplotype specific associations with level or change in CRP levels in either race group. However, after stratifying the sample by BMI level, evidence for weak associations between *IL1B* haplotypes and change in ln(CRP) levels was present among obese participants. A global haplotype effect on change in ln(CRP) between year 7 and year 15 was significant among obese blacks (nominal $p = 0.004$, multiple testing corrected $p = 0.048$). Among obese blacks, haplotype 4, was associated with a 23% higher change in CRP between year 7 and year 15, compared to haplotype 1. In addition, haplotype 8 was associated with a 27% lower change in CRP between year 7 and year 15 among obese blacks. Among obese whites, haplotype 4 was associated with 33% higher change in CRP between year 7 and year 15, compared to haplotype 1. However, global test of associations of *IL1B* haplotypes with change over time in CRP levels among obese whites was not significant. Tests of haplotype and year 15 BMI interactions were not significant among blacks and whites (*p*-values ranging from 0.174 to 0.965).

4. Discussion

Overall, we did not find significant independent associations of common *IL1B* genetic variation with CRP levels in the CARDIA population. However, our data suggests a weak to modest association between *IL1B* genetic variation and change in CRP levels among obese young adults. Obesity seems to modify the association of haplotype 4 and haplotype 8 with both the level and change in CRP among blacks and the association of haplotype 4 with change in CRP among whites. Although the *p*-value for the global haplotype and change in CRP level associations among obese blacks were marginal after correction for multiple testing and interaction tests were not significant, it should be noted that the Bonferroni correction is conservative and the study may not be powered enough for the interaction tests. Furthermore, the observations that a SNP that marks haplotype 4, SNP 7114 (rs1143642) also had similar suggestive individual association with increases in CRP while haplotype 8 includes a SNP, SNP 3298 (rs3917356) that also had suggestive individual associations with decreases in CRP strengthen the evidence for a possible association.

The associations of *IL1B* genetic variation and IL1B levels with CRP levels, inflammation and atherosclerosis has been a subject of numerous experimental and population studies [14,5, 22–25]. To date, these studies have included only three *IL1B* SNPs [22–25], denoted in the literature as −511 C > T, +3953 C > T and +3954 C > T. Determining the corresponding SNPs in the SeattleSNPs resource is imperfect because only for the −511 C > T SNP has the genomic context been published [14]. Assuming that +3954 is relative to the same landmark and that +3953 is the same SNP as +3954, −511 corresponds to SeattleSNPs position number 794 while +3954 corresponds to SeattleSNPs position number 5277. SNP 794 was not in the final set of tag-SNPs that were typed, nor was it in bins tagged by the selected tag-SNPs.

Among participants with or without angiographic evidence of coronary artery disease, individuals with *IL1B* +3954 T/T genotype had two- to threefold higher CRP levels, as compared with individuals with *IL1B* +3954 C/C genotype ($p < 0.001$) after adjustment for gender, age and smoking [24]. In a cross-sectional analysis, Latkovskis et al. reported that among patients with CAD, carrier status for *IL1B* +3954 T allele correlated with higher log-CRP values ($p < 0.01$) [25]. However, other studies of genetic variations in the *IL1B* gene and CRP levels have not demonstrated such associations [26]. Ray et al. reported no significant association between *IL1B* −511, *IL1B* +3953 and absolute levels or change between 24 and 48 h of CRP among patients with acute coronary syndrome [26]. In our study, SNP 5277 (corresponding to SNPs +3953 and +3954 in previous studies) was not associated with CRP level. Observed inconsistencies between study findings could result from differences in study population that relate to population stratification or disease/health status. Several other potential *IL1B* SNPs among blacks and whites were identified in our study that should be investigated in relation to CRP level variations in other populations.

Based on the role of *IL1B* gene on adipose tissue regulation, investigators have explored potential interrelationships between obesity, *IL1B* genotype and CRP levels [14,15]. Um et al. demonstrated that frequency of the *IL1B* +3953 T allele was significantly decreased in the overweight group (BMI 25.0–29.9) compared to frequency in the lean group (BMI < 25.0) (OR: 0.20 95% CI 0.07–0.61; *p*-value = 0.004) and this was related to significant differences in serum IL1B concentration among obese and overweight as compared to lean groups [14]. Such *IL1B* SNP 5277 allele frequency differences were not observed among groups classified by BMI in our study population. Markovic et al. found that among healthy non-smoking men, CRP and triglyceride levels were positively correlated in participants with *IL1B*−511TT genotype and not in participants with *IL1B* −511CC genotype, implying that possession of a genotype that may exacerbate inflammation may tighten the association between triglycerides

and CRP levels [15]. It may be hypothesized that the association between genotype (*IL1B*) and inflammation (CRP level) may vary by the presence or absence of another risk factor (obesity).

Several mechanisms have been postulated to account for the association between IL-1 and CRP levels [7–10]. Besides its indirect role in augmentation of production of other interleukins, such as IL-6, IL-1 directly induces CRP expression at the transcriptional level through two overlapping response elements; binding sites for CCAAT-box/enhancerbinding protein-B (C/EBP-B) and p50-nuclear factor-κB (p50-NFκB) [9,10]. Interestingly, it has been proposed that fibrates, which are PPAR-α activators, reduce formation of the complex C/EBP-B-p50-NFκB, which leads to suppression of CRP biosynthesis, suggesting that the well-known effect of fibrates on CRP levels might involve IL-1 [10].

IL1B is involved in several obesity-related functions such as adipose tissue differentiation, insulin level regulation and lipase activity [11]. Obesity has been characterized as a state of chronic low-grade inflammation with raised inflammatory markers and increased expression of inflammation-related adipokines that is characteristically different from the one observed in non-obese state [27,28]. Since IL1B has functions that are closely related to obesity and the difference in background level of inflammation among obese and non-obese individuals may alter associations of IL1B with both level and change in time CRP, similar to IL6 and CRP asso-ciations [28], obesity can play a potential effect modifier role in associations of *IL1B* genetic variations with CRP levels and change in CRP levels.

Potential limitations of our study deserve mention. Recombination can result in differences in linkage disequilibrium (LD) with unidentified loci. The differences in the MAF of some SNPs among blacks (12885, 5277, 3298, 302 and 8234) and whites (7114, 15235, 8546 and 4006) influences the statistical power to detect associations for the same SNP among blacks and whites and may account, at least in part, for the differences in SNP associations observed among the two populations. Most of the suggested potential associations related *IL1B* genetic variations to change in CRP levels, rather than cross-sectional CRP levels. Based on supporting evidence from previous investigations, it may be postulated that change in (or sub-acute or acute phase response) CRP levels may be dependent on other inflammatory genes such as *IL-1* or *IL-6* while baseline (or cross-sectional) CRP level may be highly regulated by the CRP gene [2,17,29].

Both the modest 8-year CRP change over time in this healthy population and the likelihood that *IL1B* genetic variation accounts for only a proportion of this change may have further limited the power of our study to detect associations. Evaluation at a later time and/or simultaneous consideration of variation in other genes, such as *CRP* and/or *IL-6* could prove useful. Further investigation on identified SNPs and haplotypes in other populations as well as consideration of other IL1-related genes (such as *IL-1A* and *IL-1RA*) accompanied with functional studies involving *IL1B* genetic variation and IL1B protein levels are warranted.

Evaluating associations of *IL1B* variations with CRP levels will enhance the effort to understand associations of IL1beta levels with CRP levels. Since most common genetic variations are determined at conception, the direction of relationships (potentially cause and effect) between *IL1B* variations (and by inference IL1beta levels) and CRP levels are clear in this type of study. Further, associations of *IL1B* variations and CRP levels are less likely to be confounded (less noise) by other cardiovascular risk factors than associations of IL1beta levels and CRP levels.

In summary, results from this study suggest that *IL1B* genetic variation may have a role in the regulation of CRP levels; and the association of *IL1B* genetic variation with CRP levels may potentially be modified by obesity among blacks. Further studies are needed to advance

understanding of the regulation of CRP levels and the interaction of genetic and environmental factors that influence the change in CRP levels over time.

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Table 1

Characteristics of CARDIA study population at year 15 (2000–2001)

Characteristic	Blacks		Whites	
	Men (*N* = 614)	Women (*N* = 895)	Men (*N* = 846)	Women (*N* = 934)
Age (years)	39.5 (3.7)	39.6 (3.9)	40.6 (3.3)	40.6 (3.4)
BMI (kg/m^2)	29.0 (6.1)	31.6 (7.9)	27.7 (4.8)	26.7 (6.8)
Waist circumference (cm)	93.8 (14.3)	90.3 (15.8)	93.9 (12.4)	81.6 (14.4)
SBP (mmHg)	118.7 (15.7)	116.0 (16.1)	113.7 (12.8)	106.3 (12.3)
DBP (mmHg)	78.9 (12.5)	75.5 (12.3)	75.4 (10.1)	69.5 (9.5)
Triglycerides (mg/dl)	106.1 (66.9)	83.3 (56.3)	141.0 (148)	94.5 (59.4)
Total cholesterol (mg/dl)	185.1 (40.6)	179.6 (33.2)	191.2 (38.2)	182.4 (31.9)
HDL cholesterol (mg/dl)	47.6 (13.7)	54.0 (13.6)	43.0 (11.6)	56.0 (14.8)
LDL cholesterol (mg/dl)	115.6 (35.7)	108.9 (31.1)	121.4 (32.8)	107.2 (29.1)
Fasting glucose (mg/dl)	88.2 (17.7)	86.9 (26.6)	89.3 (18.6)	82.6 (13.7)
Year 7 CRP (μg/ml)	2.7 (6.2)	4.7 (6.2)	1.7 (2.6)	2.6 (5.2)
Year 15 CRP (μg/ml)	3.1 (5.1)	4.8 (6.4)	2.0 (4.7)	2.8 (4.3)

Notes. All values are mean (S.D.). *Abbreviations*: BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2

Interleukin-1Beta (*IL1B*) tagSNPs and haplotypes in CARDIA

	TagSNPs											
SNP ID[a]	**302**	**2143**	**3298**	**4006**	**5277**	**7114**	**8234**	**8546**	**12885**	**15235**	**Blacks**[b]	**Whites**[b]
MAF [c]	11.3	46.6	27.9	27.1	12.8	21.7	14.0	34.0	16.4	40.9	-	-
Blacks (N)	(1788)	(1772)	(1695)	(1753)	(1782)	(1775)	(1723)	(1781)	(1777)	(1786)	-	-
MAF [c]	26.3	33.7	45.0	7.0	22.9	7.9	22.7	8.3	36.3	8.7	-	-
Whites (N)	(1855)	(1885)	(1827)	(1910)	(1890)	(1904)	(1842)	(1913)	(1918)	(1908)		
Reference Number	rs1143625	rs1143629	rs3917356	rs1143630	rs1143634	rs1143642	rs1071676	rs3917363	rs3917368	rs3917375		
Haplotype 1	A	T	A	C	C	C	G	C	A	C	14.9	33.6
Haplotype 2	G	C	G	C	C	C	G	C	G	C	9.4	21.7
Haplotype 3	A	T	G	C	T	C	C	C	G	C	4.5	18.6
Haplotype 4	A	C	G	A	C	T	G	T	G	G	16.8	5.8
Haplotype 5	A	T	A	C	C	C	G	C	G	C	6.2	8.0
Haplotype 6	A	T	G	C	C	C	G	C	G	C	8.8	-
Haplotype 7	A	C	G	A	T	C	C	C	G	C	5.0	-
Haplotype 8	A	T	A	C	C	C	G	T	G	G	4.9	-
Haplotype 9	A	C	G	C	C	C	G	T	G	G	4.6	-

Notes. Shaded squares represent minor alleles at each SNP position represented by the SNP identifier (SNP ID).

[a] SNP IDs are locations with respect to nucleotide position in GenBank accession AY137079.

[b] Haplotype frequencies calculated using weighed probabilities among blacks and whites.

[c] SNP minor allele frequencies (MAF) and number genotyped (N) among blacks and whites.

Atherosclerosis. Author manuscript; available in PMC 2010 March 31.

Table 3

IL1B SNPs and CRP levels among blacks and whites

SNP position	CRP level[a]		Change in CRP level[b]	
	Estimate (95% CI)	***p*-Value**	**Estimate (95% CI)**	***p*-Value**
Blacks				
8234 (G/C)	0.97 (0.68–1.10)	0.676	0.94 (0.84–1.05)	0.262
7114 (C/T)	1.04 (0.94–1.15)	0.468	**1.13 (1.03–1.23)**	**0.010** *
2143 (T/C)	0.99 (0.91–1.08)	0.815	1.08 (1.00–1.16)	0.053
12885 (G/A)	1.02 (0.91–1.14)	0.708	0.95 (0.86–1.04)	0.255
3298 (G/A)	1.01 (0.92–1.12)	0.768	**0.91 (0.83–0.99)**	**0.030** *
5277 (C/T)	0.99 (0.88–1.13)	0.934	0.78 (0.87–1.09)	0.653
15235 (C/G)	0.97 (0.89–1.05)	0.459	1.07 (0.99–1.16)	0.075
8546 (C/T)	0.96 (0.88–1.05)	0.359	1.06 (0.98–1.14)	0.169
4006 (C/A)	1.07 (0.97–1.18)	0.193	1.07 (0.98–1.17)	0.115
302 (A/G)	0.93 (0.81–1.05)	0.238	0.95 (0.85–1.07)	0.396
Whites				
8234 (G/C)	1.05 (0.96–1.15)	0.299	0.97 (0.90–1.05)	0.482
7114 (C/T)	1.02 (0.89–1.17)	0.747	0.96 (0.85–1.09)	0.517
2143 (T/C)	1.00 (0.93–1.08)	0.976	1.01 (0.95–1.09)	0.700
12885 (G/A)	0.98 (0.91–1.05)	0.537	1.01 (0.94–1.08)	0.831
3298 (G/A)	0.97 (0.90–1.04)	0.366	1.03 (0.97–1.11)	0.317
5277 (C/T)	1.03 (0.94–1.13)	0.486	0.96 (0.88–1.04)	0.295
15235 (C/G)	1.01 (0.89–1.15)	0.822	0.98 (0.87–1.10)	0.745
8546 (C/T)	1.04 (0.91–1.18)	0.600	1.00 (0.89–1.13)	0.964
4006 (C/A)	1.01 (0.88–1.17)	0.867	1.00 (0.88–1.14)	0.949
302 (A/G)	1.00 (0.92–1.09)	0.996	1.03 (0.95–1.11)	0.445

[a]Estimates are exponentiated model coefficients (of additive SNP models) and their 95% confidence intervals in GEE models (years 7 and 15) adjusted for age, sex and recruitment center.

[b]Estimates are exponentiated model coefficients (year 7 to year 15 change in ln(CRP)) of additive SNP effects and their 95% confidence intervals in log linear regression models adjusted for age, sex, recruitment center, BMI difference between year 7 and year 15, and baseline (year 7) ln(CRP).

*p-Value < 0.05.

Table 4

IL1B haplotypes and CRP levels among blacks and whites

Haplotypes	CRP levels[a]					
	All participants		Non-obese		Obese	
	Estimate (95% CI)	*p*-Value	Estimate (95% CI)	*p*-Value	Estimate (95% CI)	*p*-Value
Blacks	*N* = 1433		*N* = 788		*N* = 645	
Haplotype 1	Referent	Referent	Referent	Referent	Referent	Referent
Haplotype 2	0.98 (0.83–1.17)	0.853	1.11 (0.86–1.12)	0.422	0.94 (0.79–1.10)	0.427
Haplotype 3	1.02 (0.85–1.22)	0.834	1.02 (0.79–1.31)	0.892	0.94 (0.79–1.21)	0.817
Haplotype 4	1.09 (0.96–1.25)	0.171	1.01 (0.85–1.20)	0.933	1.16 (0.99–1.34)	0.055
Haplotype 5	1.08 (0.96–1.22)	0.219	1.13 (0.95–1.35)	0.152	0.96 (0.83–1.11)	0.560
Haplotype 6	1.07 (0.94–1.21)	0.323	1.05 (0.88–1.25)	0.587	0.99 (0.86–1.15)	0.935
Haplotype 7	0.97 (0.83–1.14)	0.710	0.95 (0.77–1.16)	0.593	1.03 (0.83–1.27)	0.792
Haplotype 8	0.98 (0.85–1.13)	0.823	1.17 (0.98–1.40)	0.083	**0.80 (0.66–0.97)**	**0.025**
Haplotype 9	0.88 (0.75–1.04)	0.133	0.88 (0.72–1.08)	0.229	0.95 (0.77–1.19)	0.672
Haplotype O[b]	0.95 (0.78–1.16)	0.632	0.87 (0.67–1.13)	0.293	0.88 (0.69–1.13)	0.306
Overall *p*-value		0.538		0.621		0.215
Whites	*N* = 1673		*N* = 1263		*N* = 410	
Haplotype 1	Referent	Referent	Referent	Referent	Referent	Referent
Haplotype 2	1.01 (0.92–1.10)	0.910	1.01 (0.92–1.10)	0.913	1.06 (0.88–1.27)	0.536
Haplotype 3	1.05 (0.95–1.15)	0.318	0.99 (0.90–1.09)	0.877	1.20 (1.00–1.44)	0.050
Haplotype 4	1.07 (0.91–1.25)	0.430	1.10 (0.92–1.29)	0.278	1.08 (0.84–1.39)	0.536
Haplotype 5	0.98 (0.90–1.07)	0.656	0.98 (0.90–1.08)	0.718	1.01 (0.84–1.21)	0.957
Haplotype O[b]	1.07 (0.93–1.23)	0.375	1.03 (0.90–1.18)	0.677	1.20 (0.91–1.60)	0.197
Overall *p*-value		0.825		0.846		0.415

[a] Exponentiated beta coefficients (95% confidence intervals) of GEE model comparing association between having one or more copy of each haplotype with the referent (haplotype 1) adjusted for age, sex and center.

[b] Haplotype O: haplotype that combines all haplotypes less than 4.5% frequency.

Table 5

IL1B haplotypes and change in CRP levels among blacks and whites

Haplotypes	Change in CRP levels[a]					
	All participants		Non-obese		Obese	
	Estimate (95% CI)	*p*-Value	Estimate (95% CI)	*p*-Value	Estimate (95% CI)	*p*-Value
Blacks	*N* = 1433		*N* = 788		*N* = 645	
Haplotype 1	Referent	Referent	Referent	Referent	Referent	Referent
Haplotype 2	0.99 (0.85–1.15)	0.876	0.99 (0.80–1.22)	0.926	1.04 (0.87–1.24)	0.692
Haplotype 3	1.08 (0.90–1.29)	0.416	1.03 (0.80–1.32)	0.837	1.14 (0.93–1.41)	0.207
Haplotype 4	1.12 (0.99–1.27)	0.084	1.01 (0.85–1.21)	0.889	**1.23 (1.05–1.44)**	**0.010**
Haplotype 5	1.10 (0.93–1.29)	0.276	1.02 (0.81–1.29)	0.850	1.15 (0.94–1.40)	0.174
Haplotype 6	1.03 (0.89–1.20)	0.695	0.96 (0.78–1.19)	0.734	1.11 (0.93–1.32)	0.239
Haplotype 7	1.02 (0.86–1.20)	0.827	1.03 (0.83–1.28)	0.769	1.04 (0.82–1.30)	0.758
Haplotype 8	0.89 (0.75–1.06)	0.187	1.04 (0.82–1.32)	0.747	**0.73 (0.58–0.93)**	**0.010**
Haplotype 9	1.02 (0.85–1.21)	0.865	1.07 (0.84–1.36)	0.575	0.95 (0.75–1.20)	0.658
Haplotype O[b]	1.16 (0.92–1.46)	0.208	1.00 (0.69–1.45)	0.986	1.18 (0.93–1.48)	0.166
Overall *p*-value		0.429		1.000		**0.004 (0.048)** ‡
Whites	*N* = 1673		*N* = 1263		*N* = 410	
Haplotype 1	Referent	Referent	Referent	Referent	Referent	Referent
Haplotype 2	1.09 (0.98–1.21)	0.094	1.08 (0.95–1.21)	0.181	1.09 (0.91–1.31)	0.336
Haplotype 3	1.03 (0.82–1.14)	0.621	1.00 (0.89–1.13)	0.988	1.06 (0.88–1.28)	0.527
Haplotype 4	1.09 (0.92–1.28)	0.317	1.05 (0.87–1.26)	0.608	**1.33 (1.02–1.74)**	**0.034**
Haplotype 5	1.07 (0.94–1.23)	0.285	1.06 (0.91–1.24)	0.439	1.03 (0.83–1.26)	0.817
Haplotype O[b]	1.04 (0.82–1.32)	0.739	1.05 (0.79–1.39)	0.759	1.19 (0.92–1.53)	0.183
Overall *p*-value		0.528		0.775		0.316

[a] Exponentiated beta coefficients (95% confidence intervals) of log linear regression model (for change in CRP between year 7 and year 15) comparing association between having one or more copy of each haplotype with the referent (haplotype 1) adjusted for age, sex, center and baseline CRP (year 7 ln(CRP)).

[b] Haplotype O: haplotype that combines all haplotypes less than 4% frequencies.

‡ *p*-Value after Bonferroni correction (for 12 global haplotype tests).