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The interaction of adiposity with the *CRP* gene affects CRP levels: Age Gene/Environment Susceptibility – Reykjavik Study

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Abstract

Objective—Common diseases often have an inflammatory component reflected by associated markers such as serum CRP levels. Circulating CRP levels have also been associated with adipose tissue as well as with specific *CRP* genotypes. We examined the interaction between measures of BMI, waist circumference and fat % (total fat measured by bioimpedance) with genotypes of the *CRP* gene in the determination of CRP levels.

Methods—The first 2296 participants (mean age 76±6 years, 42% men) in the AGES-Reykjavik Study, a multi-disciplinary epidemiological study to determine risk factors in aging, were genotyped for 10 SNPs in the *CRP* gene. General linear models with age and terms for interaction of *CRP* genotypes with BMI, waist circumference, and percent fat were used to evaluate the association of genotypes to CRP levels (high sensitivity method, range 0- 10 mg/L) in men and women separately.

Results—We focused on the SNP rs1205 which represents the allele that captures the strongest effects of the gene on CRP levels. Carriers of the rs1205 G allele had significantly higher CRP levels than non-carriers in a dose-dependent manner, The slope of the increase in CRP with increasing BMI (p=0.045) and waist circumference (p=0.014) was lower for AA homozygous men but did not reach statistical significance in women. The rs1205 interactions were not significant for total body fat suggesting an association with fat localization.

Conclusions—The rs1205 SNP in the *CRP* gene is associated with circulating CRP levels in a manner dependent on BMI and waist circumference in men. This suggests an influence of fat distribution on the production of low grade inflammatory markers.

Keywords

CRP gene; CRP levels; adiposity; gene/environment interaction; AGES-Reykjavik Study

Introduction

CRP has been implicated as a marker of systemic low-grade inflammation. Elevated circulating CRP levels have been found in Alzheimer´s disease [1, 2] as well as in common

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diseases such as cardiovascular disease [3, 4, 5, 6, 7] and type 2 diabetes mellitus T2DM [8, 9, 10] suggesting that these common diseases could have an inflammatory connection.

CRP is primarily produced in the liver and synthesis is regulated by other inflammatory cytokines such as IL-6 [11, 12, 13] However, in obese individuals an important part of the circulating CRP is produced in adipose tissue [14]. Circulating CRP levels have been shown to be associated with adipose tissue, and total body fat has been shown to be a predictor of CRP levels. There is evidence for a different degree of participation of the different adipose tissue compartments [15]. Visceral adipose tissue has been shown to be a promoter of low grade CRP-inflammation [16,17] and can produce higher levels of Il-6 than subcutaneous fat [18]

Circulating CRP levels have been associated to some extent with common variation in several genes [19] but primarily *CRP* gene variation [19,20,21]. This is reviewed in detail in an article by Fadi G. Hage, Alexander J. Szalai [6]. Katherisan *et al* [22] constructed a linkage disequilibrium map and found associations between individual SNPs and CRP levels, and one common triallelic *CRP* SNP that is modestly associated with serum CRP levels. Additionally, genetic variation asociated with CRP levels has been associated with coronary heart disease [21] or acute myocardial infarction [23]. Lange *et al* [4] found genetic association with CRP levels as well as CVD risk in the elderly. However, there are a number of other studies that have not been able to identify an association between *CRP* genotype and the risk of CVD [24,25,26].

The two major factors consistently influencing circulating CRP levels are adipose tissue [14–17] and the *CRP* gene itself [4, 20–22]. The aim of this study was to analyse the effects of *CRP* gene polymorphisms on CRP levels in a cohort of older Icelanders and determine if there is interaction between various measures of adiposity, and genotypes of the *CRP* gene in the determination of CRP levels.

Methods and Materials

Study Population

This sample is drawn from the first 2,296 participants who were enrolled in the Age Gene/Environment Susceptibility (AGES)-Reykjavik Study (mean age 76±6 years, 42% men). The AGES-Reykjavik Study is a follow up of the original Reykjavik Study [27], started in 1967 by the Icelandic Heart Association (IHA) where all inhabitants in the Reykjavik area, born 1907–1935, were invited to participate, comprising approximately 30.000 individuals. AGES-Reykjavik is an epidemiologic study that focuses on four biologic systems: vascular, neurocognitive, musculoskeletal and body composition and was initiated in 2002 to investigate the contribution of genetic and environmental risk factors and their interactions to disorders of importance in old age. All participants signed an informed consent form and the AGES-Reykjavik Study is approved by the Icelandic National Bioethics Committee (VSN: 00-063), the Data Protection Authority and the Institutional Review Board of the National Institute on Aging. A more detailed description of the AGES-Reykjavik study and collection of data can be found elsewhere[28].

Measurements

Blood pressure and anthropometric data including BMI and waist circumference were collected using standardized protocols [28]. Individuals missing either BMI or waist circumference measurements were excluded. A Xitron HYDRA ECF/ICF, Model 4200, was used to measure body composition with the bio-electrical impedance method (BIA) to assess the composition of the total body. From these BIA data, and additional variables such as age, gender and body weight, the fat-free mass (FFM, in kg) of the body can be estimated

using prediction equations. Fat mass (FM, in kg) can subsequently be calculated as body weight minus FFM.

High sensitivity CRP was measured on an Hitachi 912, using reagents from Roche Diagnostics and following the manufacturer's instructions. Both within- and between-assay quality control procedures were used and the coefficient of variation of the method was 1.3% to 3.4%, respectively, through the period of data collection. The assay could detect a minimal CRP concentraton of 0.1 mg/L and values below this level were classified as undetectable. All participants in this study had detectable CRP levels. Persons (145) with CRP levels greater than 10 mg/L were excluded, as this high level of CRP was considered to be due to the acute-phase response.

Fasting blood glucose, total cholesterol, HDL cholesterol and triglycerides were also measured on a Hitachi 912, using reagents from Roche Diagnostics and following the manufacturer's instructions. Trained interviewers administered a health history questionnaire to obtain smoking history information (ever smokers).

The ten SNPs in the *CRP* gene: rs2808630, rs2808631, rs1205, rs1130864, rs1800947, rs1417938, rs3093062, rs2027471, rs1341665 and rs2808634, were analysed using an Illumina Golden gate assay performed by Illumina in San Diego. These SNPs were chosen as candidate SNPs to cover the *CRP* gene in a larger group of candidate genes as part of a cardiovascular panel. The SNPs are overlapping with SNPs as used in other studies [21,22]. Two SNPs (rs2808631 and rs3093062) were non-polymorphic in the samples examined and DNA samples from seven individuals failed to be genotyped.

Statistical analyses

CRP was log-transformed and analysed with general linear regression models by sex and adjusted for age. rs1205 was entered as a categorical variable with genotype AA as the reference. Association with body fat measurements was estimated by genotype-specific slopes by introducing interaction terms. The significance of the interaction was found by testing the hypothesis of equal slopes between genotypes based on an F-test from the general linear model. The level of significance was set at 0.05. We analyzed the data using SAS/STAT® software, version 9.1.

Results

Table 1 shows the general characteristics of the study cohort. Women have higher CRP levels than men as expected, and higher fat mass %. There is a significant increase in serum CRP levels with increasing BMI ($r = 0.26$, $r^2 = 0.07$, $p < 0.0001$), waist circumference ($r = 0.21$, $r^2 = 0.05$, $p < 0.0001$) and fat mass % ($r = 0.21$, $r^2 = 0.05$, $p < 0.0001$) in both sexes. These factors account for 5–7% of the variance of CRP levels, shown by r^2.

The observed allele frequencies for all SNPs were consistent with expectation under Hardy-Weinberg equilibrium ($p<0.01$). Linkage disequilibrium (LD) values (r^2) are shown in Table 2a. The following individual SNPs, rs1205, rs1130864, rs1800947, rs1417938, rs2027471, and rs1341665, were significantly associated with CRP levels, when tested individually after adjusting for age and sex, (Table 2b). There was a dose dependent decrease in CRP levels with the minor allele of rs1205 in men (Table 3). Looking at the LD values in Table 2a, there are three distinct groups of tagging SNPs that can be observed: 1. rs1800947 does not capture the effect of other SNPs 2. rs1205 captures the effects of rs2027471 and rs1341665, 3. rs1130864 captures the effect of rs1417938 on CRP levels. Haplotypes derived from these SNPs were tested and no clear evidence for stronger association to CRP levels with any one haplotype as compared to individual SNPs was observed.

All SNPs were tested to see if the effects of anthropometric factors on CRP levels vary across genotypes. A significant effect was found with SNPs rs1205, rs2027471 and rs1341665. As discussed above the two latter SNPs rs2027471 and rs1341665 are in complete linkage disequilibrium with rs1205 and do not capture any signal independent of and beyond that observed between rs1205 and CRP levels, adjusted for sex and age as expected from the LD. Therefore, we focused on the SNP rs1205 which represents the allele that captures the strongest effects of the gene on CRP levels. Another SNP rs1800947 is also strongly associated with CRP levels, but the MAF of rs1800947 is so low it is difficult to fully analyse this SNP in the context of interaction with BMI.

The interaction of BMI, waist circumference and fat mass % with genotypes of rs1205 on CRP levels for both men and women is shown in Table 4. There is interaction between BMI ($p=0.045$) and rs1205 and also between waist circumference and rs1205 ($p=0.014$) in men only as shown by the beta coefficients of the association. The increase in CRP levels with BMI and waist circumference is significantly different for the AA genotype than for the GA and GG genotypes in men. This association for BMI and CRP levels is shown in Figure 1. However, this is not the case for fat mass %. BMI and waist circumference are highly correlated factors, though BMI and fat mass % are only moderately correlated. No significant interaction was found between anthropometric factors and genotype in women although the slope for the increase in CRP levels with BMI in AA homozygotes is not as steep as for the G allele carriers.

Discussion

Measuring of inflammatory markers has been used to try to improve the prediction of common diseases. CRP is one such inflammatory marker that has been associated with common disease including coronary heart disease and diabetes and therefore it is important to know what factors can influence CRP levels. The results reported here are consistent with many studies where polymorphisms in the *CRP* gene are associated with CRP levels. In addition the results presented here confirm the effect of adipose tissue on circulating CRP levels found in other studies. The novel finding in this study is the interaction of adiposity with *CRP* genotypes to influence CRP levels with the relationship stronger in men than in women. This interaction is seen between BMI and *CRP* genotype and also between waist circumference and *CRP* genotype, but is statistically significant in men only.

Total body fat has been shown to be a good predictor of circulating CRP levels but it is also important to understand the relevance of fat distribution in the production of low grade inflammatory markers. BMI, total body fat, and waist circumference, thought to be a surrogate for visceral fat, are shown here to be positively associated with CRP levels, in both men and women. The AA genotype of the rs1205 SNP is associated with low CRP levels. In men, BMI and waist circumference have a different effect on CRP levels in individuals with the AA genotype of the rs1205 SNP than carriers of the G allele. The association of the adiposity measurements with CRP levels is carried by the AG and GG genotypes. On the other hand the rs1205 interactions were not significant for total body fat. These results support other studies where visceral fat has been shown to be important as a promotor of moderately increased CRP levels [16] and in addition suggest gene/environment interaction where the fat tissue type and localization modifies the expression of the *CRP* gene. In women, the effect is in the same direction but not statistically significant. The difference between the sexes can in part be explained by the fact that men, of the same age and BMI, have a different fat distribution [17] than women, with less subcutaneous fat and proportionally more visceral fat. This in turn further supports the possibility that it is the visceral fat that produces a factor that interacts with the *CRP* gene and calls out for using more detailed fat measures.

The AA genotype of the rs1205 SNP involved in the interaction effects with adiposity measures shown in this study has also been found to be associated with lower cardiovascular mortality [4]. The effect of this genotype on CRP levels could partly explain the relationships between central body fat depots and cardiovascular risk complications. Genetic effects in common diseases are generally small [26, 29] but gene environment interaction such as reported here could be important in modulating risk for common diseases.

Many studies have put emphasis on determining haplotype effect on disease. Risk haplotypes in the *CRP* gene have been reported for cardiovascular disease [22] and diabetes [30,31] and CRP level has been shown to be an independent risk factor for both these common diseases although not over and above other known risk factors [3]. In our data these haplotypes did not add to the effect on CRP levels beyond the effect of the single SNP, rs1205. This is most likely reflected in the fact that there is extremely strong LD over the *CRP* gene as identified with our panel of SNPs and has been discussed in a recent review paper [6].

In summary, in men the effect of BMI and waist circumference on the levels of circulating CRP may be mediated through the *CRP* gene with the possibility that there may be an adipose tissue produced factor that affects the *CRP* gene expression.

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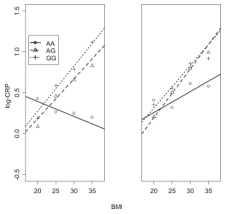

Figure 1.
The association of BMI with logCRP in rs1205 genotypes. The increase in CRP levels with BMI is significantly different ($p<0.05$) for the AA genotype than for the GA and GG genotypes in men (left view) but not in women (right view). The marks (dot, triangle, and cross) represent mean log-CRP values by genotypes around bmi values of 20, 25, 30, and 35 using bins of width 5.

Table 1

General characteristics

Characteristics	MEN		WOMEN	
	n	Mean (SD / 95%CI)	n	Mean (SD / 95%CI)
Age (years)	904	76.3 (5.6)	1226	76.2 (5.8)
SBP (mm Hg)	904	142.4 (20.4)	1226	141.6 (21.2)
Anthrompometric measures				
BMI, kg/m^2	904	26.6 (3.6)	1226	26.9 (4.8)
Waist circumference, cm	904	101.8 (10.3)	1226	99.7 (12.9)
Fat percent, %	757	32.8 (6.5)	923	42.4 (5.6)
Blood measurements				
CRP, mg/L*	904	1.73 (0.75;3.98)	1226	1.86 (0.80;4.29)
Glucose, mM	904	6.0 (1.2)	1226	5.7 (1.0)
Cholesterol, mM	904	5.3 (1.0)	1226	6.1 (1.1)
HDL, mM	904	1.4 (0.4)	1226	1.7 (0.4)
Triglycerides, mM*	904	1.07 (0.68;1.69)	1226	1.14 (0.73;1.78)

* geometric means

Table 2

a. Linkage disequilibrium of SNPs (3'-5' order) tested in the CRP gene.								
LD(r2)	**rs2808630**	**rs1205**	**rs1130864**	**rs1800947**	**rs1417938**	**rs2027471**	**rs1341665**	**rs2808634**
rs2808630	1	0,197995	0,187928	0,0281943	0,191442	0,205566	0,205915	0,975775
rs1205		1	0,222652	0,143046	0,2231	0,967392	0,965347	0,191156
rs1130864			1	0,0318752	0,994888	0,22812	0,226536	0,202133
rs1800947				1	0,0324988	0,141475	0,141725	0,0277186
rs1417938					1	0,228684	0,227288	0,204529
rs2027471						1	0,998964	0,198381
rs1341665							1	0,198719
rs2808634								1

b. Correlation of genotypes of individual SNPs in the CRP gene with CRP levels.			
SNP	**MAF**	**Beta**[†]	**p-value**
rs2808630	0.31	−0.037	0.19
rs1205	0.31	−0.116	$3.1*10^{-5}$
rs1130864	0.32	0.110	$7.7*10^{-5}$
rs1800947	0.06	−0.235	$5.2*10^{-6}$
rs1417938	0.32	0.115	$3.7*10^{-5}$
rs2027471	0.32	−0.103	$1.9*10^{-4}$
rs1341665	0.32	−0.101	$2.8*10^{-4}$
rs2808634	0.30	−0.044	0.12

[††] Beta values are relative to the major allele.

Table 3

CRP levels according to rs1205 genotypes, adjusted for age and excluding CRP >10mg/L

MEN rs1205	**CRP mg/L (95%CI)**†	**p**
AA n=77	1.33 (1.11 ; 1.60)	
AG n=411	1.69 (1.54 ; 1.80)	0.0313‡
GG n=421	1.89 (1.75 ; 2.04)	0.0007
WOMEN rs1205	**CRP mg/L (95%CI)** †	**p**
AA n=119	1.54 (1.33 ; 1.80)	
AG n=562	1.86 (1.74 ; 2.00)	0.0261
GG n=554	1.94 (1.80 ; 2.08)	0.0077

†geometric means

‡Between AG and GG p=0.0256

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Table 4

Interaction between the rs1205 genotype and anthropometric measurements on circulating CRP levels.

rs1205 genotype	**BMI**	**N=904**	**WC**	**N=904**	**F%**	**N=754**
MEN	**β-coefficient**	***SE***	**β- coefficient**	***SE***	**β-coefficient**	***SE***
AA	−0.003	0.022	−0.006	0.008	0.030	0.018
AG	0.049	0.011	0.015	0.004	0.021	0.007
GG	0.060	0.011	0.020	0.004	0.032	0.007
p for interaction	0.045		0.014		0.563	
WOMEN	**BMI**	**N=1226**	**WC**	**N=1226**	**F%**	**N=923**
AA	0.031	0.017	0.012	0.006	0.025	0.017
AG	0.065	0.007	0.017	0.003	0.028	0.007
GG p for interaction	0.048 0.088	0.007	0.015 0.780	0.003	0.050 0.054	0.007

BMI = body mass index
WC = waist circumference
F% = fat mass %