

## Brief Genetics Report

# Intercellular Adhesion Molecule-1 Concentration Is Genetically Correlated With Insulin Resistance, Obesity, and HDL Concentration in Mexican Americans

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The metabolic syndrome and type 2 diabetes are associated with endothelial activation (and thus with inflammatory processes leading to atherosclerosis), but the mechanisms that underlie these associations are not fully understood. Endothelial intercellular adhesion molecule (ICAM)-1 plays an important role in the recruitment of immune cells during the development of atherosclerotic plaque and is a marker of inflammatory disease. We performed bivariate quantitative genetic analyses to estimate genetic and environmental correlations between circulating ICAM-1 concentration and 17 phenotypes associated with the metabolic syndrome. Our study population comprised 428 adults in 20 extended Mexican-American families from the San Antonio Family Heart Study (SAFHS). Circulating ICAM-1 concentration is heritable ( $h^2 = 0.56$ ). ICAM-1 concentration showed significant positive genetic correlations (range 0.32–0.52,  $P < 0.05$ ) with fasting insulin, insulin 2 h after oral glucose challenge, homeostasis model assessment of insulin resistance, BMI, waist circumference, and leptin concentration; negative genetic correlation with HDL3 cholesterol concentration; and negative environmental correlation with adiponectin concentration. Significant genetic correlations were not found between ICAM-1 and fasting or 2-h serum glucose or systolic or diastolic blood pressure. Thus, ICAM-1 expression may share common genetic modulation with traits related to obesity, insulin resistance, and HDL3 cholesterol, but not with hyperglycemia or hypertension per se. *Diabetes* 53:2691–2695, 2004

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CVD, cardiovascular disease; ICAM, intercellular adhesion molecule; SAFHS, San Antonio Family Heart Study.

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Individuals exhibiting the metabolic syndrome, a suite of physiological conditions comprising obesity, dyslipidemia, hypertension, and type 2 diabetes (1), have a greatly increased risk of atherosclerosis and other forms of cardiovascular disease (CVD). Increasing attention has been focused on the importance of inflammatory processes in the development of atherosclerosis (2,3). The endothelial cell molecule intercellular adhesion molecule (ICAM)-1 plays an important role in the initiation of the inflammatory process (3–5). ICAM-1 is normally expressed at low levels on the surface of arterial endothelial cells; when the endothelium is activated in response to physical or chemical damage, expression is increased. ICAM-1 interacts with adhesion molecules on leukocytes as a first step toward migration of the leukocytes into the arterial intima; thus, ICAM-1 plays a key role in the recruitment of immune cells during the development of atherosclerotic plaque. Circulating soluble ICAM-1 is a biochemical marker associated with atherosclerotic progression and other inflammatory disease processes (5).

Although its role in the atherosclerotic process is now recognized, much remains to be learned about the mechanisms that regulate ICAM-1 expression. A large number of intercorrelated traits have been used to define different aspects of the metabolic syndrome, and while long-duration hyperglycemia, dyslipidemia, and hypertension are singly and jointly associated with endothelial activation, the mechanisms that underlie these associations are not fully understood.

Variance-component-based pedigree analysis may be useful in dissecting biochemical pathways when there is limited prior knowledge about the mechanisms underlying disease processes (6,7). In particular, bivariate analysis of a pair of traits can partition phenotypic correlations between the traits into presumed environmental and additive genetic components, related as

$$\rho_P = \rho_G \sqrt{h_a^2 h_b^2} + \rho_E \sqrt{(1 - h_a^2)(1 - h_b^2)} \quad (1)$$

where  $\rho_P$ ,  $\rho_G$ , and  $\rho_E$  are the phenotypic, additive genetic, and environmental correlations, respectively, between the traits, and  $h_a^2$  and  $h_b^2$  are the trait heritabilities. (The heritability is an estimate of the proportion of the phenotypic variance of the trait that is due to the additive effect

of shared alleles; consequently, “environmental” effects can also include epistatic and dominance interactions between genes [8]).

A genetic correlation significantly different from zero suggests that both traits are influenced by products of the same gene or of genes in linkage disequilibrium. Such a finding is useful for at least two reasons. First, it can provide a basis for future linkage studies: the additional information from the correlation between traits may provide more power for linkage detection than either trait could provide alone (9). Second, the nature of the correlated phenotypes (and ultimately, of positional candidate genes in the linkage regions) may provide clues about the biochemical pathways underlying the phenotypic associations. The latter outcome, in unplanned form, can be seen in the rapidly accumulating evidence from studies that, starting from different phenotypes (e.g., adiposity, hypertension, or insulin levels), find evidence of linkage to the same or overlapping genomic regions (10).

Even in the case where the genetic correlation is different from one (incomplete pleiotropy), hypotheses could theoretically be prioritized by the magnitude of their effects because the square of the genetic correlation coefficient estimates the proportion of the total variance of each trait that is due to effects of shared genes. For example, if two hypothetical traits are genetically correlated at  $r_G = 0.5$ , shared genes account for ~25% of the additive genetic variance of either trait. This is a meaningful effect, given that the regulation of complex trait expression almost certainly involves the products of multiple genes that in turn are involved in multiple biochemical pathways. The identification of genetically correlated traits provides a rational starting point for future dissection of this complex genetic architecture. As an exploratory step in the quantitative genetic analysis of ICAM-1 expression, we have sought to develop such hypotheses explicitly by examining the correlation of ICAM-1 to a suite of traits of the metabolic syndrome in a population with elevated prevalence of obesity and type 2 diabetes.

**The San Antonio Family Heart Study.** The San Antonio Family Heart Study (SAFHS) is an ongoing project to investigate the genetics of CVD and its risk factors in Mexican Americans (11). For this study, we measured ICAM-1 concentration in serum samples from 428 participants from 20 SAFHS families (Table 1). This subset is representative of the full study cohort in age, sex ratio, menopause status, and diabetes prevalence (Table 2).

**Metabolic syndrome phenotypes.** SAFHS participants have been measured for anthropometric traits and a number of biochemical phenotypes, as described elsewhere (7,11,12). For comparison to ICAM-1, we chose phenotypes relating to four aspects of the metabolic syndrome (1): 1) glucose homeostasis (fasting plasma glucose and insulin levels, glucose and insulin levels at 2 h after oral glucose challenge, and the homeostasis model assessment of insulin resistance [13]), 2) obesity (BMI, waist circumference, and serum levels of the adipose cytokines leptin [7] and adiponectin [14]), 3) hypertension (systolic and diastolic blood pressure), and 4) dyslipidemia (plasma total cholesterol, LDL cholesterol, LDL median particle diameter, total HDL cholesterol, HDL3 cholesterol subfraction, and triglycerides). Table 3 sum-

TABLE 1  
Distribution of relative pairs by relationship type in 20 SAFHS families ( $n = 428$ )

Type of relationship	Coefficient of relationship	Number of pairs
Parent-offspring	0.5000	350
Full siblings	0.5000	479
Grandparent-grandchild	0.2500	85
Avuncular	0.2500	778
Half siblings	0.2500	50
Great grandparent/child	0.1250	1
Grand avuncular	0.1250	234
Half avuncular	0.1250	177
First cousins	0.1250	957
Great grand avuncular	0.0625	2
Half grand avuncular	0.0625	12
First cousins, once removed	0.0625	904
Half first cousins	0.0625	241
First cousins, twice removed	0.0312	6
Second cousins	0.0312	211
Second cousins, once removed	0.0156	1
Double first cousins	0.2500	8
Double first cousins, once removed	0.1250	19
Double second cousins	0.0625	10
Half first cousins and second cousins	0.0937	4
Total number of pairs	—	4,529

marizes the distributions of these phenotypes in the study sample (sample sizes vary because of missing observations for some phenotypes). There is no significant difference in mean ICAM-1 concentration in study participants with diabetes using antidiabetic medication (median [interquartile range]: 581.82 ng/ml [483.49–765.86],  $n = 36$ ), with diabetes not using medication (561 [402.93–758.38],  $n = 32$ ), or without diabetes (581.82 [434.26–719.10],  $n = 360$ ) (ANOVA,  $\log_e$ -transformed data:  $F = 0.8192$ ,  $P = 0.44$ ).

Additive genetic heritability ( $h^2$ ) was estimated for each phenotype using the quantitative genetic analysis software package SOLAR (6), with sex, age, and menopause status as covariates. ICAM-1 concentration is significantly heritable ( $h^2 = 0.56$ ,  $P = 1.7 \times 10^{-15}$ ). The heritability of adiponectin concentration in this sample is 0.59 ( $P = 3.7 \times 10^{-10}$ ), supporting the previous finding of a substantial additive genetic component to variation in this trait in a population of northern European ancestry (14). All other traits we examined are significantly heritable in our sample (Table 3), consistent with previous findings (7,11,12,15) in this population.

**Genetic and environmental correlations.** Bivariate analyses were performed in SOLAR for pairwise combinations of ICAM-1 and each of the metabolic syndrome phenotypes, with sex, age, and menopause status as covariates (Table 4). Significant positive phenotypic and genetic correlations were found between ICAM-1 and three phenotypes related to glucose homeostasis (insulin at fasting and 2-h postglucose challenge and homeostasis model assessment) but not fasting or 2-h plasma glucose. ICAM-1 level was also significantly phenotypically and genetically correlated with three obesity-related phenotypes: BMI, waist circumference, and serum leptin, which is known to vary positively with adiposity. In addition, a significant negative environmental correlation was found

TABLE 2  
Characteristics of the study sample and study population

Characteristic	Study sample			SAFHS cohort		
<i>n</i>	428			1,431		
Sex (M/F) [ <i>n</i> (% men)]	189/239 (44.16)			582/849 (40.67)		
Diabetes [ <i>n</i> (% of total)]	68 (15.89)			222 (15.51)		
Postmenopause [ <i>n</i> (% of women)]	47 (19.66)			192 (22.62)		
	<i>n</i>	Median	Mean ± SE	<i>n</i>	Median	Mean ± SE
Age (years)	428	38	38.51 ± 0.79	1,431	37	39.29 ± 0.44
Age at diabetes onset, if affected (years)	62	46	48.52 ± 1.84	209	46	47.89 ± 1.01
Diabetes duration, if affected (years)	62	5	8.17 ± 1.29	209	2	6.06 ± 0.57

Age at diabetes onset and duration of diabetes were not available for some affected participants. There are no significant differences (threshold  $P < 0.05$ ) between sample and cohort by  $\chi^2$  test for sex, diabetes prevalence, or menopause status or by two-tailed  $t$  test of means for age, age at diabetes onset, or diabetes duration.

between ICAM-1 and serum adiponectin. The sign of this correlation agrees with previous findings (14) that adiponectin is negatively (phenotypically) correlated with adiposity. No significant correlations were found between ICAM-1 and either systolic or diastolic blood pressure.

Numerous studies associate increased risk of CVD with elevated levels of cholesterol and triglycerides, elevated LDL (especially small, dense LDL), and lower levels of HDL. In this study, ICAM-1 was negatively correlated with HDL cholesterol (the genetic correlation was marginally significant,  $P = 0.050$ ) and in particular with the HDL3 cholesterol subfraction (both phenotypic and genetic correlations significant at  $P < 0.05$ ). Notably, higher levels of HDL are reported to be protective against atherosclerosis; in particular, the smaller-diameter HDL3 subfraction is reported (16,17) to have especially high antioxidant activity. None of the other lipid phenotypes we examined showed significant correlations with ICAM-1.

The metabolic syndrome-related traits that are significantly correlated with ICAM-1 expression in this study fall into three classes: insulin resistance, obesity, and one component of dyslipidemia. However, significant genetic

correlations were not found with traits representative of two other components of the metabolic syndrome: hypertension and hyperglycemia.

Our negative findings with respect to plasma glucose levels may seem surprising, since several studies report increased ICAM-1 expression in response to acute hyperglycemia in endothelial cell culture (18–20), although there is at least one recent discordant study (21). However, experimental results in human subjects offer less clear evidence for an effect of acute hyperglycemia on ICAM-1. Separate studies (22,23) report that oral glucose challenge increases in vivo-circulating levels of some other cell adhesion molecules, but not ICAM-1. In any case, our ICAM-1 measurements were made in samples from fasting individuals and thus should not reflect acute hyperglycemic effects. Also, as noted, we did not find a significant difference in ICAM-1 levels in individuals with and without diabetes. Our results do not exclude an independent causal relationship between hyperglycemia and endothelial activation, but do suggest that this association involves mechanisms other than shared genetic regulation with ICAM-1.

TABLE 3  
Clinical and biochemical characteristics of the study sample

Phenotype	<i>n</i>	Median (interquartile range)	Heritability ± SE*
ICAM-1 (ng/ml)	428	554.73 (433.63–722.61)	0.56 ± 0.09†
Fasting glucose (mmol/l)	428	4.87 (4.49–5.38)	0.20 ± 0.07‡
2-h glucose (mmol/l)	408	5.66 (4.60–7.54)	0.31 ± 0.09†
Fasting insulin (pmol/l)	422	68.40 (41.10–121.50)	0.43 ± 0.09†
2-h insulin (pmol/l)	397	312 (174.6–597.3)	0.32 ± 0.11‡
HOMA-IR	422	2.52 (1.48–5.03)	0.44 ± 0.08†
BMI (kg/m <sup>2</sup> )	422	28.82 (25.12–33.35)	0.50 ± 0.09†
Waist circumference (mm)	422	930 (840–1,035)	0.43 ± 0.01†
Leptin (ng/ml)	414	8.82 (3.79–15.45)	0.44 ± 0.11†
Adiponectin (µg/ml)	334	8.56 (6.42–10.92)	0.59 ± 0.11†
Systolic blood pressure (mmHg)	422	116.5 (109–127)	0.32 ± 0.09†
Diastolic blood pressure (mmHg)	422	71 (64–77)	0.22 ± 0.09‡
Total cholesterol (mmol/l)	428	4.76 (4.16–5.42)	0.43 ± 0.08†
LDL cholesterol (mmol/l)	424	2.75 (2.31–3.34)	0.43 ± 0.09†
LDL median particle diameter (nm)	428	26.65 (26.62–26.96)	0.33 ± 0.08†
Total HDL cholesterol (mmol/l)	428	1.27 (1.06–1.50)	0.67 ± 0.09†
HDL3 cholesterol (mmol/l)	427	1.11 (0.96–1.24)	0.54 ± 0.10†
Triglycerides (mmol/l)	428	1.37 (1.12–1.88)	0.42 ± 0.09†

\*All measures except LDL cholesterol and LDL mean particle diameter were log<sub>e</sub> transformed prior to heritability analysis. Significance levels (likelihood ratio test): † $P < 0.0001$ ; ‡ $P < 0.001$ . HOMA-IR, homeostasis model assessment of insulin resistance.

TABLE 4  
Phenotypic, additive genetic, and environmental correlations between ICAM-1 and traits of the metabolic syndrome

	<i>n</i>	$\rho_P \pm SE$	$\rho_G \pm SE$	$\rho_E \pm SE$
Glucose homeostasis				
Fasting glucose	428	0.01 ± 0.05	0.05 ± 0.19	-0.01 ± 0.09
2-h glucose	408	0.07 ± 0.05	0.21 ± 0.17	-0.04 ± 0.11
Fasting insulin	422	0.25 ± 0.04*	0.45 ± 0.13†	0.06 ± 0.11
2-h insulin	397	0.18 ± 0.05‡	0.51 ± 0.19§	-0.05 ± 0.12
HOMA-IR	422	0.22 ± 0.05*	0.41 ± 0.13§	0.05 ± 0.11
Obesity related				
BMI	422	0.21 ± 0.05*	0.32 ± 0.15§	0.07 ± 0.12
Waist circumference	422	0.26 ± 0.04‡	0.45 ± 0.15†	0.07 ± 0.12
Leptin	414	0.22 ± 0.05*	0.52 ± 0.15†	-0.07 ± 0.12
Adiponectin	334	-0.18 ± 0.05‡	-0.08 ± 0.15	-0.31 ± 0.15
Hypertension				
Systolic blood pressure	422	0.05 ± 0.05	0.03 ± 0.18	0.05 ± 0.11
Diastolic blood pressure	422	0.04 ± 0.05	0.05 ± 0.20	0.02 ± 0.10
Dyslipidemia				
Total cholesterol	428	-0.07 ± 0.05	-0.12 ± 0.15	-0.04 ± 0.11
Total LDL cholesterol	424	0.01 ± 0.05	0.06 ± 0.16	-0.07 ± 0.11
LDL mean particle diameter	428	-0.08 ± 0.05	0.04 ± 0.16	-0.17 ± 0.10
Total HDL cholesterol	428	-0.24 ± 0.05*	-0.27 ± 0.14	-0.13 ± 0.14
HDL3 cholesterol	427	-0.23 ± 0.05*	-0.37 ± 0.14§	-0.05 ± 0.12
Total triglycerides	428	0.06 ± 0.05	-0.05 ± 0.16	0.14 ± 0.11

All measures, except LDL cholesterol and LDL mean particle diameter, were  $\log_e$  transformed prior to analysis. Significance levels (likelihood ratio tests): \* $P < 0.0001$ ; † $P < 0.01$ ; ‡ $P < 0.001$ ; § $P < 0.05$ ; ||marginally significant at  $P = 0.050$ . HOMA-IR, homeostasis model assessment of insulin resistance.

The association between ICAM-1 expression and insulin resistance found in this study is consistent with clinical evidence relating insulin resistance and inflammation. The molecular basis of this relationship is obscure, but intriguing studies have begun to reveal the effects of macrophage-generated inflammatory cytokines on insulin signaling, as well as the expression of inflammatory cytokines by macrophages within adipose tissue, and by adipocytes themselves (24). Genetic correlations between insulin resistance and ICAM-1 could reflect joint effects of cytokine expression; alternatively, variation in ICAM-1 regulation could lead to macrophage activation and thus indirectly to insulin resistance. To address this question, the present study could be extended to examine genetic relationships between levels of ICAM-1 and inflammatory cytokines in the context of obesity.

The National Cholesterol Education Program Adult Treatment Panel III includes "prothrombotic and proinflammatory states" as components of the metabolic syndrome, although these are not part of the clinical definition (1). In this study, we find strong phenotypic and genetic correlations between ICAM-1 levels and insulin resistance, obesity, and depressed HDL. These findings suggest that measures of inflammatory status, including ICAM-1 levels, may be useful as additional clinical indicators of the metabolic syndrome.

#### RESEARCH DESIGN AND METHODS

All participants were in the SAFHS, which recruited large, lower-income Mexican-American families without prior ascertainment of CVD or diabetes status, as described (11). All procedures were approved by the institutional review board of the University of Texas Health Science Center at San Antonio, and all participants gave informed consent.

**Phenotypic assessments.** The collection of phenotypic data in SAFHS has been described more fully elsewhere (7,11,12,15). Items of particular note are summarized below.

Plasma glucose and insulin levels were measured at fasting and 2 h after

administration of 75 g oral glucose, as described (11). For this study, participants were classified as having diabetes by the diagnostic criteria of the American Diabetes Association Clinical Practice Recommendations 2004 (fasting plasma glucose level  $\geq 126$  mg/dl [7.0 mmol/l], plasma glucose  $\geq 200$  mg/dl [11.1 mmol/l] at 2 h after oral glucose challenge, or both) (25). In addition, individuals were classified with diabetes if they reported using antidiabetic medication (10).

Plasma insulin concentrations are assessed as total immunoreactive insulin levels as determined by a commercial radioimmunoassay kit (Diagnostic Products, Los Angeles, CA). Homeostasis model assessment of insulin resistance values were calculated from fasting glucose and insulin measures according to the formula (fasting glucose [mmol/l]  $\times$  fasting insulin [ $\mu$ U/ml]/22.5) (13). HDL cholesterol was measured in plasma after precipitation of apolipoprotein B-containing particles with dextran sulfate-Mg<sup>2+</sup>, and HDL3 cholesterol was measured after dual precipitation, as described (11).

Adiponectin was measured in plasma (diluted 1:500) by radioimmunoassay using a commercial kit (Linco Research, St. Charles, MO). ICAM-1 was measured in serum (diluted 1:20) by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN).

**Statistical methods.** Microsoft Excel was used to estimate phenotype distribution parameters and perform group comparisons (ANOVA, *t* test, or  $\chi^2$  test). Genetic analyses were performed with the software package SOLAR (SFBR, San Antonio, TX) (6,9), with sex, age, and menopause status as covariates. Details of statistical methods are provided in an online appendix (available from <http://diabetes.diabetesjournals.org>).

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