Serum C3 but Not Plasma Acylation-Stimulating Protein Is Elevated in Finnish Patients With Familial Combined Hyperlipidemia

Kati Ylitalo, Päivi Pajukanta, Seppo Meri, Rita M. Cantor, Niina Meri-Matikainen, Juha Vakkilainen, Ilpo Nuotio, Marja-Riitta Taskinen

Abstract—A trapping defect of fatty acids due to impaired function of acylation-stimulating protein (ASP) has been suggested as one mechanism underlying the metabolic abnormalities in familial combined hyperlipidemia (FCHL). The study aimed at defining the role of ASP and complement C3 in 35 Finnish FCHL families. There was no difference in plasma ASP levels between the 66 hypertriglyceridemic FCHL patients and their 84 normotriglyceridemic relatives. No response in plasma ASP could be observed after a fatty meal in 10 FCHL patients or in 10 control subjects. In familial correlation analyses, C3 exhibited a significant sibling-sibling correlation. The FCHL patients had higher serum C3 levels than their unaffected relatives ($P<0.001$). Furthermore, serum C3 levels correlated significantly with several lipid parameters. The correlations between ASP and lipid variables were weaker than those of C3. These analyses suggest that common genes might contribute to the regulation of serum C3, triglycerides, HDL-C, free fatty acids, and insulin. The present data do not support the hypothesis that defects of the ASP pathway are reflected in plasma lipoproteins or in impaired plasma lipid clearance postprandially. (Arterioscler Thromb Vasc Biol. 2001;21:838-843.)

Key Words: acylation-stimulating protein • complement • familial hyperlipidemia • postprandial • atherosclerosis

Familial combined hyperlipidemia (FCHL) is a common hereditary dyslipidemia that predisposes the patients to premature coronary heart disease (CHD). The affected members of FCHL families present different lipid phenotypes: hypercholesterolemia, hypertriglyceridemia, or combined hyperlipidemia, as well as high serum levels of apolipoprotein B (apoB). Insulin resistance with impaired free fatty acid (FFA) suppression is also commonly encountered. It has been proposed that the failure of adipose tissue to efficiently “trap” FFA would result in an excessive FFA flux to liver and increased VLDL apoB production.

Acylation-stimulating protein (ASP) is, in vitro, a potent stimulator of triglyceride (TG) synthesis in human adipocytes. ASP mediates its effect by stimulating diacylglycerol acyltransferase, a key enzyme in TG synthesis, and by enhancing glucose uptake. Reduced capacity of TG esterification and resistance to the action of ASP have been reported in vitro in patients with hyperapobetalipoproteinemia, a lipid disorder closely related to FCHL. So far, only a few in vivo studies have investigated the effect of ASP on lipid metabolism.

Interestingly, the primary structure of ASP is identical to the inactive cleavage product of complement C3a, C3a-desArg. Adipocytes are able to secrete complement factors, including C3, from which ASP is generated through activation of the alternative complement pathway. We have previously shown that Finnish male FCHL patients have higher serum levels of complement C3 than their unaffected relatives. No data exist, however, on plasma ASP in FCHL patients.

The aim of this study was to examine the role of plasma ASP in Finnish FCHL families. The study included 150 FCHL family members from 35 FCHL families (4 to 5 subjects per family). We (1) tested whether plasma ASP or serum C3 concentrations are associated with TG levels, (2) tested whether chylomicrons induce in vivo a response in plasma ASP levels, and (3) calculated familial correlations of ASP and C3 with several FCHL-related traits.

Methods

Subjects

The study subjects were recruited at the Helsinki and Turku University Central Hospitals in Finland as a part of the European Multicenter Study on Familial Dyslipidemias (EUFAM). The FCHL probands were required to be 30 to 60 years of age, have verified CHD, and have serum total cholesterol (TC) and/or TG greater than or equal to the age- and sex-specific 90th population percentiles.

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Families with ≥2 affected family members presenting different lipid phenotypes were included. The study protocol has been presented in detail previously.14,15

Because ASP is expected to affect primarily FFA and TG metabolism and only secondarily serum cholesterol levels, we divided the study subjects into 2 groups, affected and unaffected, according to only the age- and sex-specific 90th percentile of TG, instead of using both the TG and TC levels. A total of 150 FCHL family members (66 affected and 84 unaffected, according to the serum TG level) had data on plasma ASP and were included in the study. The subjects had no secondary causes for hyperlipidemia. None of the subjects were on lipid-lowering medication when examined.

Subjects Receiving Oral Fat Loads
Ten healthy, normoglycemic FCHL subjects (5 men and 5 women) with serum TG exceeding the age- and sex-specific 90th percentile (lipid phenotypes IIB or IV), and 10 age-, sex-, and body mass index (BMI)–matched normolipidemic control subjects were enrolled in the fat-load study (Table 2). One female patient and her control subject smoked 15 cigarettes per day. One patient and the corresponding control subject were postmenopausal.

The ethics committee of the Department of Medicine in Helsinki University Central Hospital and the joint ethics committee of Turku University and the Turku University Central Hospital had approved the study protocol. Informed consent was obtained from all participants.

Experimental Procedures
Blood samples for determinations of serum lipid, lipoprotein, C3, plasma ASP, and other biochemical parameters were collected during the oral glucose tolerance test (OGTT) visit of the EUFAM study or later when the patients were reexamined during an optional visit.15 Venous blood was collected in the morning after a 12-hour fast. ASP samples were centrifuged immediately at +4°C and frozen at −80°C.

Plasma ASP concentrations were measured from EDTA-plasma by ELISA (Quidel) with monoclonal human anti–C3a-desArg used as a detecting antibody. Each measurement was performed in triplicate. The interassay and intra-assay coefficients of variation were 11.9% and 2.2%, respectively. We compared the Quidel-ELISA kit with the sandwich ELISA used by Salch et al16 by determining ASP concentrations of 73 samples (not included in the present study) by both methods. The Spearman correlation coefficient for the 2 methods was 0.59, *P < 0.001.

Serum complement component C3 was determined by nephelometry using an antibody against C3c (Behringwerke AG) and a BN-100 nephelometer (Hoechst Fennica). The interassay coefficient of variation for C3 determinations was 7.6%.

Measurement of Lipids and Other Metabolic Parameters
Levels of lipids and other metabolic parameters were measured as described in detail previously.14 Briefly, serum TC, TG, and HDL cholesterol (HDL-C) (after precipitation procedures) were determined by enzymatic methods, and serum apoB by an immunoturbidimetric method. LDL was separated by sequential flotation as a detecting antibody. Each measurement was performed in triplicate. The assay and intra-assay coefficients of variation were 11.9% and 2.2%, respectively. We compared the Quidel-ELISA kit with the sandwich ELISA used by Salch et al16 by determining ASP concentrations of 73 samples (not included in the present study) by both methods. The Spearman correlation coefficient for the 2 methods was 0.59, *P < 0.001.

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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Oral Fat Load Test</th>
<th>Test meal</th>
<th>Fat content</th>
<th>Fat load</th>
<th>Energy</th>
<th>Sugar</th>
<th>Other ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1000-kcal mixed meal</td>
<td>72 g fat</td>
<td>50 g carbohydrates</td>
<td>38 g protein</td>
<td>12 hours</td>
<td>glucose</td>
<td>FFA and insulin</td>
</tr>
</tbody>
</table>

Density-Gradient Ultracentrifugation
Plasma obtained at the various time points during the fat-load test was separated by density-gradient ultracentrifugation14,15 to isolate lipoprotein fractions corresponding to chylomicrons (Svedberg flotation units [Sf] >400) and large VLDL particles (VLDL2, Sf 60 to 400).

Familial Correlations
Familial correlations of plasma ASP and serum C3 were calculated with the FCOR2 program of the SAGE release 4.0 Beta 6 using the uniform weight to pedigrees.20 The FCOR2 program performs correlation analyses in families taking into account the lack of independence between family members in assessing the significance of the correlation. All parameters used in the analyses were adjusted for age and sex before analysis by calculating residuals for these variables by linear regression analysis.

Other Statistical Analyses
Statistical comparisons were performed with version 9.0 of the SPSS for Windows software (SPSS Inc). To compare the groups for continuous variables, 2-way ANOVA was used. Because we collected the data from whole families, the study subjects were not independent. Family number was used as a random variable in ANOVA and as an independent variable in correlation analyses (multivariate analysis) to correct some of the nonindependence of study subjects. The *χ2* test was used to compare the groups for categorical variables. Probability values are presented in text and all tables assuming that all study subjects are independent. A log10 transformation was applied to the following variables: ASP, C3, TG, HDL-C, BMI, glucose AUC, fasting insulin and FFA, and the respective AUC values. AUC calculations were performed by the trapezoidal rule.

In the oral fat-load study, the subject characteristics, baseline, and area measurements were compared by the nonparametric Mann-Whitney *U* test for continuous variables and *χ2* test for categorical variables. Within-group changes from baseline to postprandial values and differences between postprandial responses of the 2 groups were assessed by repeated-measures ANOVA with the Greenhouse-Geisser adjustment.21 Logarithmic transformations were used before an ANOVA when appropriate. AUC and incremental AUC (IAUC) values were calculated as described by Matthews et al.22

Results
Patient Characteristics
Clinical and biochemical characteristics of study subjects are shown in Table 1. Men and women were distributed equally in the 2 groups. By definition, the groups differed significantly from each other in plasma levels of TG and also HDL-C and apoB. Subjects with high serum TG tended to be more obese than their normotriglyceridemic relatives (*P = 0.048). Consequently, the affected individuals also were more insulin resistant, as judged by glucose AUC, fasting insulin, and insulin AUC.

Effect of Plasma ASP and C3 on TG Phenotype
The average plasma ASP level (mean ± SD) of the 66 hypertriglyceridemic FCHL patients (144 ±49 ng/mL, range 62 to 267 ng/mL) was not significantly different from that of the 84 normotriglyceridemic relatives (125 ±43 ng/mL, range 52 to 300 ng/mL), *P = 0.19*. Serum C3 level was significantly higher in FCHL patients with high TG (1.63 ±0.43 g/L, range 0.83 to 3.38 g/L) than in the unaffected family members whose serum C3 level was 1.27 ±0.33 g/L (range 0.75 to 3.66 g/L), *P < 0.001*. The differences between the groups remained
similar when adjusted for age, sex, BMI, and fasting insulin (data not shown).

**Oral Fat Load**

Table 2 shows that the study subjects were well matched for age and BMI. The fasting ASP level (median; interquartile range) was not higher in FCHL patients than in control subjects (26 ng · mL⁻¹ · h⁻¹; 65 to 88 ng · mL⁻¹ · h⁻¹ versus 149 ng · mL⁻¹ · h⁻¹; -17 to 234 ng · mL⁻¹ · h⁻¹, P=0.10).

In both groups, plasma total TG increased significantly postprandially (P<0.001 for both groups). TG-IAUC was higher in FCHL subjects than in control subjects (7.20 mmol · L⁻¹ · h⁻¹; 4.88 to 12.06 mmol · L⁻¹ · h⁻¹ versus 3.10 mmol · L⁻¹ · h⁻¹; 2.48 to 3.97 mmol · L⁻¹ · h⁻¹, P=0.001).

TG concentration of chylomicrons (Figure 2) and VLDL₁ fractions were also significantly higher in FCHL patients at baseline (Table 2).

The individual longitudinal postprandial responses of plasma ASP are illustrated in Figure 1. There was no significant postprandial change in plasma ASP in FCHL patients (P=0.31) or control subjects (P=0.25), and the responses did not differ between the 2 groups (P=0.47, repeated-measures ANOVA). The average IAUC of ASP (median; interquartile range) was not higher in FCHL patients than in control subjects (26 ng · mL⁻¹ · h⁻¹; 65 to 88 ng · mL⁻¹ · h⁻¹ versus 149 ng · mL⁻¹ · h⁻¹; -17 to 234 ng · mL⁻¹ · h⁻¹, P=0.10).

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**TABLE 1. Subject Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FCHL-Affection Status by Age- and Sex-Specific 90th Percentile of Serum TG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affected</td>
</tr>
<tr>
<td>Age, y</td>
<td>66</td>
</tr>
<tr>
<td>Male, % (M/F)</td>
<td>66</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>66</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>66</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>66</td>
</tr>
<tr>
<td>TGmax, mmol/L</td>
<td>66</td>
</tr>
<tr>
<td>Apo B, mg/dL</td>
<td>66</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>66</td>
</tr>
<tr>
<td>Glucose AUC, mmol · L⁻¹ · h⁻¹</td>
<td>64</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>66</td>
</tr>
<tr>
<td>Insulin AUC, mU/L · L⁻¹ · h⁻¹</td>
<td>65</td>
</tr>
<tr>
<td>FFA AUC, μmol · L⁻¹ · h⁻¹</td>
<td>62</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>66</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>66</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>66</td>
</tr>
</tbody>
</table>

*Interquartile range.

**TABLE 2. Clinical and Metabolic Characteristics of Oral Fat Load Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>FCHL Patients (n=10)</th>
<th>Control Subjects (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.7 (37.7–48.6)</td>
<td>43.8 (35.2–48.2)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.6 (26.2–28.6)</td>
<td>27.6 (25.9–29.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.89 (0.85–0.97)</td>
<td>0.88 (0.82–0.94)</td>
<td>NS</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>2.77 (2.03–3.46)</td>
<td>1.14 (0.90–1.23)</td>
<td>NS</td>
</tr>
<tr>
<td>Apo B, mg/dL</td>
<td>125 (111–150)</td>
<td>88 (82–94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chylo-TG, mmol/L</td>
<td>0.13 (0.04–0.21)</td>
<td>0.01 (0.00–0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL₁-TG, mmol/L</td>
<td>1.18 (0.80–1.79)</td>
<td>0.33 (0.15–0.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.2 (4.3–5.4)</td>
<td>5.0 (4.5–5.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>6.6 (5.1–9.0)</td>
<td>5.2 (3.5–7.1)</td>
<td>NS</td>
</tr>
<tr>
<td>FFA, μmol/L</td>
<td>609 (425–647)</td>
<td>518 (420–617)</td>
<td>NS</td>
</tr>
<tr>
<td>ASP, ng/mL</td>
<td>121 (110–140)</td>
<td>92 (76–108)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

**Figure 1.** Individual plasma ASP responses after the fatty meal in 10 FCHL patients (A) and 10 control subjects (B). P values indicate the postprandial change within the group after the fatty meal. P values were calculated by repeated-measures ANOVA.
than in control subjects (\( P=0.05 \)). There was no significant change in serum apoB or blood glucose concentrations during the test (data not shown).

Correlation Analyses
In correlation analyses, all variables studied were adjusted for age and sex. Serum C3 correlated significantly with TG, apoB, TC, and HDL-C (Table 3). Pairwise correlations between ASP and lipid variables were weaker than those with C3, and no significant correlation with TC was observed. When variables related to the metabolic syndrome were studied, we found significant correlations between C3 and fasting glucose, glucose AUC, fasting insulin, insulin AUC, and FFA AUC. Of these parameters, ASP correlated only with fasting insulin (\( r=0.18, P<0.05 \)). Both C3 and ASP correlated significantly with BMI and waist-to-hip ratio, but again the correlations were stronger with C3 than with ASP. The correlation coefficient between ASP and C3 was 0.38 (\( P<0.05 \)).

Familial Correlations
Age- and sex-adjusted values obtained by calculating residuals for the traits were used in the analyses. We found a significant parent-offspring correlation for ASP (\( r=0.24, P<0.05 \)) and a significant sibling-sibling correlation for C3 (\( r=0.26, P<0.01 \)) (Table 4), suggesting that plasma ASP and serum C3 levels may be familial. The sibling-sibling correlation of ASP was not significant (\( r=0.06 \)), however, even though the number of pairs studied was higher for siblings (103 pairs) than for parents and offspring (55 pairs).

Lipid and other FCHL-related traits were included in the familial correlation analyses with ASP and C3. No significant familial correlations were observed between plasma ASP and the other traits. Serum C3 correlated significantly with TG, HDL-C, and FFA AUC in siblings. The parent-offspring correlations showed significant positive values between C3 and insulin and BMI and a negative correlation with HDL-C. The small number of marital couples did not permit us to assess this correlation or to estimate the influence of a common environment.

Discussion
We found no evidence supporting the concept that abnormal plasma ASP concentrations have a major effect on lipid levels of FCHL patients. Although the average plasma ASP level of the 66 FCHL patients was higher than that of the 84 unaffected relatives, the difference was not significant. ASP was found to correlate significantly with HDL-C, TG, apoB, and insulin, but each of these correlations was clearly weaker than the one with C3. Familial correlations of parent’s and offspring’s plasma ASP concentrations were significant. The sibling-sibling correlation of ASP was not significant, however, even with a higher number of sibling pairs than parent-offspring pairs. Therefore, any interpretation of parent-offspring correlation should be cautious.

Affected FCHL subjects had significantly higher serum C3 concentrations than the subjects with TG levels below the 90th percentile. The positive and significant sibling-sibling correlation for C3 (\( r=0.26 \)) was a novel finding, indicating that C3 may be a familial trait. Furthermore, correlation analyses between C3 and other FCHL-related traits imply that C3 may share a common genetic background with TG, HDL-C, insulin, FFA, and BMI. Alternatively, C3 synthesis or catabolism may be regulated by factors similar to those of the other traits. Our present finding of elevated serum C3 levels in hypertriglyceremic subjects is consistent with earlier reports that have shown associations with serum TG, apoB, BMI, LDL-C, systolic blood pressure, blood glucose, and insulin.14–25

Why is serum C3 elevated in dyslipidemia and atherosclerosis? It is possible that adipocyte C3 secretion is increased to maintain fatty acid trapping, but other explanations also emerge. As an acute-phase protein, serum concentration of C3 is elevated in various inflammatory states, such as systemic lupus erythematosus and rheumatoid arthritis. Recently, atherosclerosis has also been suggested to be an inflammatory disease. Complement components have been isolated from atherosclerotic lesions, and atherosclerotic lesions contain lipid components that can activate complement.26 Therefore, C3 can be compared with C-reactive protein, which also may constitute an independent risk factor for CHD. The molecular mechanisms behind this association,
impaired function) of the putative ASP receptors. As long as elevated lipid levels would counteract the reduced number (or speculated that the elevated ASP detected in association with promote ASP production. Cianflone et al were the first to report that plasma ASP increased after an oral fat load. In the ASP receptor has not been identified, however, specula-
tion about a receptor defect may not be justified.

According to the ASP-pathway hypothesis, a reduced ASP level or impaired ASP action results in an ineffective FFA trapping, a concurrent increase in plasma FFA, and finally an increased VLDL apoB secretion from the liver. A recent report by Wetsel and coworkers strongly contradicts the concept that the lack of ASP is followed by an elevation of apoB and plasma lipids. No differences in plasma lipid, apoB, or FFA levels could be observed between C3- (and thus ASP-) deficient mice and wild-type animals. Furthermore, families with C3 deficiency have not been observed to have an increased risk of atherosclerosis, although they were not specifically studied in this respect. Cianflone and colleagues observed significantly higher plasma ASP levels in patients with CHD than in age-matched control subjects. It has been speculated that the elevated ASP detected in association with elevated lipid levels would counteract the reduced number (or impaired function) of the putative ASP receptors. As long as the ASP receptor has not been identified, however, speculation about a receptor defect may not be justified.

A key step in the ASP concept is that chylomicrons will promote ASP production. Cianflone et al were the first to report that plasma ASP increased after an oral fat load. In the reports by Charlesworth et al and Weyer and Pratley, no significant postprandial increase in plasma ASP could be detected in healthy subjects. Wetsel et al did not observe a significant difference in plasma levels of TG or FFA after an oral fat load between the ASP-deficient and the wild-type mice. This was later disputed by Sniderman et al, who found a delayed TG clearance in young male ASP-knockout mice compared with wild-type mice.

We believe that the present study is the first to examine the response of ASP after an oral fat load in patients with dyslipidemia. Despite the marked postprandial lipemia especially in FCHL subjects, we observed no response of plasma ASP to an oral fat load in either group. The lack of ASP response suggests that chylomicrons do not serve as a physiological trigger for ASP formation in plasma. The work of Saleh and coworkers from Sniderman’s laboratory demonstrates that ASP generation in adipose tissue is accentuated postprandially in vivo. Thus, it is possible that the postpran-
dial response of ASP will occur in the adipose tissue only and cannot be detected in peripheral plasma.

In conclusion, we found significantly elevated serum levels of C3 in FCHL patients compared with their unaffected relatives. This difference was not significant for ASP. Consistent with several earlier reports, C3 correlated strongly with several lipid parameters and insulin. The correlations were weaker for ASP. It is possible that common genes may play a role in regulating serum levels of C3, TG, HDL-C, insulin, and BMI. Because we did not study ASP release in adipose tissue, we cannot completely rule out the possibility that ASP plays a role in FFA and TG metabolism locally. The present data, however, do not support the idea that the potential defects of the ASP pathway are reflected in plasma concentrations of ASP or lipoproteins or in impaired plasma lipid clearance postprandially.

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References


TABLE 4. Familial Correlations Between Serum C3 and Other FCHL-Related Traits

<table>
<thead>
<tr>
<th>Trait</th>
<th>C3</th>
<th>ASP</th>
<th>TG</th>
<th>TC</th>
<th>ApoB</th>
<th>HDL-C</th>
<th>BMI</th>
<th>Insulin</th>
<th>FFA</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent-offspring*</td>
<td>0.15 (54)</td>
<td>−0.13 (55)</td>
<td>0.04 (55)</td>
<td>−0.17 (55)</td>
<td>0.12 (53)</td>
<td>−0.32§ (55)</td>
<td>0.21‡ (55)</td>
<td>0.21‡ (54)</td>
<td>0.04 (52)</td>
<td></td>
</tr>
<tr>
<td>Offspring-parent†</td>
<td>0.15 (54)</td>
<td>0.15 (54)</td>
<td>0.11 (54)</td>
<td>−0.01 (54)</td>
<td>−0.26 (51)</td>
<td>−0.38§ (54)</td>
<td>0.13 (54)</td>
<td>−0.10 (54)</td>
<td>0.16 (45)</td>
<td></td>
</tr>
<tr>
<td>Sibling-sibling C3</td>
<td>0.26§ (103)</td>
<td>−0.08 (103)</td>
<td>0.22§ (103)</td>
<td>0.02 (103)</td>
<td>−0.03 (101)</td>
<td>−0.20‡ (103)</td>
<td>0.03 (103)</td>
<td>0.16 (103)</td>
<td>0.24§ (91)</td>
<td></td>
</tr>
</tbody>
</table>

Number of pairs studies is shown in parentheses.
*Parent’s C3 with offspring’s other trait.
†Offspring’s C3 with parent’s other trait.
‡P < 0.05, §P < 0.01.


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