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A SNP in the 5′ flanking region of the *SAA1* gene is associated with serum levels of serum amyloid A and cardiovascular risk factors

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Abstract

Background: Elevated serum levels of serum amyloid A (SAA) are associated with increased risk of cardiovascular disease. In this study, we examine associations between allelic variation in the rs11024595 single nucleotide polymorphism (SNP) in the 5′ flanking region of the *SAA1* gene and adipose tissue gene expression, serum levels of SAA and cardiovascular risk factors.

Methods: DNA samples from 729 participants in the SibPair study, comprising weight discordant siblings and their biological parents, and 3542 participants (1783 patients treated with bariatric surgery and 1759 controls) from the Swedish Obese Subjects (SOS) study were used. The rs11024595 SNP was genotyped in both cohorts using Pyrosequencing or the Sequenom MassARRAY platform, respectively. Blood chemistry and anthropometry were assessed at study start. Adipose tissue *SAA1* gene expression and serum levels of SAA in the SibPair study were analyzed with DNA microarray or immunoassay, respectively.

Results: In the SibPair study, the rs11024595 SNP was associated with serum levels of SAA ($P=0.0050$) where T allele carriers displayed lower levels of SAA ($P=0.0025$) but no association between genotype and adipose tissue *SAA1* gene expression was found. In the SOS study, the rs11024595 SNP was associated with serum levels of HDL cholesterol ($P=0.0045$), triglycerides ($P=0.025$) and apolipoprotein E ($P=0.026$). Moreover, T allele carriers had lower levels of HDL cholesterol ($P=0.0148$), but higher levels of triglycerides ($P=0.0418$) and apolipoprotein E ($P=0.028$) compared to C allele homozygotes. The rs11024595 SNP was also associated with plasma glucose ($P=0.044$).

Conclusions: The rs11024595 SNP in the 5′ flanking region of the *SAA1* gene is associated with both serum levels of SAA and other cardiovascular risk factors. Future studies are required to elucidate whether the rs11024595 SNP can affect the risk of cardiovascular events.

Trial registration: ClinicalTrials.gov Identifier: NCT01479452 Registered 24 November 2011 - retrospectively registered.

Keywords: Serum amyloid A, Polymorphism, Adipose tissue, Cardiovascular risk factors

Background

Established risk factors for cardiovascular disease include obesity, smoking, diabetes, dyslipidemia and hypertension [1–3]. In addition, studies have shown that chronic inflammation plays a role in the pathophysiology of atherosclerosis [4], and markers of

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inflammation, such as serum amyloid A (SAA), are modestly elevated in patients with atherosclerosis and in patients with obesity and insulin resistance [5–9].

SAA functions as an exchangeable apolipoprotein [10], mainly of high density lipoprotein (HDL) [10] but also of low density lipoprotein (LDL) and very low density lipoprotein (VLDL) [11]. It has been suggested that SAA modifies the function of lipoproteins resulting in a proatherogenic effect [12], although the role of SAA in the pathophysiology of cardiovascular disease is not clear [13]. Serum levels of SAA are usually in the range of 1–2 μg/ml in healthy individuals but can rise 1000-fold during an acute phase reaction [14] due to increased production of SAA in the liver [14]. However, during non-acute phase we [7, 15] and others [16] have previously shown that adipocytes are the main source of SAA in individuals with obesity, and both *SAA* expression in adipose tissue and serum levels of SAA are reduced after diet-induced weight loss [15].

In humans, SAA comprises a family of proteins encoded by four different *SAA* genes (*SAA1*, *SAA2*, *SAA3*, *SAA4*) located at chromosome 11p15.1. The *SAA1* and *SAA2* genes encode the acute phase SAA and share the most homology among the *SAA* gene family [14]. The promoter regions of the *SAA1* and *SAA2* genes contain transcription factor recognition sequences that allow induction of gene expression by IL-1, IL-6, NF kappa-B [17–19] and SAA activating factor [20]. The rs11024595 SNP is located in the 5' flanking sequence of the *SAA1* coding region and thus could possibly affect *SAA1* transcription [21]. However, whether this SNP has an impact on *SAA1* gene expression in adipose tissue, serum levels of SAA or is associated with cardiovascular risk factors has not been investigated.

We here examine if allelic variation in the rs11024595 SNP (-13T/C) in the 5' flanking region of the *SAA1* gene influences *SAA1* gene expression in adipose tissue, serum levels of SAA and if the rs11024595 SNP is associated with cardiovascular risk factors in the SOS study comprising of patients with obesity and the SibPair study, a study of adult weight discordant siblings and their biological parents.

Methods

Ethics statement

All study protocols were approved by seven regional ethics committees (Göteborg, Linköping, Lund/Malmö, Stockholm, Umeå, Uppsala and Örebro). All participants gave informed consent to participate. The studies were performed in accordance with the Declaration of Helsinki.

The SibPair study

The SibPair study consists of 732 individuals from 154 families with a pair of adult siblings with a BMI difference of 10 kg/m^2 or more [22]. DNA was only available for 729 individuals, who were included in the current analysis. An examination including venous blood sampling was performed at study start. Blood chemistry was analyzed at the central laboratory of the Sahlgrenska University Hospital (accredited according to International Organization for Standardization/International Electrochemical Commission 15189:2007 standards). Analysis of serum levels of SAA was performed on frozen serum from 654 individuals with a human SAA immunoassay kit (Invitrogen, Carlsbad, CA, USA) according to the protocol.

Levels of *SAA1* gene expression in subcutaneous adipose tissue were available for 376 offsprings from the SibPair study. RNA extraction and subsequent gene expression analysis with DNA microarray (Human Genome U133 plus 2.0 Affymetrix, Santa Clara, CA, USA) was performed as previously described [23]. *SAA1* gene expression was assessed by the 214456_x_at probe set.

The swedish obese subjects (SOS) Study

The SOS study is an ongoing study with 2007 patients with obesity who underwent bariatric surgery, and 2040 matched controls who received usual obesity care at primary health care centers as previously described [22]. In brief, the patients were recruited between September 1, 1987 and January 31, 2001. Inclusion criteria were a body mass index (BMI) of 34 kg/m^2 or more for men and 38 kg/m^2 or more for women and an age between 37 and 60 years [22]. A physical examination including venous blood sampling was performed at study start. All blood chemistry was analyzed at the central laboratory, Sahlgrenska University Hospital.

Genotyping of the rs11024595 SNP

In the SibPair study, the *SAA1* gene was amplified from DNA using PCR (Applied Biosystems, Foster City, CA, USA) and subsequent genotyping of the rs11024595 SNP was performed with Pyrosequencing using the PyroMark Gold Q96 platform (Qiagen, Hilden, Germany). Primer sequences for *SAA1* DNA amplification and the probe sequence for genotyping of the rs11024595 SNP are presented in supplementary Table 1.

In the SOS study, the rs11024595 SNP was genotyped using the Sequenom MassARRAY platform (Sequenom, San Diego, CA, USA) at the Mutation Analysis Facility, MAF, Clinical Research Center, Karolinska University

Hospital, Stockholm, Sweden. The MassARRAY Assay Design 3.1 Software (Sequenom) was used for assay design.

Statistical analyses

Genotype frequencies were analyzed for deviations from the Hardy-Weinberg equilibrium. Differences in baseline characteristics were analyzed with independent T-test or Fisher's exact test in the SOS study and with mixed model adjusted for non-independence among related individuals in the SibPair study. All continuous variables were transformed by Box-Cox power transformation to obtain approximate normal distribution prior to analysis. A mixed model analysis was used to assess the association of the rs11024595 SNP and adipose tissue *SAA1* gene expression, SAA serum levels and cardiovascular risk factors in the SibPair study. The mixed model analyses were adjusted for BMI, age, sex and non-independence among related individuals in all analyses except for analyses including indices for adiposity (BMI and sagittal diameter) that were adjusted only for sex, age and non-independence among related individuals. Due to convergence problems, seven individuals from four families were excluded in the mixed model analysis with genotype data. General linear models, adjusted for age and sex, were used for analyses of associations between the rs11024595 SNP with anthropometry and cardiovascular risk factors in the SOS study. In analyses not including indices of adiposity, models were also adjusted for BMI. The parameter estimates from the models provide an adjusted estimate of difference in mean values among the C allele homozygotes compared with the T allele carriers. All analyses were performed as dominant genetic models because of few T allele homozygotes. All statistical analyses were performed with SAS v.9.4 (SAS institute, Cary, North Carolina, USA).

Results

Participant characteristics

Characteristics of participants in the SibPair study and the SOS study are presented in Tables 1 and 2, respectively. No significant differences in proportion of men/women or age were observed between the T allele carriers and homozygote carriers of the C allele in neither the SibPair study, nor the SOS study (Tables 1 and 2, respectively).

In the SibPair study, a 98.6% success rate yielded genotypes for 719 subjects. Of these, 623 participants (86.6%) were homozygotes for the C allele, 91 participants (12.7%) were carriers of the heterozygotes (C/T) and 5 participants (0.7%) were homozygotes for the T allele.

In the SOS study, a 99.3% success rate yielded genotypes for 3542 subjects. Of these, 3146 (88.8%) were

Table 1 Patient characteristics in the SibPair Study

	C/C	C/T or T/T	p-value
n	623	96	
Age, years	48.2 ± 15.6	49.2 ± 15.5	0.825
Male sex, n (%)	240 (38.5)	41 (42.7)	0.322
BMI, kg/m^2	28.9 ± 7.0	28.0 ± 6.2	0.295
Weight, kg	84.9 ± 20.4	82.3 ± 19.6	0.333
Height, cm	171.6 ± 8.7	171.6 ± 9.1	0.787
Sagittal diameter, cm	23.2 ± 4.6	22.4 ± 4.0	0.105
Bodyfat, %	33.5 ± 10.4	32.5 ± 9.6	0.174
P-glucose, mmol/L	5.32 ± 1.82	5.44 ± 2.75	0.641
S-insulin, mIU/L	9.82 ± 8.34	9.71 ± 7.06	0.866
HOMA-IR	2.52 ± 3.05	2.47 ± 2.53	0.844
Diabetes, n (%)	48 (7.7)	7 (7.3)	0.977
S-cholesterol, mmol/L	4.72 ± 1.07	4.83 ± 1.00	0.408
S-HDL cholesterol, mmol/L	1.25 ± 0.34	1.28 ± 0.33	0.558
S-triglycerides, mmol/L	1.17 ± 0.73	1.28 ± 0.75	0.128
Systolic blood pressure, mmHg	123 ± 20	121 ± 20	0.304
Diastolic blood pressure, mmHg	73 ± 11	72 ± 11	0.665

Differences between T-allele carriers and C allele homozygotes were analyzed with mixed model adjusted for non-independence among related individuals

Table 2 Patient characteristics in the SOS study

	C/C	C/T or T/T	p-value
Number	3146	396	
Age, years	47.9 ± 6.1	47.9 ± 6.1	0.870
Male sex, n (%)	948 (30.1)	112 (28.3)	0.485
BMI, kg/m^2	41.2 ± 4.7	41.3 ± 4.8	0.761
Weight, kg	117.9 ± 16.9	117.1 ± 16.4	0.363
Height, cm	169.1 ± 9.2	168.4 ± 9.3	0.093
Sagittal diameter, cm	28.1 ± 3.7	28.0 ± 3.8	0.536
P-glucose, mmol/L	5.65 ± 2.14	5.86 ± 2.40	0.0545
S-insulin, mIU/L	19.71 ± 12.96	19.85 ± 11.67	0.452
HOMA-IR	5.24 ± 5.00	5.56 ± 5.80	0.169
Diabetes, n (%)	474 (15.1)	64 (16.2)	0.553
S-Cholesterol, mmol/L	5.73 ± 1.09	5.80 ± 1.16	0.312
S-HDL cholesterol, mmol/L	1.36 ± 0.33	1.31 ± 0.30	0.0148
ApoA1, g/L	1.41 ± 0.25	1.39 ± 0.22	0.259
ApoB, g/L	1.27 ± 0.30	1.29 ± 0.31	0.181
ApoE, g/L	0.061 ± 0.044	0.066 ± 0.064	0.0280
S-triglycerides, mmol/L	2.14 ± 1.54	2.25 ± 1.56	0.0418
Systolic blood pressure, mmHg	142 ± 19	141 ± 18	0.916
Diastolic blood pressure, mmHg	88 ± 11	87 ± 11	0.893

Differences between T-allele carriers and C allele homozygotes were analyzed with independent T-test or Fisher's exact test for dichotomous variables. Continuous variables were box cox transformed to achieve normal distribution before analysis

homozygotes for the C allele, 379 were (10.7%) heterozygotes (C/T) and 17 participants (0.5%) were homozygotes for the minor T allele.

Genotypes were in Hardy-Weinberg equilibrium in both cohorts. No mendelian inconsistencies were found in the SibPair study.

The rs11024595 SNP, serum levels of SAA and adipose tissue SAA1 gene expression in the SibPair study

We have previously shown that adipocytes are the main source of SAA in individuals with obesity [7, 15] and that adipose tissue gene expression is associated with serum levels of SAA [15]. The association between adipose tissue *SAA1* gene expression and serum levels of SAA was also confirmed in the SibPair study ($P<0.0001$; parameter estimate 0.26; 95% CI 0.14–0.37). Since the rs11024595 SNP is located in the 5' flanking region of the *SAA1* gene [21] it may influence *SAA1* gene transcription. A bioinformatic analysis for the rs11024595 SNP was performed on Gene Browser UCSC using the tool JASPAR CORE 2022 to search for predicted transcription factors binding sites that could be affected by the SNP [24]. Three transcription factors were identified, CTCFL (CCCTC-binding factor like), ZNF610 (Zinc finger protein 610) and ISNM1 (INSM transcriptional repressor 1), but we were unable to identify reports suggesting an effect of these factors on SAA1 transcription from the literature. Moreover, we investigated associations between the rs11024595 SNP and serum levels of SAA and adipose tissue *SAA1* gene expression. The rs11024595 SNP was associated with serum levels of SAA ($P=0.0050$; parameter estimate 0.32; 95% CI 0.10–0.53), and serum SAA levels were lower in the T allele carriers compared with the C allele homozygotes ($P=0.0025$; Fig. 1 A). However,

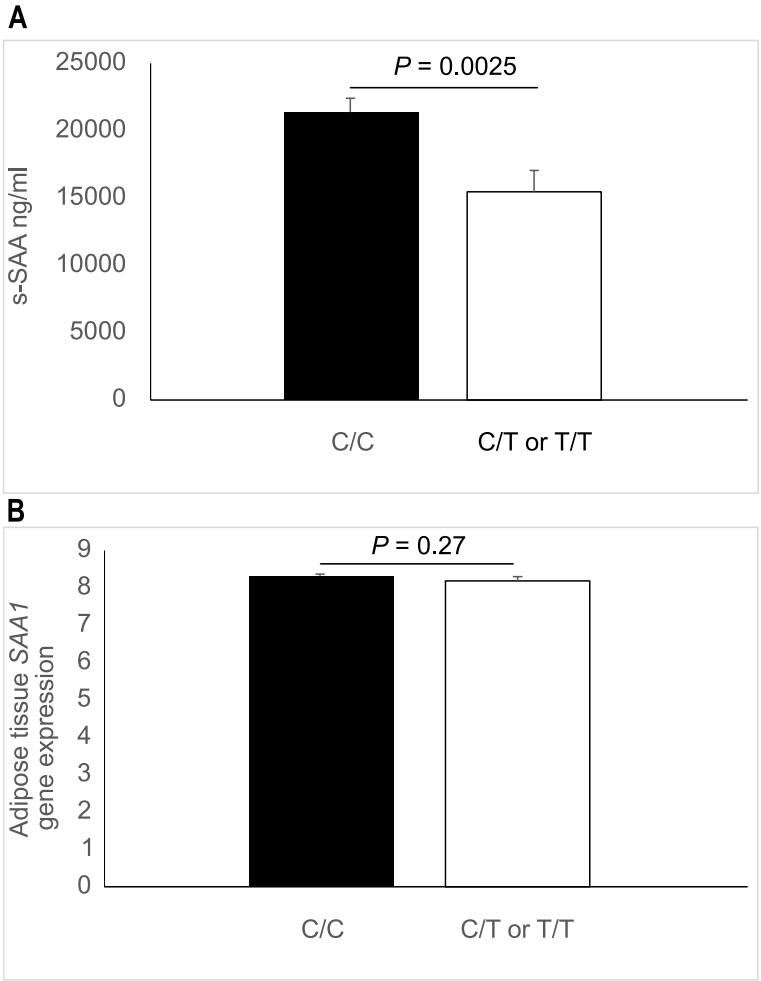

Fig. 1 **A** SAA serum levels (s-SAA) and **B** adipose tissue *SAA1* gene expression stratified by the rs1102495 genotype in the SibPair study. Data are presented as mean values adjusted for non independence among related individuals and standard errors

no association between the rs11024595 SNP and *SAA1* gene expression in adipose tissue was observed ($P=0.99$; parameter estimate −0.00098; 95% CI -0.25–0.25) and there was no difference in *SAA1* adipose tissue gene expression between the C allele homozygotes and carriers of the T allele ($P=0.27$; Fig. 1B).

Serum levels of SAA and cardiovascular risk factors in the SibPair study

Elevated serum levels of SAA are associated with increased risk of cardiovascular disease [5, 6] so we aimed to investigate associations between serum levels of SAA and cardiovascular risk factors. In the SibPair study, serum levels of SAA were positively associated with indices of adiposity (BMI, sagittal diameter, body fat) and metabolic parameters such as s-insulin, HOMA-IR, s-cholesterol, and s-triglycerides. *P*-values and parameter estimates for the associations between serum levels of SAA and investigated metabolic parameters are shown in supplementary Table 2.

The rs11024595 SNP and cardiovascular risk factors in the SOS study and SibPair study

Serum levels of SAA were associated with multiple cardiovascular risk factors in the SibPair study and our data also show an association between rs11024595 genotype and serum levels of SAA. Hence, we analyzed whether there were significant associations between the rs11024595 SNP and metabolic parameters. Serum levels of triglycerides, HDL-cholesterol and apolipoprotein E (ApoE) were associated with the rs11024595 SNP in the SOS study (Table 3). T allele carriers had higher serum levels of triglycerides, lower serum levels of HDL-cholesterol and higher levels of ApoE compared with the C allele homozygotes ($P=0.0418$; $P=0.0148$; $P=0.0280$ respectively). Furthermore, an association between the rs11024595 SNP and p-glucose levels was observed ($P=0.044$). An association between the SNP rs11024595 and serum levels of triglycerides was also found in the SibPair study ($P=0.041$, Table 3).

Discussion

We here demonstrate that allelic variation in the rs11024595 SNP located in the 5' flanking region of the *SAA1* gene is associated with serum levels of SAA and cardiovascular risk factors such as HDL-cholesterol, apoE, triglycerides and p-glucose. T allele carriers displayed lower serum levels of SAA, which according to previous studies, could be cardioprotective [5, 6]. However, T allele carriers also displayed a worse metabolic profile with respect to lipid metabolism, which seems contradictive in relation to the lower SAA levels in terms of cardiovascular risk.

Our results show that the rs11024595 SNP is associated with serum levels of SAA and that the T allele carriers display significantly lower levels. We [7, 15] and others [16] have previously shown that adipocytes are the main source of SAA in individuals with obesity and our initial hypothesis was that the rs11024595 SNP could alter the adipose tissue *SAA1* gene expression and thereby affect the serum levels of SAA. However, adipose tissue *SAA1* gene expression was similar in the different genotype

Table 3 Associations between the rs11024595 SNP and investigated cardiovascular risk factors

	SibPair study		SOS study	
	P	Parameter estimate (95% confidence interval)	*P*	Parameter estimate (95% confidence interval)
BMI, kg/m^2	0.29	0.093 (-0.084, 0.27)	0.88	0.0077 (-0.090, 0.11)
Sagittal diameter, cm	0.052	0.14 (-0.0012, 0.28)	0.72	-0.018 (-0.12, 0.80)
P-glucose, mmol/L	0.76	0.038 (-0.21, 0.29)	0.044	0.10 (0.0029, 0.20)
S-insulin, mIU/L	0.19	-0.10 (-0.25, 0.052)	0.36	0.044 (-0.049, 0.14)
HOMA-IR	0.27	-0.093 (-0.26, 0.076)	0.12	0.075 (-0.021, 0.17)
S-cholesterol, mmol/L	0.35	-0.095 (-0.30, 0.11)	0.29	0.055 (-0.046, 0.16)
S-triglycerides, mmol/L	0.041	-0.22 (-0.43, -0.0097)	0.025	0.12 (0.015, 0.22)
S-HDL cholesterol, mmol/L	0.77	-0.030 (-0.23, 0.17)	0.0045	-0.14 (-0.24, -0.045)
ApoA1, g/L	-	-	0.19	-0.066 (-0.16, 0.032)
ApoB, g/L	-	-	0.17	0.071 (-0.029-0.17)
ApoE, g/L	-	-	0.026	0.083 (0.010–0.16)

P-values and parameter estimates for the associations between the rs11024595 SNP and investigated cardiovascular risk factors in the SibPair study and the SOS study. The analyses were adjusted for age, sex and BMI except for analysis including indices of adiposity where only adjustment for age and sex was performed. Additional adjustment for non-independence among related individuals was applied in the SibPair study. The parameter estimates are used as an indication of the impact that the rs11024595 SNP has on a variable

groups in our study. A previous study has shown that the T allele of the rs11024595 SNP is associated with higher *SAA* gene expression in a hepatocyte cell line [25], which is contradictive to our results if the higher *SAA* gene expression in liver also results in higher serum levels of SAA. However, there are other mechanisms that could explain lower serum levels of SAA in the T allele carriers in our study. The T allele of the rs11024595 SNP has been reported to be in strong linkage disequilibrium to the *SAA1.1* haplotype in a Caucasian population [21], and a previous study has shown that carriers of the *SAA1.1* haplotype have a faster plasma clearance than carriers of other *SAA* haplotypes (*SAA1.5*) which could result in lower serum levels of SAA [26].

The T allele of the rs11024595 SNP was associated with higher levels of triglycerides and lower levels of HDL-cholesterol. Low HDL-cholesterol is traditionally associated with a higher risk of cardiovascular disease [27] because of the cardioprotective role of HDL in the reverse cholesterol transport [28]. However, the T allele carriers in our study also displayed lower levels of SAA which in previous studies have been associated with a lower cardiovascular risk [5, 6, 8]. Previous studies investigating links between serum levels of SAA and the risk for cardiovascular event report different results regarding the relationship between serum levels of SAA and HDL-cholesterol. While Ridker et al. report higher levels of SAA in patients with cardiovascular disease together with lower levels of HDL-cholesterol [6], Johnson et al. report a positive correlation between HDL-cholesterol and serum levels of SAA [8].

Our results with lower serum levels of SAA together with lower HDL-cholesterol levels in T allele carriers may seem contradictive in terms of cardiovascular risk. However, a previous study has shown that a high cholesterol efflux capacity from peripheral tissues is associated with a lower risk of coronary artery disease, independent of HDL-cholesterol levels [29]. SAA is an apolipoprotein of HDL [10] and has been suggested to alter the HDL function in the reverse cholesterol transport and change the function of the HDL-particle to become proatherogenic [12]. Interestingly, a previous study has shown that high HDL-levels in combination with high SAA levels was associated with increased all-cause and cardiovascular mortality whereas low SAA levels in combination with high HDL-cholesterol levels were associated with lower all-cause and cardiovascular mortality [30]. In addition, we here also show that T-allele carriers had higher levels of apoE, an apolipoprotein that can be associated with the HDL-particle [31]. Previous studies have shown that that high levels of ApoE-HDL cholesterol are associated with lower cardiovascular risk [32–34] and thus, it is possible that the lower SAA levels and higher ApoE levels in the T allele carriers can be cardioprotective regardless of HDL-cholesterol levels.

Hypothetically, there are two possible mechanisms that could explain how the rs11024595 SNP affect cardiovascular risk via serum lipids. We here show the rs11024595 SNP is associated with circulating levels of SAA which can exert a proatherogenic effect of the HDL-particle in a dose-response manner. However, it is also possible that the rs11024595 SNP is in linkage disequilibrium with other polymorphisms in the *SAA1* gene that leads to a functional amino acid change in the SAA protein, which in turn can affect the proatherogenic function of the HDL-particle. Future studies are needed to investigate the role of the rs11024595 SNP in SAA binding to the HDL-particle and its effects on cardiovascular disease.

The rs11024595 SNP was also associated with levels of plasma glucose in the SOS study, and it has previously been reported that other polymorphisms in the SAA1 gene are associated with plasma glucose levels [35]. Indeed, several studies have investigated the link between serum amyloid A and impaired glucose homeostasis, which is associated with increased cardiovascular risk [36]. Elevated circulating levels of SAA are associated with insulin resistance [7, 9] and depletion of SAA in antisense oligonucleotide SAA treated mice prevented development of insulin resistance [37]. In addition, recombinant SAA regulates the expression of genes related to glucose homeostasis in adipocytes [38, 39]. However, the results regarding the role of SAA in development of insulin resistance are conflicting [40] and hard to interpret since the endogenous SAA does not exhibit the same proinflammatory characteristics as the recombinant form [41]. Thus, the role of SAA in the development of insulin resistance requires further investigation.

This study has limitations. We could not confirm our results of an association between the rs11024595 SNP and serum levels of HDL cholesterol or plasma glucose observed in the SOS study in the SibPair study. This could be due to lack of power, with fewer study participants and additional adjustment for non-independence among related individuals in the mixed model analyses. Another limitation of this study is that the human SAA immunoassay kit used in this study was not able to distinguish between the different SAA protein isoforms. SAA1 and SAA2 share an extremely high sequence homology and in the circulation these forms represent acute phase SAA [14]. Hence, although SAA1 is the dominating SAA protein in the circulation [42], the higher levels of SAA detected in the rs11024595 C allele carriers may partly be due to SAA2.

Conclusions

In conclusion, we here show that the T allele carriers of the rs11024595 SNP display lower levels of circulating SAA, which according to previous studies may have a cardioprotective effect, but at the same time also display a worse metabolic profile with dyslipidemia. How these findings relate to cardiovascular risk remains unclear and whether allelic variation in the rs11024595 SNP is associated with differences in risk of cardiovascular event require further studies.

Abbreviations

ApoA1: Apolipoprotein A1; ApoB: Apolipoprotein B; ApoE: Apolipoprotein E; BMI: Body Mass Index; CTCFL: CCCTC-binding factor like; HDL: High density lipoprotein; HOMA-IR: Homeostatic model assessment for insulin resistance; ISNM1: INSM transcriptional repressor 1; IL-1: Interleukin 1 ; IL- 6: Interleukin 6; LDL: Low density lipoprotein; SAA: Serum amyloid A; SNP: Single nucleotide polymorphism; SOS: Swedish Obese Subjects; VLDL: Very low density lipoprotein; ZNF610: Zinc finger protein 610.

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s41231-022-00119-3.

Additional file 1. Supplementary Material 1

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Authors' contributions

KS, LMSC, ML and PJ designed the studies. SA, ML, MT, JCAA, KS and PAS performed the genotyping, gene expression analysis and analysis of serum levels of SAA. KS, SA, ML and MP performed the statistical analysis and contributed to the interpretation of the data. SA, ML and KS wrote the manuscript and LMSC, PJ, MT, JCAA, PAS and MP contributed substantially in revising the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data is subject to legal restrictions according to national legislation. Confidentiality regarding personal information in studies is regulated in the Public Access to Information and Secrecy Act (SFS 2009:400), OSL. There is a possibility to apply to get access to public documents that an authority holds. In this case, the University of Gothenburg is the specific authority that holds the documents. A request to get access to public documents can be rejected or granted with reservations. If the authority refuses to disclose the documents the applicant is entitled to get a written decision that can be appealed to the administrative court of appeal.
Contact person, data inquiries from fellow researchers: Jan Borén, Professor, Prefect; Head of Institute of Medicine, the Sahlgrenska Academy, University of Gothenburg jan.boren@wlab.gu.se.

Declarations

Ethics approval and consent to participate

All study protocols were approved by seven regional ethics committees (Göteborg, Linköping, Lund/Malmö, Stockholm, Umeå, Uppsala and Örebro). All participants gave informed consent to participate. The studies were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

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