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Association of Variation at the *ABO* Locus with Circulating Levels of sICAM-1, sP-selectin and sE-selectin: A Meta-Analysis

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Abstract

Background—Circulating levels of soluble intercellular adhesion molecule-1 (sICAM-1), soluble P-selectin (sP-selectin), and soluble E-selectin (sE-selectin) have been associated with variation at the *ABO* locus. To evaluate these associations and the effect sizes, we performed a meta-analysis with new and previous reported data for polymorphism rs579459.

Methods and Results—Compared with major allele homozygotes, heterozygotes and minor allele homozygotes had 4.6% (95%CI=3.4–5.8%, $p=7.3\times10^{-14}$) and 7.2% (95%CI=4.7–9.7%, $p=1.5\times10^{-8}$), respectively, lower sICAM-1 levels (n=33,671). An allele dose dependent association also was observed for sP-selectin (n=4,921), with heterozygotes and minor allele homozygotes having 11.5% (95%CI=7.2–15.8%, $p=1.7\times10^{-7}$) and 18.6% (95%CI=9.1–28.1%, $p=1.2\times10^{-4}$), respectively, lower levels than in major allele homozygotes. A larger effect size, again consistent with an additive genetic model, was seen for sE-selectin (n=2,860) whose level was 25.6% (95%CI=19.0–32.2%, $p=2.1\times10^{-14}$) lower in heterozygotes and 43.3% (95%CI=36.9–49.3%, $p=4.3\times10^{-42}$) lower in minor allele homozygotes, than in major allele homozygotes.

Conclusions—The data support the association of variation at the *ABO* locus with sICAM-1, sP-selectin and sE-selectin levels.

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Keywords

Cell adhesion molecules; plasma; genetics; cardiovascular disease

Leukocyte recruitment plays an important role in inflammatory diseases.[1] It typically begins with leukocyte rolling on the endothelium, followed by leukocyte attachment to endothelial cells and subsequently trans-endothelial migration. Rolling involves the interaction of leukocytes with P-selectin and E-selectin on endothelial cells, whilst leukocyte attachment to endothelial cells is mediated by intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1.[1]

Blood contains soluble forms of ICAM-1 (sICAM-1), P-selectin (sP-selectin) and E-selectin (sE-selectin), generated by shedding of ectodomains of the membrane-bound forms of these molecules or produced from transcript variants lacking the transmembrane domain.[2] Increased circulating levels of sICAM-1, sP-selectin and/or sE-selectin have been associated with a number of diseases such as coronary heart disease and diabetes.[3–7] The levels of sICAM-1, sP-selectin and sE-selectin are under genetic influences, with heritability estimates being 0.24–0.63, 0.45–0.70, and 0.50–0.64, respectively.[8–10] Genome-wide association studies of sICAM-1, sP-selectin and sE-selectin levels have shown that they are associated with single nucleotide polymorphisms (SNPs) at the *ABO* locus.[11–14] Interestingly, genome-wide association studies of coronary heart disease (CHD) have revealed an association between CHD and variation at the *ABO* locus.[15;16]

To more robustly evaluate the associations of sICAM-1, sP-selectin and sE-selectin with the *ABO* locus, and more reliably estimate the effect sizes, we performed a meta-analysis. We included new data from the Bruneck Study, data from several reported studies,[11–14] and additional data from one of these reported studies.[11]

Methods

To identify association studies of SNPs at the *ABO* locus in relation to levels of sICAM-1, sP-selectin and/or sE-selectin, we performed systematic searches of PubMed, scanned the reference lists of original reports, and communicated with authors of the included studies. The electronic searches combined search terms related to polymorphisms at the *ABO* locus (e.g. ABO, polymorphism, SNP, variation, and variant) and ICAM-1, P-selectin, or E-selectin. The searches identified four publications. In two of these publications,[12;13] SNP rs579459 showed the strongest association with sP-selectin or sE-selectin levels among all tested SNPs at the *ABO* locus. In another study (in which rs579459 was not directly typed),[11] SNP rs507666 had the most significant association with sICAM-1 levels among all tested SNPs at this locus. In the fourth study (which also did not type rs579459 directly),[14] SNP rs651007 was the top SNP at the *ABO* locus associated with sICAM-1 and sE-selectin levels. An analysis using the SNAP program (http://www.broadinstitute.org/mpg/snap/) with data from the 1000 Genomes Project showed that rs579459 was in perfect linkage disequilibrium (LD) with rs651007 and in near perfect LD (r^2=0.96) with rs507666, in individuals of European ancestry.

We genotyped the Bruneck cohort[17] for SNP rs579459 using the KASPar method. sICAM-1, sP-selectin, and sE-selectin levels in the Bruneck cohort had been measured by enzyme-linked immunosorbent assay as described previously.[17;18] The Bruneck Study was approved by the local ethics committee and all participants gave their written informed consent.

We performed a meta-analysis with data from the Bruneck cohort and the four reported studies[11–14] as well as additional data from one of these reported studies, the WGHS study[11] for which ethic approval was granted by the institutional review board. For the meta-analysis, we only used summary statistic data from the cohorts and did not receive individual participant data. The meta-analysis included seven datasets for sICAM-1, four for sP-selectin, and four for sE-selectin. For the meta-analysis, data of unadjusted mean and standard deviation of sICAM-1, sP-selectin and sE-selectin levels according to genotypes were provided by authors of three of the previous studies[11;12;14] where this information was not available in the papers, and were extracted from the report of the other study.[13] With the use of the StatsDirect and Comprehensive Meta Analysis Version 2.0 software, we performed meta-analysis of weighted mean difference (wmd) in the percentage of and the unbiased standardized effect size (estimator d[19]) for each adhesion molecule, comparing minor allele homozygotes to heterozygotes and separately minor allele homozygotes to major allele homozygotes. The StatsDirect software provided the pooled mean effect size estimate (wmd+ or d+) with a 95% confidence interval, a chi-square statistic and probability of this pooled effect size being equal to zero.[19] Consistency of findings across studies was assessed by the I^2 statistic.[20] Evidence of publication bias was assessed using funnel plots and the Egger test.[21] Possible reasons for heterogeneity were investigated by meta-regression analysis.

Results and Discussion

The characteristics of study subjects are summarized in Table 1. A total of 33,671 subjects were available for the meta-analysis of sICAM-1, 4,921 for sP-selectin, and 2,860 for sE-selectin.

The meta-analysis showed that sICAM-1 levels were 4.6% (95% CI 3.4–5.8%) lower in heterozygotes and 7.2% (4.7–9.7%) lower in minor allele homozygotes, than in major allele homozygotes ($p=7.3\times10^{-14}$ and $p=1.5\times10^{-8}$, Figure 1A). Similarly, an allele dose dependent association was observed for sP-selectin, with heterozygotes and minor allele homozygotes having 11.5% (7.2–15.8%) and 18.6% (9.1–28.1%), respectively, lower levels than in major allele homozygotes ($p=1.7\times10^{-7}$ and $p=1.2\times10^{-4}$, Figure 1B). An allele dose dependent association also was seen for sE-selectin whose level was 25.6% (19.0–32.2%) lower in heterozygotes and 43.3% (36.9–49.3%) lower in minor allele homozygotes, than in major allele homozygotes ($p=2.1\times10^{-14}$ and$p=4.3\times10^{-42}$, Figure 1C). Standardized effect size was larger for sE-selectin than for sICAM-1 and sP-selectin (Supplemental Figures S1 to S3). We noted heterogeneity (Supplemental Table 1) which a meta-regression analysis indicated was not attributed to differences among individual studies in age, sex, type of subjects (population-based or diabetics), number of subjects (n>1000 or <1000), type of blood sample used (plasma or serum) or which SNP studied, although the meta-regression analysis had low power due to the relatively small numbers of individual studies. There was no evidence of publication bias. We observed correlations between sICAM-1, sP-selectin and sE-selectin levels (Supplemental Table 2).

SNP rs507666 is located within the *ABO* gene, and SNP rs579459 and rs651007 are in its proximity. The *ABO* gene encodes a glycosyltransferase that transfers sugar residues to the H antigen and determines the ABO blood group.[22] Group A has two subtypes, i.e. A1 and A2, respectively. It has been shown that the A1 subtype has over 30-fold higher transferase activity than the A2 subtype.[23] The A1 allele is perfectly tagged by the minor allele of SNP rs507666.[11] SNP rs507666 is in near perfect LD ($r^2=0.96$) with rs579459 and rs651007. Thus, the associations of these SNPs with sICAM-1, sP-selectin and sE-selectin levels may represent an effect of the ABO group A1 subtype. It has been suggested that the increased glycosyltransferase activity in individuals carrying the A1 allele might have an effect on the

shedding, clearance or secretion of adhesion molecules, thereby influencing their levels in the circulation.[11;12]

Adhesion molecules are crucial to platelet leukocyte interaction and leukocyte migration into the vessel wall and thus important players in the atherosclerosis process underlying CHD.[2;24] In a number of previous studies increased CHD risk has been associated with high sICAM-1, sP-selectin and sE-selectin levels.[3;5;6] Unexpectedly, variants at the *ABO* locus conferring elevated CHD risk[15;16;25], like the minor allele of SNP rs579459[16], were associated with decreased levels of soluble adhesion molecules in our meta-analysis. One possible explanation for this seeming paradox may be that soluble adhesion molecules, although elevated in the case of endothelial dysfunction, actually compete with leukocyte adhesion to the endothelium (competition to cell surface adhesion molecules). Another possibility may be that the lower levels of soluble adhesion molecules might arise because of lower shedding of ectodomains, potentially leaving higher levels of intact cell surface adhesion molecules to recruit leukocytes to the blood vessel wall. To date, it is not known whether elevated levels of soluble adhesion molecules in vascular high-risk patients represent an epiphenomenon of vessel wall pathology, a true risk factor or a counter-regulatory per se protective mechanism as indicated by preliminary experimental data[16]. Experimental studies are required to further elaborate the pathophysiological role of soluble adhesion molecules and to clarify whether the prominent alterations in sICAM-1, sP-selectin and sE-selectin observed in this study are relevant to the recently discovered association between *ABO* SNPs and CHD risk.

Some limitations to our study warrant mentioning. First, the mechanism underlying the association of SNPs at the *ABO* locus with sICAM-1, sP-selectin and sE-selectin levels has remained unclear. Second, since SNP rs579459 is in strong LD with a number of other SNPs at this locus, it remains unknown which SNP is the causal variant. Third, since this study was conducted in individuals of European ancestry, the findings may not be generalizable to other races/ethnicity.

In conclusion, our study provides compelling evidence of an allele dose dependent association of variation at the *ABO* locus with circulating sICAM-1, sP-selectin and sE-selectin levels. These results contribute to the knowledge of genetic influences on these adhesion molecules which play important roles in many inflammatory diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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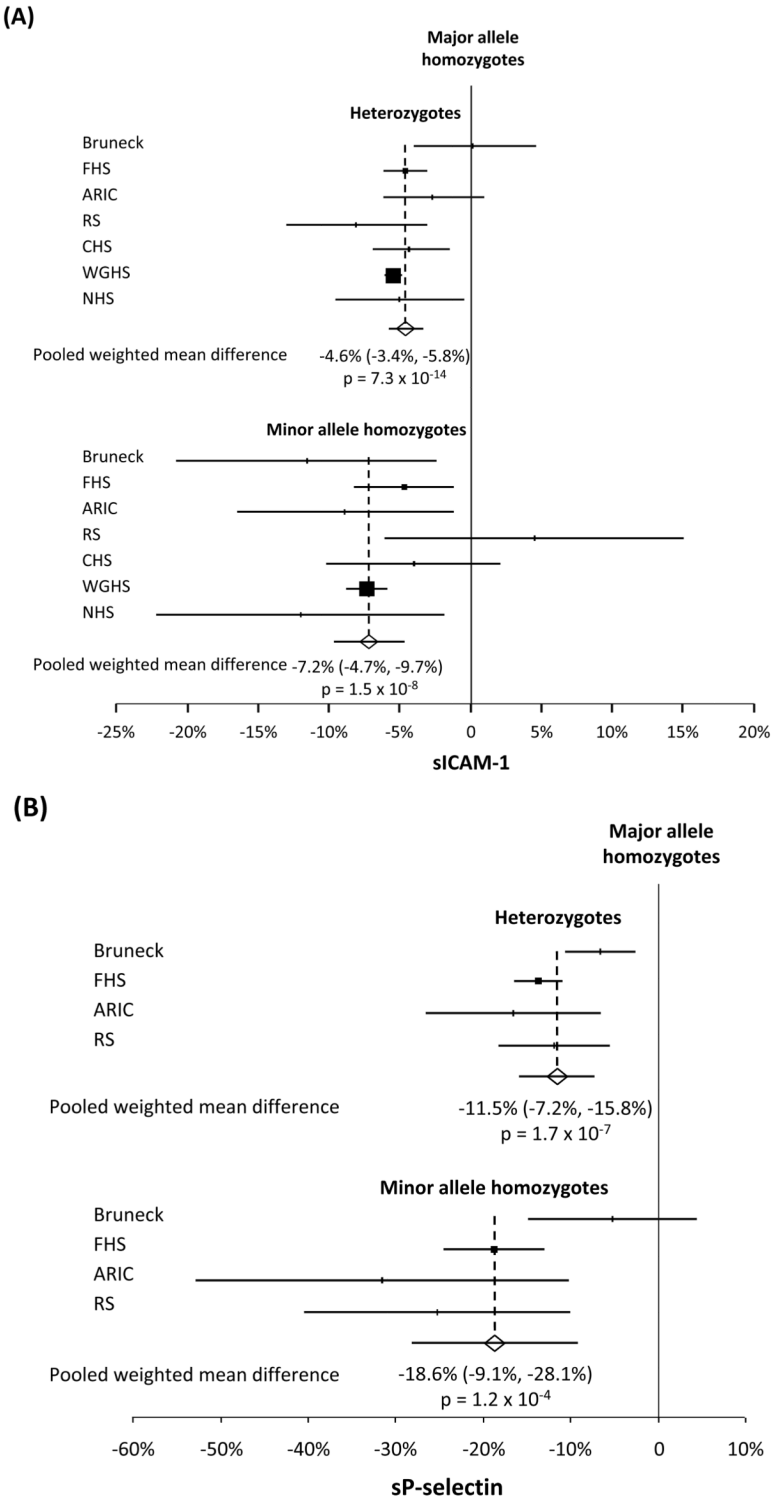

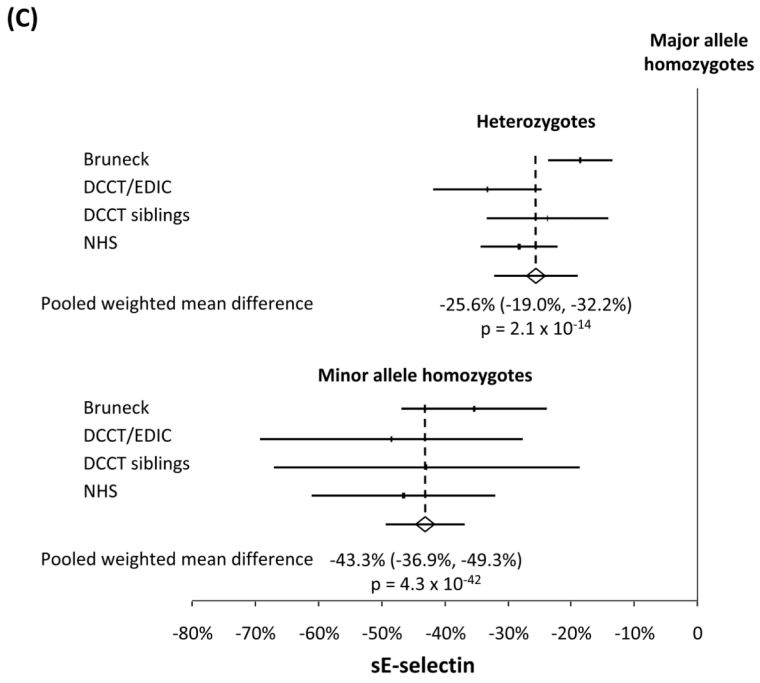

Figure 1.

Weighted mean difference by genotype in soluble intercellular adhesion molecule-1 (sICAM-1), soluble P-selectin (sP-selectin), and soluble E-selectin (sE-selectin) levels. Data shown are weighted mean difference ± 95% confidence interval in circulating levels of sICAM-1 (panel A), sP-selectin (panel B) and sE-selectin (panel C), comparing heterozygotes or minor allele homozygotes, to major allele homozygotes, in a random-effects model.

Table 1

Summary of participating studies for the meta-analysis

	Participating studies	Subjects	Age (years)*	Female (%)	Assay				SNP	Number of subjects			
					Sample	Method	Intra assay CV	Inter assay CV		A/A genotype	A/a genotype	a/a genotype	Total
sICAM-1	Bruneck[17]	Population-based	63±11	51.1	Plasma	ELISA	5.1%	6.9%	rs579459	440	268	33	741
	FHS[12]	Community-based	49±14	45.9	Serum	ELISA	3.9%	3.9%	rs579459	4,176	2,340	329	6,845
	ARIC[12]	Community-based	56±5	38.4	Plasma	ELISA	4.0%	5.1%	rs579459	495	287	43	825
	RS[12]	Community-based	70±9	53.3	Plasma	ELISA		6.9%	rs579459	351	214	35	600
	CHS[12]	Population-based	73±6	42.8	Plasma	ELISA	5.0%		rs579459	855	556	69	1,480
	WGHS[11]	Population-based	55±7	100	Plasma	ELISA	6.7%		rs507666†	14,391	6,857	936	22,184
	NHS[14]	Type 2 diabetes	56±7	100	Plasma	ELISA	3.3–4.8%		rs651007‡	612	337	47	996
sP-selectin	Bruneck[17]	Population-based	63±11	51.1	Plasma	ELISA	5.5%	6.9%	rs579459	440	268	33	741
	FHS[12]	Community-based	61±10	45.6	Plasma	ELISA	3.2%		rs579459	1,872	1,000	164	3,036
	ARIC[12]	Community-based	57±5	35.7	Plasma	ELISA	3.9%	5.8%	rs579459	432	265	41	738
	RS[12]	Community-based	69±9	48.8	Plasma	ELISA	<5%	<10%	rs579459	253	135	18	406
sE-selectin	Bruneck[17]	Population-based	63±11	51.1	Plasma	ELISA	4.8%	7.4%	rs579459	440	268	33	741
	DCCT/EDIC[13]	Type 1 diabetes	39±7	46	Serum	SLPA	<2%	5%	rs579459	452	209	24	685
	DCCT siblings[13]	Non-diabetics	45±9	57	Serum	SLPA	<2%	5%	rs579459	280	143	15	438
	NHS[14]	Type 2 diabetes	56±7	100	Plasma	ELISA	4.5–6.2%		rs651007‡	612	337	47	996

All participants were of European ancestry. FHS, Framingham Heart Study; ARIC, Atherosclerosis Risk in Communities; RS, Rotterdam Study; CHS, Cardiovascular Health Study; WGHS, Women's Genome Health Study; NHS, Nurses' Health Study; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Intervention and Complications.

Genotype distributions in the various cohorts were all consistent with Hardy-Weinberg equilibrium except for WGHS (sICAM-1, p=0.001) and FHS (sP-selectin, p=0.046). SNP, single nucleotide polymorphism; A/A genotype, major allele homozygotes; A/a genotype, heterozygotes; a/a genotype, minor allele homozygotes; CV, coefficient of variation; ELISA, Enzyme-linked immunosorbent assay; SLPA; SearchLight™ Proteome Array.

*mean ± standard deviation.

†in nearly complete linkage disequilibrium with SNP rs579459 (r^2 = 0.96) based on data from the 1000 Genomes Project;

‡in complete linkage disequilibrium with SNP rs579459 (r^2 = 1) based on data from the 1000 Genomes Project