BMC
Cardiovascular Disorders

RESEARCH ARTICLE

Open Access

Chromosome 1p13 genetic variants antagonize the risk of myocardial infarction associated with high ApoB serum levels

Bruna Gigante[1,2*], Karin Leander[1], Max Vikström[1], Shu Ye[4] and Ulf de Faire[1,3]

Abstract

Background: Genetic variation at 1p13 modulates serum lipid levels and the risk of coronary heart disease through the regulation of serum lipid levels. Here we investigate if the interaction between genetic variants at 1p13 and serum lipid levels affects the risk of non-fatal myocardial infarction (MI) in the Stockholm Heart Epidemiology Program (SHEEP), a large population based case control study.

Methods: In the present study only non fatal MI cases (n = 1213, men/women: 852/361) and controls (n = 1516, men/women =1054/507) matched by age, sex and residential area, were included. Three SNPs 12740374 G/T, rs599839A/G and rs646776T/C mapping at 1p13 were analysed for association with serum lipid levels and the risk of MI by a weighted least square regression and logistic regression analyses, respectively. To analyse the effect of the interaction between genetic variants and serum lipid levels on the risk of MI, we applied the biological model of interaction that estimates the difference in risk, expressed as OR (95%CI), observed in the presence and in the absence of both exposures. One derived measure is the Synergy index (S) and 95%CI, where S > 1 indicates synergy and S < 1 antagonism between the two interaction terms.

Results: Rs12740374G/T and rs646776T/C were in strong linkage disequilibrium (LD) ($r^2 = 0.99$), therefore only rs599839A/G and rs646776 were included in the analysis. Consistently with published data, presence of the rare genotypes was associated with reduced total-, LDL-cholesterol and ApoB serum levels (all p < 0.05) as compared to the reference genotype, but was not associated with the risk of MI.

However, the increased risk of MI observed in individual exposed to high (≥75th percentile) serum lipid levels was offset in subjects carrying the rare alleles G and C. In particular, the risk of MI associated with high ApoB serum levels OR (95%CI) 2.27 (1.86-2.77) was reduced to 1.76 (1.33-2.34) in the presence of the G allele at rs599839 with an S of 0.47 (0.20-0.90).

Conclusions: These results indicate that an antagonism between ApoB serum levels and genetic variants at 1p13 contributes to reduce the risk of non-fatal MI in the presence of high ApoB serum levels.

Background

Genome wide association studies (GWAS) performed in large international consortia have demonstrated that variation at chromosome 1p13 is associated with the risk of coronary artery disease (CAD) mainly through its association with LDL and cholesterol serum levels [1-6]. Two leading SNPs mapping at this locus rs646776T/C

---

* Correspondence: bruna.gigante@ki.se
[1]Division of Cardiovascular Epidemiology, Institute of Environmental Medicine (IMM), Karolinska Institutet, Stockholm, Sweden
[2]Division of Cardiovascular Medicine, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
Full list of author information is available at the end of the article

and rs599839A/G explain 1% of the genetic variation in circulating LDL-cholesterol levels and the rare alleles are associated with reduced LDL-cholesterol levels [5]. Chromosome 1p13 maps in close proximity to the cadherin EGF LAG seven-pass G-type receptor (*CELSR2*) and the proline/serine-rich coiled-coil protein 1 (*PSRC1*) genes, involved in the regulation of cell adhesion, proliferation and intracellular trafficking, and in proximity to the gene coding sortilin (*SORT1*) a cell surface receptor involved in the glucose and lipid uptake. Functional studies have shown that the genetic variants at this locus modulate cholesterol metabolism through the

regulation of sortilin expression and LDL uptake in hepatocytes and influence the diameter of the circulating LDL particles [7,8].

The estimated risk [expressed as odds ratio (OR) and 95% confidence interval (95%CI)] of CAD in individuals carrying the allele associated with high LDL-cholesterol levels ranges from 1.20 (1.1-1.3) [6] to 1.29 (1.2-1.4) [9] and 1.19 (1.13-1.26) for the early onset myocardial infarction (MI) [10]. Consistently, the rs599839 G allele, associated with low LDL-cholesterol levels, was associated with a 13% 90%CI (10-17) reduction in the risk of CAD [7].

The actual effect of a genetic variant on the risk of complex diseases can vary across different studies [11] and populations depending on the genetic architecture, the outcome of the study and the exposure to different risk factors [12-14]. To overcome these limitations and fully explain the risk of cardiovascular diseases associated with these newly discovered genetic variants, different approaches have been proposed and applied. In particular, fine mapping of the region of interest [15], the analysis of the association with more specific traits and the analysis of gene and environment interactions [14] have been recently proposed to fill in the so called "missing heritability" gap.

Here we investigate if an interaction between variants at chromosome 1p13 and serum lipid levels was associated with the risk of non-fatal MI. We performed the present study in the Stockholm Heart Epidemiology Program, SHEEP, a large case control population recruited in the Stockholm area specifically designed to investigate the role of genetic and environmental factors in the occurrence of MI in men and women.

Methods

Study population

SHEEP [16] was designed as a population based case control study to dissect both genetic and environmental factors underlying the occurrence of MI and to compare the effects of the different risk factors in men and women. Cases were identified during the period 1992 to 1994. The sources were the coronary and intensive care units, the discharge charts from the hospitals in the Stockholm County area and the death certificates from the Swedish National Causes of Death Register. The criteria for myocardial infarction included changes in the CK and LDH blood levels, presence of specified ECG changes and/or the autopsy finding of a myocardial necrosis whose age was compatible with the time of disease onset. Only patients who survived at least 28 days after the MI event were included in the present study (n = 1213, men = 852; women = 361). One control per case was randomly selected from the Stockholm County population registry after stratification for age (with a 5-years interval),

sex and residential area. In addition other 5 controls were selected at the same time to replace eventual non-responders. When the initial control replied late, both the initial and the already enrolled substitute control have been included in the study. This resulted in the inclusion of more controls (n = 1561, men = 1054; women = 507) than cases.

Anthropometric measures were recorded at physical examination and blood samples were collected about three months after the MI [16]. Biochemical measurements were done as previously reported [17]. Family history of CAD was defined as having at least one close relative affected before the age of 65.

Ethics

The Ethical Committee at Karolinska Institutet approved the SHEEP study design in 1991 (Protocol Number 1991, 91:259). All the study participants gave their informed oral consent to be enrolled in the study, since at the time the study was initiated (1992) no forms for the written consent were available or in current use. The Ethical Committee at Karolinska Institutet has then approved molecular genetic analyses to be performed on the SHEEP material in 2001 (Protocol Number 2001, 01-097).

Single nucleotide polymorphism (SNP) genotyping

Three SNPs showing the strongest association in the published GWAs studies [6,10] with LDL-serum levels were genotyped and analysed in the present study: two intergenic SNPs, rs599839 and rs646776, and rs12740374 that maps at the 3´UTR of the *CELSR2* gene. Rs599839 was genotyped by Taqman and rs12740374 and rs646776 through the Sequenom iPLEX MassARRAY platforms. Random DNA samples were genotyped twice to check for concordance of genotyping. The call rates were 0.98 (rs599839) and 0.99 (rs12740374 and rs646776).

Statistical analysis

Continuous traits were expressed as median ± inter-quartile range (IQTR) and the differences in the distribution of quantitative traits and categorical variables calculated by Kruskal-Wallis and $\chi 2$ test, respectively. Kolmogorov-Smirnov test was used to test the normality of the distribution of the lipid serum levels as well as of dependant biomarkers. Pairwise linkage disequilibrium (LD) was estimated by calculation of the r^2 metric using the software Plink [18]. Concordance to the Hardy-Weinberg equilibrium was tested in cases and controls by the $\chi 2$ test with 1DF and threshold p-value of 0.05.

Serum lipid levels were not normally distributed in the SHEEP. To test the effect of the SNPs under investigation on lipid serum levels, a weighted least squares regression,

a linear regression analysis that does not assume constant variance for the regression residuals, was used to estimate the regression-coefficient (b) and standard error (SE) under the hypothesis of an additive model, i.e. change in serum levels according to the number of risk alleles (i.e. 00 vs 01 vs 11). To test the association with MI, a logistic regression analysis was performed and odds ratios (OR) with 95% confidence interval (95%CI) were estimated under the assumption of an additive (i.e. 00 vs 01 vs 11), dominant (00 vs 01 + 11) and recessive (00 + 01 vs 11) model of inheritance. The crude ORs (95%CI) were adjusted by age, sex and residential area. Further adjustments including BMI, smoking, hypertension, hypercholesterolemia, hypertriglyceridemia and diabetes mellitus were performed in the adjusted analysis.

The interaction between genotypes and the serum lipid parameters (total-, LDL-cholesterol and ApoB serum levels) was calculated using the biological approach [19]. The biological interaction estimates the difference in the risk, expressed as OR (95%CI), associated with the exposure to only one factor (e.g. ApoB or genotype) and the risk associated with the exposure to both factors as compared to the risk observed in the absence of exposure to both factors. The ratio between the risk observed in the presence of both factors and the risk observed in the reference group can be used to derive the Synergy index (S) [20]. A S > 1 indicates the presence of a synergism while a S < 1 indicates the presence of an antagonism between the two interaction terms [20,21]. In the interaction analysis we have defined the exposure to high serum levels as exposure to serum levels higher or equal to the 75th percentile of total-cholesterol ≥6.6 mmol/L, LDL-cholesterol ≥4.6 mmol/L and ApoB ≥1.7 g/L; the exposure to the genotype as presence of the minor allele versus absence of the minor allele (e.g. AG + GG vs AA). For the purpose of interaction analysis ORs (95%CI) were only adjusted by age, sex and residential area.

Calculations were carried out by SAS (vers 9.1, SAS Institute Inc. Cary, NC).

Results

Table 1 summarizes the demographic characteristics, serum lipids and biomarkers in the SHEEP study. Men were aged 60 (53-65) and women 61 (54-66). Cardiovascular risk factors were more often observed in cases than in controls. In particular, cases had a higher proportion of hypercholesterolemia than controls (42% vs 30%, p < 0.0001).

Rs12740374 and rs646776 showed a high degree of pairwise LD ($r^2 = 0.99$), while rs599839 was in moderate LD with rs12740374 and rs646776 (both $r^2 = 0.51$) therefore only rs646776 and rs599839 were analysed for association.

Table 1 Study population: age, serum lipids, biomarkers and cardiovascular risk factor distribution in cases and controls

	Cases (N = 1213)	Controls (N = 1561)	P
Age (years) M (IQTR)	60 (53-65)	61 (54-66)	0.03
Sex (M/F) (N)	852/361	1054/507	0.06
SBP (mmHg) M (IQTR)	130 (117-145)	140 (125-155)	<0.0001
DPB (mmHg) M (IQTR)	80 (72-86)	82 (77-90)	<0.0001
BMI (kg/m²) M (IQTR)	26 (23-28)	25.1 (23-27)	<0.0001
Lipid lowering therapy N(%)	59 (4.8)	55 (3.6)	0.55
Biochemistry M(IQTR)			
T-Chol (mmol/L)	6.1 (5.4-6.9)	5.9 (5.2-6.6)	<0.0001
LDL-Chol (mmol/L)	4.2 (3.6-4.8)	3.9 (3.3-4.6)	<0.0001
HDL-Chol (mmol/L)	1 (0.9-1.3)	1.2 (1.0-1.5)	<0.0001
TG (mmol/L)	1.7 (1.2-2.4)	1.3 (0.9-1.8)	<0.0001
ApoA1 (g/L)	1.3 (1.2-1.5)	1.5 (1.3-1.7)	<0.0001
ApoB (g/L)	1.6 (1.4-1.9)	1.4 (1.2-1.7)	<0.0001
Risk Factors N(%)			
Family History	400 (32)	358 (23)	<0.0001
Hypertension	561 (46)	817 (53)	0.001
Diabetes	151 (12)	72 (4.7)	<0.0001
Hypercholesterolemia	514 (42)	467 (30)	<0.0001
Hypertriglyceridemia	314 (25)	200 (13)	<0.0001
BMI > 30 kg/m²	227 (19)	197 (13)	<0.0001
Current Smokers	580 (48)	455 (29)	<0.0001
Physical Inactivity	523 (43)	536 (34)	0.001

T-Chol = Total-Cholesterol; TG = Triglycerides.

Genotype and allele frequencies were concordant with those predicted by the Hardy-Weinberg proportions in both cases (rs599839 p = 0.85 and rs646776 p = 0.91) and controls (rs599839 p = 0.30 and rs646776 p = 0.24).

We tested the association of genotypes at rs599839 and rs646776 with lipid serum levels (Table 2). In the presence of the genotype GG at rs599839 and CC at rs646776 lower levels of ApoB, serum total - and LDL-cholesterol were observed. This observation is consistent with published data [1,4-6] where the presence of the G at rs599839 and of the C allele rs646776 were associated with LDL-cholesterol serum levels about 0.2 mmol/L (6-7 mg/dl) lower than the alternate allele and with lower total-cholesterol serum levels [about 0.5 mmol/L (19 mg/dl)]. The effect of each SNP on lipid serum levels is reported in Table 2 and indicates a progressive reduction in total-, LDL-cholesterol and ApoB serum levels associated with the G and the C alleles.

When the analysis was performed in men and women separately, only men consistently showed reduced serum

Table 2 Distribution across the genotype strata of total-, LDL-cholesterol and ApoB serum levels and effect of rs599839 and rs646776 on total-, LDL-cholesterol and ApoB serum levels in the SHEEP study

		Total-Chol (N = 2646)	P	LDL-Chol (N = 2599)	P	ApoB (N = 2643)	P
rs599839	AA	6.0 (5.3-6.7)		4.1 (3.4-4.7)		1.5 (1.3-1.8)	
	AG	5.8 (5.2-6.6)		3.9 (3.3-4.6)		1.5 (1.3-1.7)	
	GG	5.8 (4.9-6.5)	0.003	3.9 (3.2-4.4)	0.007	1.4 (1.2-1.7)	0.03
B (SE)		−0.65 (0.019)	0.001	−0.62 (0.020)	0.002	−0.65(0.019)	0.001
rs646776	TT	6.0 (5.3-6.7)		4.1 (3.5-4.7)		1.5 (1.3-1.8)	
	CT	5.9 (5.2-6.7)		3.9 (3.3-4.6)		1.5 (1.2-1.7)	
	CC	5.8 (5.1-6.4)	0.04	3.9 (3.2-4.4)	0.0003	1.4 (1.2-1.7)	0.00001
B (SE)		−0.63 (0.019)	0.001	−0.82 (0.020)	<0.0001	−0.83 (0.020)	<0.0001

Total- and LDL-cholesterol serum levels are expressed in mmol/L and ApoB serum levels in g/L. Median ± IQRT are reported at each genotype strata. The effect of each SNP on total-, LDL-cholesterol and ApoB serum levels is reported in the last row of each section and expressed as beta coefficient (b) along with the standard error (SE).

levels of ApoB, total-cholesterol and LDL-cholesterol serum levels (Additional file 1: Table S1).

No significant association of the G at rs599839 as well as of the C allele at rs646776 allele with serum levels of triglycerides, HDL-cholesterol, ApoA1 was observed in men or in women (Additional file 1: Table S2).

No significant differences were observed in genotype and allele frequencies at these two SNPs between MI cases and controls and no association with the risk of MI was observed in this population. Table 3 shows the genotype and allele frequencies of the two SNPs and the analysis of association with the risk of MI under the three different models of inheritance. Allele G frequency at rs599839 was 0.18 in cases and 0.17 in controls, while the allele C frequency at rs646776 was 0.23 in both cases and controls. No association of any of the two SNPs with the risk of MI was observed at the univariate analysis [OR (95%CI)] using three different analytical models, additive [rs599839 1.08(0.93-1.26); rs646776 0.97 (0.85-1.11)], dominant, [rs599839 1.07(0.91-1.27); rs646776 0.95 (0.82-1.11)], and recessive [rs599839 1.36(0.79-2.13); rs646776 1.07 (0.75-1.53)]. Adjustment for the other covariates did not substantial change the risk estimates as shown in Table 3.

We have then tested the hypothesis that, in the SHEEP, the interaction between the genetic variants at 1p13 and serum lipid levels was an important player in explaining the lack of association between the 1p13 genetic variants and the MI risk. Given the causal association between serum lipid levels and MI, we analysed the interaction between serum lipid levels and genotypes using the biological approach. As reported in Table 4 and Figure 1 (top panel), presence of the allele G at rs599839 antagonizes the risk associated with the exposure to high (≥75th percentile) serum levels of ApoB. The calculated S of 0.47 (0.24-0.90) indicates antagonism between the two interaction terms. When the analysis was

performed in men and women the protective effect of the rare allele was observed only in men with a S of 0.26 (0.07-0.91) (Figure 1, top panel, middle bar graph). The actual ORs (95%CI) for the gender specific interaction analysis are reported in the Additional file 1: Table S3. A trend toward a reduction in MI risk in men carrying the G allele and exposed to increased total- and LDL cholesterol levels was also observed with a S lower than 1,

Table 3 Genotype, allele frequencies and risk of MI associated with rs599839 and rs646776 in the SHEEP

		MI	P
		Cases/Controls	
rs599839	AA	779/1035	
	AG	340/431	
	GG	33/33	0.5
Allele G		0.18/0.17	0.5
		Crude	Adjusted
		OR (95%CI)	OR (95%CI)
Additive		1.08 (0.93-1.26)	1.10 (0.93-1.30)
Dominant		1.07 (0.91-1.27)	1.10 (0.91-1.33)
Recessive		1.36 (0.79-2.13)	1.23 (0.69-2.17)
rs646776			
	TT	686/875	
	CT	413/561	
	CC	58/70	0.7
Allele C		0.23/0.23	0.8
		Crude	Adjusted
		OR (95%CI)	OR (95%CI)
Additive		0.97 (0.85-1.11)	0.97 (0.84-1.13)
Dominant		0.95 (0.82-1.11)	0.94 (0.78-1.12)
Recessive		1.07 (0.75-1.53)	1.15 (0.76-1.73)

Table 4 Effect of interaction between serum lipid levels and genetic variants at 1p13 on the risk of MI expressed as Odds Ratio (OR) and 95%CI in the SHEEP

		N	OR (95%CI)		N	OR (95%CI)		N	OR (95%CI)
Rs599839	ApoB ≥75th perc	617	2.27 (1.86-2.77)	Tot-chol ≥75th perc	611	1.72 (1.40-2.10)	LDL-chol ≥75th perc	1304	1.63 (1.32-2.01)
	AG + GG vs AA	601	1.34 (1.10-1.64)	AG + GG vs AA	562	1.13 (0.93-1.37)	AG + GG vs AA	188	1.13 (0.94-1.37)
	Both	234	1.76 (1.33-2.34)	Both	474	1.80 (1.36-2.37)	Both	474	1.68 (1.24-2.27)
S (95%CI)			0.47 (0.24-0.90)			0.94 (0.46-1.92)			0.89 (0.38-2.06)
Rs646776	ApoB ≥75th perc	536	2.18 (1.76-2.70)	Tot-chol ≥75th perc	582	1.79 (1.45-2.20)	LDL-chol ≥75th perc	416	1.54 (1.23-1.93)
	CC + CT vs TT	787	1.09 (0.90-1.33)	CC + CT vs TT	751	0.98 (0.81-1.19)	CC + CT vs TT	837	0.94 (0.79-1.13)
	Both	312	1.79 (1.38-2.32)	Both	350	1.76 (1.37-2.25)	Both	243	1.68 (1.27-2.23)
S (95%CI)			0.62 (0.34-1.12)			0.97 (0.50-1.89)			1.39 (0.53-3.63)

The table provides the OR (95%CI) relative to the risk of MI associated with the exposure to high serum levels of ApoB, total-cholesterol (tot-chol), LDL-cholesterol (LDL-chol) in the absence of the allele G at rs599839 and of the allele C at rs646776 in the first row of the two sections; the risk associated with the exposure to the allele G or C in the absence of the exposure to high lipid serum levels in the second row of each section and the risk associated with the exposure to both serum levels and genotype in the third row of each section. The last row of each section reports the S index along with the 95%CI.

however the results fell short of statistical significance (Table 4).

The analysis of the interaction between high ApoB serum levels and the C allele at rs646776 also suggested the presence of an antagonistic effect with and S index of 0.62 (0.34-1.12) (Table 4 and Figure 1, bottom panel) that was also confirmed in men with a S 0.40 (0.14-1.09), but with a larger 95%CI (Additional file 1: Table S2 and Figure 1 bottom panel).

Discussion

The intergenic SNPs rs599839 and rs646776 have been identified through GWAs as novel genetic markers for two complex and related traits, serum lipid levels and CAD. In the present study, performed in the SHEEP, a large Swedish population, we confirmed the association of these two genetic variants with serum lipid levels; however we have not observed a direct association between these two genetic variants and the risk of non-fatal MI. We have therefore tested the hypothesis that the interaction between these two SNPs and serum lipid levels contributed to the risk of non-fatal MI in the SHEEP.

The analysis of the association of genetic variants with complex phenotypes may largely vary among different populations. Genes do not have large effect on complex traits and differences in the definition of the trait under investigation as well as the genetic structure of the loci may create large differences in the association results.

Although the lack of association in the SHEEP population might partly reflect a reduced power in the association analysis as compared to the analysis of genetic association in large international consortia, several other factors should be taken into account. In the populations formerly investigated different criteria have been used to identify to cases, the phenotype under investigation was either CAD [6] or early myocardial infarction in patients with at least one first degree relative with premature CAD [1] and the matching criteria for the controls were sometimes incompletely described [6,9]. In the current study, only MI patients who survived at least 28 days after the MI event have been included and the referent population has been matched according to age, sex and residential area. Therefore lack of direct association of 1p13 variants with MI in the SHEEP might be related to the differences in the definition of cases as well as to the controls selection. In addition, differences in the genetic structure of the populations under investigation may hamper the replication of genetic associations. With regard to the chromosome 1p13 locus we have observed that in the SHEEP the pairwise LD value between rs599839 and rs646776 is different from the one currently reported in the Hapmap Consortium (www.hapmap.org) for the European population ($r^2 = 0.51$ observed vs 0.87 reported). These data speak in favor of a different genetic structure of this locus in the Swedish population and are consistent with the hypothesis raised
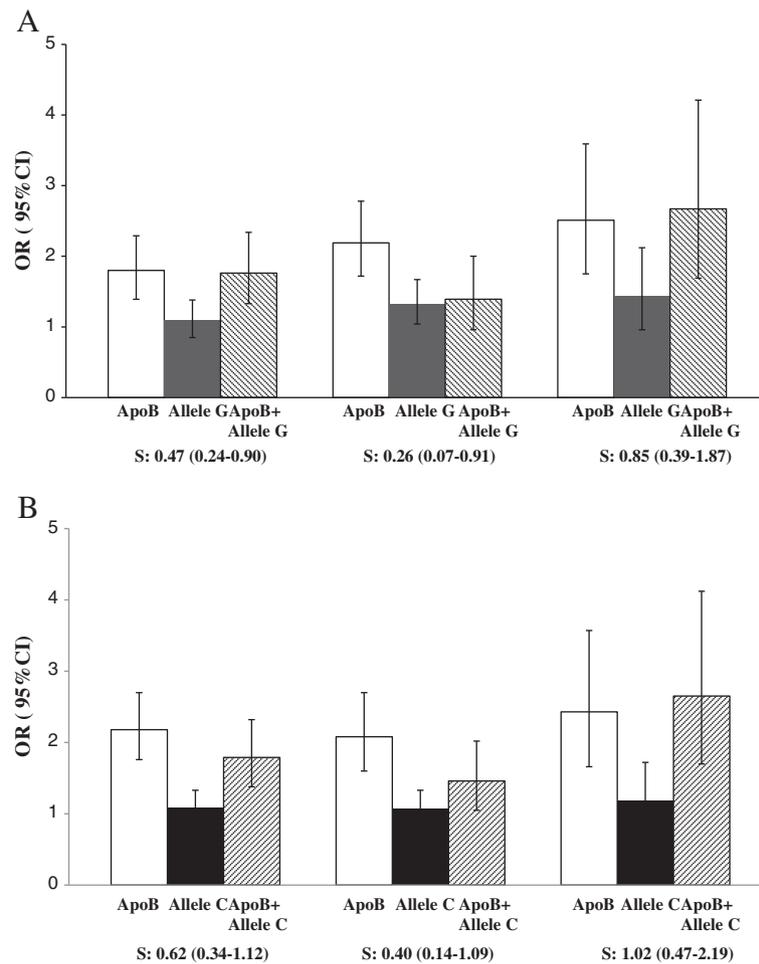
Figure 1 Top panel (A). Biological interaction (left to right striped bars) between the exposure to high (≥75th percentile) ApoB serum levels (white bars) and the presence of the rare allele at rs599839 (gray bars) in all SHEEP participants (left), in men (middle) and in women (right). Bottom panel (**B**). Biological interaction (right to left striped bars) between the exposure to high (≥75th percentile) ApoB serum levels (white bars) and the presence of the rare allele and at rs646776 (black bars), in all SHEEP participants (left), in men (middle) and in women (right). The reference group is represented by the individuals not exposed to ApoB serum levels nor to the G or C alleles. Error bars indicate the 95%CI; S: Sinergy Index.

by evolutionary geneticists stating that European populations have a composite genetic structure due to recent gene selection events (10 000-20 000 years ago) that might have changed pairwise LD values [22]. In addition, the G allele frequency at rs599839 in the SHEEP (17%) is lower than previously reported in former studies (23%) [2,4,5] and in the European panel of the HapMap (33%). Such findings underscore the importance of the knowledge of the locus structure when analysing the effect of genetic variants on a phenotype even within populations of the same ethnicity [17,23-25] and may well explain discrepancies in the genetic effect of even truly genetic susceptibility variants [12,26].

In the SHEEP, the risk of MI was increased in the presence of high ApoB serum levels and presence of the rare allele at rs599839, and to a lesser extent of the rare allele at rs647767, was found to antagonize the increased

risk due to the exposure to high ApoB serum levels, as shown by the results of the interaction analysis. Although we cannot provide proof of a biological mechanism, this interpretation is in line with the results of the original GWAs studies, where the protective effect of 1p13 was observed in populations where the proportion of cases with dyslipidemia ranged from 76 to 80% [4,6] and was therefore higher than the proportion reported in the SHEEP that is about 40%.

The analysis of interaction represents a powerful tool to integrate genetic association data into the complexity of multifactorial traits [19]. In the present study we have utilized the biological method to analyze the effect of the interaction between genetic variants at 1p13 and serum lipid levels because they participate in the same causal mechanism that leads to MI. The elucidation of the mechanisms underlying interactions between genetic

variants and environmental factors or, as in the present study exposure that may be modulated by pharmacological interventions, might have important implication in the assessment of the individual cardiovascular risk as well as in the clinical practice. Exposure to a specific agent may in fact have more or less detrimental effect in different genotype groups if an interaction between the genotype and the exposure exists [27]. In this perspective gene environment interaction analyses hold the promise to contribute to a better understanding of the effect of genetic variants on the risk of cardiovascular diseases.

The association with reduced serum lipid levels was evident only in men. A gender specific association of genetic variants with MI and intermediate phenotypes has already been reported in the SHEEP [17,28] and may reflect the selective effect of risk factors in men and women [29].

Several limitations of the present study should be acknowledged. The choice of the SNPs to be investigated in the present studies relies on published data and does not include the other two tagSNPs, rs4970834 and rs611917, at chromosome1p13. The interaction analyses may be hard to interpreter and require large study population to achieve a sufficient power, therefore the replication of our findings in a larger and independent population is warranted.

Conclusions

In conclusion, our results demonstrate that genetic variants at chromosome 1p13 reduce the MI risk in this Swedish population mainly through the interaction with ApoB serum levels, thus supporting the evidence for a causal role of this locus in the occurrence of MI.

Additional file

Additional file 1: Table S1. Total-, LDL-cholesterol, ApoB, serum levels according to genotype at rs599839 and rs646776 in men and women. **Table S2.** Serum levels of HDL-cholesterol, ApoA1 and triglycerides (TG) according to genotype at rs599839 and rs646776 in the SHEEP population. **Table S3.** Interaction analysis: Risk of MI expressed as OR and 95%CI associated with the exposure to ApoB serum levels, the rare allele at rs599839 and rs646776 and the interaction term in men and women.

Competing interests

The authors declare no conflict of interest.

Authors' contributions

BG has made substantial contributions to conception and design, analysis and interpretation of data; has drafted and revised the manuscript; KL has made substantial contributions to analysis and interpretation of data; has been involved in revising critically the manuscript for important intellectual content; MV has made substantial contributions to analysis and interpretation of data; SY has made substantial contributions to acquisition of data, analysis and interpretation of data; has been involved in revising the manuscript critically for important intellectual content; UdF has made substantial contributions to conception and design of the study, analysis and interpretation of data; has been involved revising the manuscript critically for important intellectual content. All Authors have given final approval of the manuscript version to be published.

Author details

[1]Division of Cardiovascular Epidemiology, Institute of Environmental Medicine (IMM), Karolinska Institutet, Stockholm, Sweden. [2]Division of Cardiovascular Medicine, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden. [3]Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden. [4]Centre of Clinical Pharmacology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK.

References

1. Karvanen J, Silander K, Kee F, Tiret L, Salomaa V, Kuulasmaa K, Wiklund PG, Virtamo J, Saarela O, Perret C, et al: **The impact of newly identified loci on coronary heart disease, stroke and total mortality in the MORGAM prospective cohorts.** *Genet Epidemiol* 2009, **33**(3):237–246.
2. Kathiresan S, Melander O, Anevski D, Guiducci C, Burtt NP, Roos C, Hirschhorn JN, Berglund G, Hedblad B, Groop L, et al: **Polymorphisms associated with cholesterol and risk of cardiovascular events.** *N Engl J Med* 2008, **358**(12):1240–1249.
3. Kathiresan S, Melander O, Guiducci C, Surti A, Burtt NP, Rieder MJ, Cooper GM, Roos C, Voight BF, Havulinna AS, et al: **Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans.** *Nat Genet* 2008, **40**(2):189–197.
4. Samani NJ, Braund PS, Erdmann J, Gotz A, Tomaszewski M, Linsel-Nitschke P, Hajat C, Mangino M, Hengstenberg C, Stark K, et al: **The novel genetic variant predisposing to coronary artery disease in the region of the PSRC1 and CELSR2 genes on chromosome 1 associates with serum cholesterol.** *J Mol Med (Berl)* 2008, **86**(11):1233–1241.
5. Sandhu MS, Waterworth DM, Debenham SL, Wheeler E, Papadakis K, Zhao JH, Song K, Yuan X, Johnson T, Ashford S, et al: **LDL-cholesterol concentrations: a genome-wide association study.** *Lancet* 2008, **371**(9611):483–491.
6. Willer CJ, Sanna S, Jackson AU, Scuteri A, Bonnycastle LL, Clarke R, Heath SC, Timpson NJ, Najjar SS, Stringham HM, et al: **Newly identified loci that influence lipid concentrations and risk of coronary artery disease.** *Nat Genet* 2008, **40**(2):161–169.
7. Linsel-Nitschke P, Heeren J, Aherrahrou Z, Bruse P, Gieger C, Illig T, Prokisch H, Heim K, Doering A, Peters A, et al: **Genetic variation at chromosome 1p13.3 affects sortilin mRNA expression, cellular LDL-uptake and serum LDL levels which translates to the risk of coronary artery disease.** *Atherosclerosis* 2010, **208**(1):183–189.
8. Eagle KA, Ginsburg GS, Musunuru K, Aird WC, Balaban RS, Bennett SK, Blumenthal RS, Coughlin SR, Davidson KW, Frohlich ED, et al: **Identifying patients at high risk of a cardiovascular event in the near future: current status and future directions: report of a national heart, lung, and blood institute working group.** *Circulation* 2010, **121**(12):1447–1454.
9. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, et al: **Genomewide association analysis of coronary artery disease.** *N Engl J Med* 2007, **357**(5):443–453.
10. Kathiresan S, Voight BF, Purcell S, Musunuru K, Ardissino D, Mannucci PM, Anand S, Engert JC, Samani NJ, Schunkert H, et al: **Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants.** *Nat Genet* 2009, **41**(3):334–341.
11. Ioannidis JP: **Prediction of cardiovascular disease outcomes and established cardiovascular risk factors by genome-wide association markers.** *Circ Cardiovasc Genet* 2009, **2**(1):7–15.

12. Greene CS, Penrod NM, Williams SM, Moore JH: **Failure to replicate a genetic association may provide important clues about genetic architecture.** *PLoS One* 2009, **4**(6):e5639.
13. Zondervan KT, Cardon LR: **Designing candidate gene and genome-wide case-control association studies.** *Nat Protoc* 2007, **2**(10):2492–2501.
14. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, *et al*: **Finding the missing heritability of complex diseases.** *Nature* 2009, **461**(7265):747–753.
15. Sanna S, Li B, Mulas A, Sidore C, Kang HM, Jackson AU, Piras MG, Usala G, Maninchedda G, Sassu A, *et al*: **Fine mapping of five loci associated with low-density lipoprotein cholesterol detects variants that double the explained heritability.** *PLoS Genet* 2011, **7**(7):e1002198.
16. Reuterwall C, Hallqvist J, Ahlbom A, De Faire U, Diderichsen F, Hogstedt C, Pershagen G, Theorell T, Wiman B, Wolk A: **Higher relative, but lower absolute risks of myocardial infarction in women than in men: analysis of some major risk factors in the SHEEP study. The SHEEP Study Group.** *J Intern Med* 1999, **246**:161–174.
17. Gigante B, Vikstrom M, Meuzelaar LS, Chernogubova E, Silveira A, Hooft FV, Hamsten A, de Faire U: **Variants in the coagulation factor 2 receptor (F2R) gene influence the risk of myocardial infarction in men through an interaction with interleukin 6 serum levels.** *Thromb Haemost* 2009, **101**(5):943–953.
18. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, *et al*: **PLINK: a tool set for whole-genome association and population-based linkage analyses.** *Am J Hum Genet* 2007, **81**(3):559–575.
19. Gigante B, Bennet AM, Leander K, Vikstrom M, de Faire U: **The interaction between coagulation factor 2 receptor and interleukin 6 haplotypes increases the risk of myocardial infarction in men.** *PLoS One* 2010, **5**(6):e11300.
20. Rothman KJ: **The estimation of synergy or antagonism.** *Am J Epidemiol* 1976, **103**(5):506–511.
21. Lundberg M, Fredlund P, Hallqvist J, Diderichsen F: **A SAS program calculating three measures of interaction with confidence intervals.** *Epidemiology* 1996, **7**(6):655–656.
22. Schmegner C, Hoegel J, Vogel W, Assum G: **A comparison of the variability spectra of two genomic loci in a European group of individuals reveals fundamental differences pointing to selection or a population bottleneck.** *Ann Hum Genet* 2007, **71**(Pt 3):370–378.
23. Liu YJ, Papasian CJ, Liu JF, Hamilton J, Deng HW: **Is replication the gold standard for validating genome-wide association findings?** *PLoS One* 2008, **3**(12):e4037.
24. Jakkula E, Rehnstrom K, Varilo T, Pietilainen OP, Paunio T, Pedersen NL, de Faire U, Jarvelin MR, Saharinen J, Freimer N, *et al*: **The genome-wide patterns of variation expose significant substructure in a founder population.** *Am J Hum Genet* 2008, **83**(6):787–794.
25. Salmela E, Lappalainen T, Liu J, Sistonen P, Andersen PM, Schreiber S, Savontaus ML, Czene K, Lahermo P, Hall P, *et al*: **Swedish population substructure revealed by genome-wide single nucleotide polymorphism data.** *PLoS One* 2011, **6**(2):e16747.
26. Altshuler D, Daly MJ, Lander ES: **Genetic mapping in human disease.** *Science* 2008, **322**(5903):881–888.
27. Dempfle A, Scherag A, Hein R, Beckmann L, Chang-Claude J, Schafer H: **Gene-environment interactions for complex traits: definitions, methodological requirements and challenges.** *Eur J Hum Genet* 2008, **16**(10):1164–1172.
28. Zotova E, Lyrenas L, de Faire U, Morgenstern R, Gigante B, Bennet AM: **The myeloperoxidase gene and its influence on myocardial infarction in a Swedish population: protective role of the -129A allele in women.** *Coron Artery Dis* 2009, **20**(5):322–326.
29. Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R: **Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women.** *Circulation* 1998, **97**(21):2110–2116.