Rare SCARB1 mutations associate with high-density lipoprotein cholesterol but not with coronary artery disease

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Aims
Scavenger receptor Class B Type 1 (SR-BI) is a major receptor for high-density lipoprotein (HDL) that promotes hepatic uptake of cholesterol from HDL. A rare mutation p.P376L, in the gene encoding SR-BI, SCARB1, was recently reported to associate with elevated HDL cholesterol (HDL-C) and increased risk of coronary artery disease (CAD), suggesting that increased HDL-C caused by SR-BI impairment might be an independent marker of cardiovascular risk. We tested the hypothesis that alleles in or close to SCARB1 that associate with elevated levels of HDL-C also associate with increased risk of CAD in the relatively homogeneous population of Iceland.

Methods and results
Using a large resource of whole-genome sequenced Icelanders, we identified thirteen SCARB1 coding mutations that we examined for association with HDL-C (n = 136 672). Three rare SCARB1 mutations, encoding p.G319V, p.V111M, and p.V32M (combined allelic frequency = 0.2%) associate with elevated levels of HDL-C (p.G319V: β = 11.1 mg/dL, P = 8.0 × 10⁻⁷; p.V111M: β = 8.3 mg/dL, P = 1.1 × 10⁻⁶; p.V32M: β = 10.2 mg/dL, P = 8.1 × 10⁻⁴). These mutations do not associate with CAD (36 886 cases/306 268 controls) (odds ratio = 0.90, 95% confidence interval 0.67–1.22, P = 0.49), despite effects on HDL-C comparable to that reported for p.P376L, both in terms of direction and magnitude. Furthermore, HDL-C raising alleles of three common SCARB1 non-coding variants, including one previously unreported (rs61941676-C: β = 1.25 mg/dL, P = 1.7 × 10⁻¹⁸), and of one low frequency coding variant (p.V135I) that independently associate with higher HDL-C, do not confer increased risk of CAD.

Conclusion
Elevated HDL-C due to genetically compromised SR-BI function is not a marker of CAD risk.

Keywords
SR-BI • HDL cholesterol • Mutation • Coronary artery disease
**Introduction**

Despite marked improvements in treatment and prevention, cardiovascular diseases remain the most common cause of death in Iceland like in other European countries. Epidemiological studies consistently show an inverse relationship between levels of high-density lipoprotein cholesterol (HDL-C) and the risk of coronary artery disease (CAD). This relationship has been explained by a potential antiatherogenic properties of HDL, including its role in reverse cholesterol transport, in which cholesterol from peripheral tissues is returned to the liver for excretion in bile. However, neither Mendelian randomization studies nor interventional studies returned to the liver for excretion in bile. However, neither Mendelian randomization studies nor interventional studies have clearly demonstrated. Three rare missense mutations in leading to increased risk of CAD. This would suggest that high HDL-C function in humans causes impaired reverse cholesterol transport, and attenuated atherosclerosis.

A recent study reported that a rare missense mutation p.P376L in SCARB1 encoding the scavenger receptor Class B Type I (SR-BI), associates with impaired function of the encoded protein and elevated HDL-C levels. The mutation was also found to associate with CAD in a meta-analysis of 16 studies with an odds ratio (OR) of 1.79 and \( P = 0.018 \). The investigators concluded that reduced hepatic SR-BI function in humans causes impaired reverse cholesterol transport, leading to increased risk of CAD. This would suggest that high HDL-C might in some cases be an independent marker of increased risk of cardiovascular disease.

Hepatic overexpression of SR-BI in mice has the opposite effect; enhanced hepatocellular cholesterol uptake and increased cholesterol secretion to bile, and facilitating the secretion of cholesterol into bile. In SR-BI deficient mice biliary cholesterol is decreased, but HDL-C levels in blood are elevated, and there is acceleration of atherosclerosis. Hepatic overexpression of SR-BI in mice has the opposite effect; enhanced hepatocellular cholesterol uptake and increased cholesterol secretion to bile, and attenuated atherosclerosis. Scavenger receptor Class B Type 1 up-regulation in mouse models is also associated with biliary cholesterol hypersecretion and increased gallstone formation.

**Translational perspective**

The current study shows that decreased function of Scavenger receptor Class B Type 1 (SR-BI), resulting in reduced hepatic reverse cholesterol transport and increased high-density lipoprotein cholesterol levels, does not translate into increased coronary artery disease risk. Thus, increasing hepatic reverse cholesterol transport through pharmacological activation of SR-BI is not likely to improve outcome. However, the study provides evidence that modulating other functions of SR-BI might do so. The results highlight the complexities of potential therapeutic development with SR-BI modulating agents.

**Methods**

The study was approved by The National Bioethics Committee in Iceland (Approval no. 07-085, with amendments) and the Data Protection Authority of Iceland (Approval no. 07–085, with amendments). All participating subjects donating samples signed informed consents. Personal identities of the phenotypes and biological samples were encrypted by a third party system provided by the Icelandic Data Protection Authority. Enrolment of participants, the phenotypic definitions for CAD, information on lipid measurements, genotyping, imputation methods, and association analysis have previously been described in detail (see also Supplementary material online, Note). Briefly, lipid measurements were obtained from three of the largest clinical laboratories in Iceland. We used HDL-C measurements from 136,672 Icelanders, 93,169 were chip-typed and directly imputed, and 43,503 were first and second degree relatives of chip-typed individuals and had their genotypes inferred based on genealogy. Coronary artery disease cases \( n = 36,886 \) of which 17,591 were chip-typed were identified based on International Classification of Diseases-9 and 10 discharge codes from Landspítali—The National University Hospital of Iceland, and from death registries. The controls \( n = 306,268 \) of which 121,163 were chip-typed included population controls from the Icelandic genealogical database and individuals recruited through different genetic studies at deCODE genetics. Description of genetic risk scores is provided in Supplementary material online, Note.

**Results and discussion**

Using our population-based resource of 8453 whole-genome sequenced Icelanders, we identified thirteen SCARB1 coding variants...
and one splice region variant (Supplementary material online, Table S1) that we imputed into chip-genotyped Icelanders and their close relatives and tested for association with HDL-C (n = 136,672). Three very rare SCARB1 missense variants that never occur together on the same chromosome, p.G319V, p.V111M, and p.V32M (allelic frequency 0.056%, 0.111%, and 0.026%, respectively) associate with elevated levels of HDL-C (p.G319V: β = 11.1 mg/dL, P = 8.0 × 10⁻⁴; p.V111M: β = 8.3 mg/dL, P = 1.1 × 10⁻⁶; p.V32M: β = 10.2 mg/dL, P = 8.1 × 10⁻⁶) (Table 1). The associations of these variants with HDL-C have not been reported before. Overall, one in 250 Icelanders carries one of these three variants and none of them associates with other lipid fractions (Supplementary material online, Table S3). Although the missense variants p.P376L, p.P297S, and p.S112F (reported effects: 8.4–18.9 mg/dL) were not observed in Iceland, the three rare missense variants identified have effects in the same direction and of comparable magnitude (8–11 mg/dL) as the published ones. Similar to all previously described HDL-C increasing variants in SCARB1,¹¹,¹²,¹⁴,²⁵ the variants encoding p.G319V and p.V111M occur in the large extracellular loop of the SR-BI protein, within highly conserved regions and are predicted to be damaging (Supplementary material online, Table S1). The missense variant p.V32M is predicted to be benign, and is in a region less conserved between species (Supplementary material online, Table S1). In addition to the rare variants, we observed one low frequency missense variant p.V135I (frequency 1.23%) that associates with increased HDL-C, albeit with considerably less effect (β = 2.1 mg/dL, P = 6.4 × 10⁻⁶) than the rare ones (Table 1). Two of the rare coding sequence variants (p.G319V and p.V111M) are reported in the Genome Aggregation Database (gnomAD at http://gnomad.broadinstitute.org, assessed March 2018) in European populations, but at much lower frequencies than in Iceland.

We tested the missense variants encoding p.G319V, p.V111M, p.V32M, and p.V135I with association with CAD among 36,886 cases and 306,268 controls (Table 1). None of the variants associates with CAD risk (P > 0.05). To increase power to detect association we aggregated the three rare large impact variants p.G319V, p.V111M, and p.V32M (combined allelic frequency = 0.2%) and tested for association with increased risk of CAD. This aggregate test gives an OR_CAD = 0.90, 95% confidence interval (CI) 0.67–1.22; P = 0.49 (Supplementary material online, Table S2).

We further tested three common non-coding variants that independently associate with HDL-C, for association with CAD in Iceland and in the publicly available CARDIOGRAM+C4D 1000G data (Table 2). Of these common HDL-C associating variants one is novel (rs61941676) and two represent previously reported GWAS signals (rs838876 and rs838909) (Supplementary material online, Note and Table S3). In the combined results from the Icelandic and CARDIOGRAM+C4D datasets, two of the three common variants show weak evidence for association with CAD (rs61941676-C: OR = 0.97, 95% CI 0.95–1.00; P = 0.03 and rs838876-A: OR = 0.98, 95% CI 0.96–0.99; P = 0.0026) (Table 2), with the HDL-C increasing allele trending towards reduced risk of CAD.

In light of the seemingly discrepant effects of rare SCARB1 variants on the risk of CAD, it could be argued that the three Icelandic rare variants that associate with raised HDL-C could do so without inhibiting the hepatocellular trafficking of cholesterol to bile; thus explaining the lack of association with CAD. In this scenario, enhancement of cholesteryl ester transfer protein (CETP)-mediated exchange of cholesteryl esters from HDL to apoB containing lipoproteins, would counteract the genetically compromised SR-BI, resulting in minimal or no net effect on the hepatic cholesterol removal in carriers of the Icelandic variants. These effects would contrast the hindered hepatic cholesterol uptake observed in the SR-BI deficient mice (mice do not express CETP) and in hepatocytes derived from human induced pluripotent stem cells, carrying the p.P376L mutation.¹¹ To test the impact of the Icelandic SCARB1 mutations, and other HDL-C associating variants at the locus, on transhepatic cholesterol flux, we used gallstone risk as a proxy. It has been shown that gallstone formation largely results from cholesterol hypersecretion to bile,²¹,²²,²³ and in mice, overexpression of SR-BI associates with biliary cholesterol hypersecretion and increased gallstone formation. The effects of the SCARB1 variants on gallstone risk was assessed in 8281 cases and 377,474 controls. Three of the seven HDL-C

### Table 1 Association of SCARB1 locus variants with high-density lipoprotein cholesterol and the corresponding effect on coronary artery disease

| Comment on variant | Variant type | rs-name | A1/A2 | EA freq. (%) | HDL-C (n = 136 672) | CAD (n = 36 886/306 268) |
|--------------------|--------------|---------|-------|-------------|---------------------|------------------------|
| Rare coding        | Missense (p.G319V) | rs150728540 | A/C | 0.056 | 8.0 × 10⁻⁷ | 11.19 | 2.253 | 0.365 | 0.788 | 0.47–1.32 |
| Rare coding        | Missense (p.V111M) | rs5890 | T/C | 0.111 | 1.1 × 10⁻⁶ | 8.254 | 1.691 | 0.775 | 1.063 | 0.70–1.62 |
| Rare coding        | Missense (p.V32M) | rs771427110 | T/C | 0.026 | 8.1 × 10⁻⁴ | 10.198 | 3.046 | 0.377 | 0.703 | 0.32–1.54 |
| Low frequency coding | Missense (p.V135I) | rs5891 | T/C | 1.226 | 6.4 × 10⁻⁴ | 2.063 | 0.457 | 0.584 | 1.031 | 0.92–1.15 |
| Common novel       | Intronic     | rs61941676 | A/C | 84.8 | 1.7 × 10⁻¹⁸ | 1.245 | 0.140 | 1.2 × 10⁻³ | 0.945 | 0.92–0.98 |
| Common GWAS        | Downstream   | rs838876 | A/G | 34.1 | 2.4 × 10⁻¹⁷ | 0.921 | 0.107 | 0.083 | 0.977 | 0.95–1.00 |
| Common GWAS        | Intronic     | rs838909 | G/A | 53.9 | 1.9 × 10⁻¹⁷ | 0.870 | 0.102 | 0.788 | 1.003 | 0.98–1.02 |

The combined allele frequency for p.G319V, p.V111M, and p.V32M is ~0.2% (~0.4% carrier frequency). This corresponds to 147 carriers (of any of the three rare HDL-C raising mutations) among the 36,886 CAD cases and 1225 carriers among the 306,268 controls. Effects, β in mg/dL, and OR, are given for the A1, except for rs61941676 and rs838909 the effects are given for the A2. Variant type, with coding changes in protein sequence NP_001076428.1 given in bracket.

A1, minor allele; A2, major allele; CAD, coronary artery disease; CI, confidence interval; EA freq., effect allelic frequency; GWAS, signal previously reported in genome wide association study; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; SE, standard error.
Table 2  Meta-analyses of the association of SCARB1 locus variants with coronary artery disease in Iceland and CARDIOGRAM/C4D

| CAD variant | HDL-C variant | HDL-C variant | HDL-C variant |
|-------------|---------------|---------------|---------------|
| rs11057837  | rs11057837    | rs61941676    | rs838909      |
| EA freq. = 0.5% | EA freq. = 84.8% | EA freq. = 9.5% | EA freq. = 53.9% |
| P-value | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) |
| CAD (Iceland) | 1.2 × 10^{-4} | 1.108 (1.06–1.15) | 0.0012 | 0.945 (0.92–0.98) | 0.137 | 0.981 (0.96–1.01) | 0.788 | 1.003 (0.98–1.02) |
| CAD (CARDIOGRAM/C4D) | 9.5 × 10^{-4} | 1.058 (1.02–1.09) | 0.894 | 0.998 (0.97–1.03) | 7.8 × 10^{-5} | 0.973 (0.95–0.99) | 0.177 | 0.987 (0.97–1.01) |
| Combined | 1.9 × 10^{-4} | 1.08 (1.05–1.11) | 0.03 | 0.97 (0.95–1.00) | 2.6 × 10^{-5} | 0.98 (0.96–0.99) | 0.40 | 0.99 (0.98–1.01) |

The reported CAD variant rs11057830 (R^2 = 0.71 with rs11057837) associates with CAD with OR = 1.085, P = 1.6 × 10^{-5} in Iceland. Effects are calculated based on the EA given in [ ]. Results from the Icelandic and CARDIOGRAM/C4D case-control groups were combined using inverse variance weighted fixed effect model.

**Table S2**

| rs11057837 | rs61941676 | rs838876 | rs838909 |
|------------|------------|----------|----------|
| [A]        | [C]        | [A]      | [A]      |
| P-value     | OR (95% CI) | P-value  | OR (95% CI) |
| CAD (Iceland) | 1.2 × 10^{-4} | 1.108 (1.06–1.15) | 0.0012 | 0.945 (0.92–0.98) |
| CAD (CARDIOGRAM/C4D) | 9.5 × 10^{-4} | 1.058 (1.02–1.09) | 0.894 | 0.998 (0.97–1.03) |
| Combined | 1.9 × 10^{-4} | 1.08 (1.05–1.11) | 0.03 | 0.97 (0.95–1.00) |

No relationship between elevated HDL-C levels due to genetically compromised SR-BI function and increased risk of CAD

- Scavenger receptor class B, type I (SR-BI), encoded by the SCARB1 gene is a major receptor for HDL.
- Impaired SR-BI function hinders flux of cholesterol from HDL to the liver, resulting in elevated HDL-C levels.

- Three novel SCARB1 missense mutations encoding p.G319V, p.V111M, and p.V32M associate with elevated HDL-C levels.
- These HDL-C raising mutations do not affect CAD susceptibility in humans.

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**Take home figure** Schematic showing the role of SR-BI in reverse cholesterol transport; promoting hepatic uptake of cholesterol from HDL and cholesterol secretion to bile. Rare missense mutations that compromise this SR-BI function do not affect the risk of coronary artery disease.

- Scavenger receptor class B, type I (SR-BI), encoded by the SCARB1 gene is a major receptor for HDL.
- Impaired SR-BI function hinders flux of cholesterol from HDL to the liver, resulting in elevated HDL-C levels.

- Three novel SCARB1 missense mutations encoding p.G319V, p.V111M, and p.V32M associate with elevated HDL-C levels.
- These HDL-C raising mutations do not affect CAD susceptibility in humans.

variants showed nominally significant association with gallstones (Supplementary material online, Table S3). A genetic risk score for HDL-C, constructed on the basis of seven SCARB1 HDL-C associating variants, associates with gallstones. For each standard deviation (SD), increase in HDL-C due to the genetic risk score, the risk of gallstones decreases by 61% (OR = 0.39, 95% CI 0.24–0.63; P = 1.0 × 10^{-3}) (Supplementary material online, Table S2). This finding supports the conclusion that SCARB1 variants associating with increased HDL-C in humans impair cholesterol excretion through bile, thus playing a role in the late stages of reverse cholesterol transport, as described in the mouse and for other SCARB1 mutations.124 However, in concordance with the results for individual variants, the SCARB1 HDL-C genetic risk score does not associate with CAD risk (for one SD of genetically elevated HDL-C; OR = 0.84, 95% CI 0.58–1.22; P = 0.36, Supplementary material online, Table S2) further tilting the scale against the hypothesis that hindered flux of HDL-C to the liver due to SR-BI impairment increases CAD susceptibility in humans.

Although we have demonstrated that SCARB1 variants leading to decreased flux of HDL-C to the liver do not increase CAD risk (Take home figure), other SR-BI functions may still do so. In the Icelandic data a common SCARB1 intronic variant rs11057837-T (allele frequency = 9.5%) associates with CAD (OR = 1.11, P = 1.2 × 10^{-6}) (Table 2), but not with HDL-C or gallstones after adjusting for HDL-C variants in the region (Supplementary material online, Table S3 and Note). Rs11057837-T also associates with CAD in the public 1000G data from CARDIOGRAM/C4D (OR = 1.08 and P = 1.9 × 10^{-8} for Iceland and CARDIOGRAM/C4D combined) (Table 2). The
rs11057837 correlates ($R^2 = 0.7$) with other intrinsic variants (rs11057841, rs11057830, and rs10846744) that have previously been found to associate with Lp-PLA2 activity and mass, vitamin E levels, subclinical atherosclerosis, and with CAD. The association of variants with vitamin E levels support the notion that rs11057837 mediates its effect through SCARB1, rather than other genes in the region, since in vitro studies have demonstrated the influence of SR-BI on tissue antioxidant uptake (vitamin E and carotenoids). These effects, or other functions that have been linked to SR-BI, such as the effect on endothelial cell nitric oxide metabolism, bacterial or viral recognition and degradation, or induction of apoptosis, are mechanisms that could explain the association of rs11057837 with CAD. Further, effects on other genes in the region cannot be ruled out.

To summarize, the HDL-C increasing effects (8–11 mg/dL) of the three rare SCARB1 missense variants described in our study, encoding p.G319V, p.V111M, and p.V32M, are comparable to the HDL-C of apoptosis, are mechanisms that could explain the association of three rare CAD. Specifically, this striking difference in carrier frequency, to the association of similar degree as the one reported, is significantly different from the OR of 1.79 reported for p.P376L. Importantly the 95% CI indicates that OR above 1.22 is unlikely. Assuming a true association between the HDL-C raising variants and increased risk of CAD, we have 90% power to detect variant association with OR = 1.29 at P-value <0.05. It is conceivable that the mutation encoding p.P376L has CAD susceptibility effects that are not shared by other HDL-C raising variants. However, given that it is relatively specific to Ashkenazi Jews (carried by about 1 in 20 Ashkenazi Jews vs. about 1 in 10 000 Europeans that are not Ashkenazi Jews) it is more likely that differences in population substructure between cases and controls is the main explanation of the reported association of p. P376L with CAD. Specifically, this striking difference in carrier frequency, together with a relatively small imbalance in the number of Ashkenazi Jews between CAD cases and controls, could introduce a false association of similar degree as the one reported.

In conclusion, our results do not support a relationship between elevated HDL-C levels due to genetically compromised SR-BI function and increased risk of CAD. These findings are in keeping with recent genetic and interventional studies failing to show causal relationship between HDL-C levels and atherosclerosis and support current dyslipidaemia guidelines.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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**Conflict of interest:** The authors A.H., P.S., G.T., G.T., B.O.J., G.A.A., U.T., D.F.G., H.H., and K.S. are affiliated with deCODE genetics/Amgen, Inc. and are employed by the company.

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