

Genetic variants associated with celiac disease and the risk for coronary artery disease

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Abstract Epidemiological evidence suggests that patients with celiac disease are at increased risk for coronary artery disease (CAD). Genetic-epidemiological analyses identified many single nucleotide polymorphisms (SNPs) associated with celiac disease. If there is a causal relation between celiac disease and CAD, one might expect that risk alleles primarily associated with celiac disease also increase the risk of CAD. In this study we identified from literature 41 SNPs that have been previously described to be genome-wide associated with celiac disease ($p < 5 \times 10^{-08}$). These SNPs were evaluated for their association with CAD in the Coronary ARtery Disease Genome-wide Replication and Meta-analysis (CARDIoGRAM) dataset, a

meta-analysis comprising genome-wide SNP association data from 22,233 CAD cases and 64,762 controls. 24 out of 41 (58.5 %) risk alleles for celiac disease displayed a positive association with CAD (CAD-OR range 1.001–1.081). The remaining risk alleles for celiac disease ($n = 16$) revealed CAD-ORs of ≤ 1.0 (range 0.951–1.0). The proportion of CAD associated alleles was greater but did not differ significantly from the proportion of 50 % expected by chance ($p = 0.069$). One SNP (rs653178 at the *SH2B3/ATXN2* locus) displayed study-wise statistically significant association with CAD with directionality consistent effects on celiac disease and CAD. However, the effect of this locus is most likely driven by pleiotropic effects on multiple other diseases. In conclusion, this genetically based approach provided no convincing evidence that SNPs associated with celiac disease contribute to the risk of CAD. Hence, common non-genetic factors may play a more important role explaining the coincidence of these two complex disease conditions.

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Introduction

Accumulating evidence from epidemiological studies indicates an increased cardiovascular risk in patients with celiac disease (Ludvigsson et al. 2011; Viljamaa et al. 2006; Wei et al. 2008), even though not all studies were in line with this observation (West et al. 2004; Whorwell et al. 1976). The largest study so far ($n = 28,190$) reported a circa 20 % increase in the relative risk for incident ischemic heart disease in patients with different degrees of celiac disease (Ludvigsson et al. 2011); another study reported even higher odds ratios (Wei et al. 2008). Beside coronary artery disease (CAD), arrhythmias and dilated cardiomyopathy might also add to the burden of cardiovascular diseases and the increased risk of cardiovascular disease (CVD) death in patients with celiac disease (Poddar et al. 2014; Emilsson et al. 2013b). It is not clear, whether celiac disease itself might trigger chronic inflammatory processes which promote the development of atherosclerotic disease. To further explore the etiology of the increased CVD risk in celiac disease patients, we assessed whether genetic variants primarily associated with celiac disease also increase the risk for CAD. If celiac disease is truly a contributing cause to CVD, one would expect celiac disease-related SNPs to display a directionality consistent association with CAD, i.e., alleles which increase celiac disease risk also predispose to CAD. Therefore, we tested 41 SNPs that have previously been genome-wide associated with celiac disease for their association with CAD in the CARDIoGRAM dataset, which includes genetic data of 22,233 CAD cases and 64,762 population-based controls.

Methods

Study sample

Fourteen population-based and clinical cohorts contributed their genome-wide association data on CAD to build up a large meta-analysis platform for CAD: the CARDIoGRAM consortium (Preuss et al. 2010). In total, the data base included genetic information of 22,233 CAD cases and 64,762 controls. The key results and the statistical analysis plan of this meta-analysis have been reported elsewhere (Preuss et al. 2010; Schunkert et al. 2011). Briefly, the associations between SNPs and CAD were tested within each contributing sample using a logistic regression model, thereby adjusting for age, sex and potential population

stratification, assuming an additive genetic model. Study-specific effect estimates and their standard errors were meta-analyzed using random effects or fixed effects models as appropriate. Observed associations between celiac disease-SNPs and CAD are expressed as odds ratios (ORs) and their 95 % Wald confidence intervals (CI).

SNP selection

We identified genetic variants associated with celiac disease on a genome-wide significant scale by using the GWAS catalogue from the National Human Genome Research Institute (<http://www.genome.gov/gwastudies/>; access date: 04/15/2014) and the GRASP database (<http://apps.nhlbi.nih.gov/gras>; access date: 04/15/2014).

In addition, we performed a search on PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) using the terms “celiac disease, genome(–)wide association stud(y)ies”. If celiac disease-SNPs did not pass quality control in CARDIoGRAM, we searched for proxies by using the SNP annotation and proxy search-tool (SNAP) (Johnson et al. 2008). We identified SNPs by searching with a R^2 -threshold of 0.8 and a distance limit of 500 kb. These proxy-SNPs were then tested for their association with CAD in CARDIoGRAM.

Statistical methods

We assessed the proportion of celiac disease-related alleles that display a directionality consistent association with CAD ($OR > 1$). Thus, for each genome-wide significant SNP, we identified the allele that was associated with a higher relative risk for celiac disease, and we evaluated whether the same allele also predisposes to CAD (with an $OR > 1$). We tested whether the proportion of SNPs with an $OR > 1$ for CAD is larger than 50 % (expected proportion of alleles with $OR > 1$ by chance) using an exact binomial test.

For each celiac disease-associated allele, we also compared the strength of the association with CAD as observed in CARDIoGRAM to the expected strength of association with CAD, using an independent t test assuming homogeneity of variance.

The expected effects were calculated as follows: First, each genome-wide significant SNP confers a defined risk increase for celiac disease per risk-allele as reported in the GWAS databases or literature (β_1 in Fig. 1). Second, a large Swedish population-based analysis revealed a relative risk for ischemic heart disease of 1.19 in patients with celiac disease as compared to controls (β_2 in Fig. 1) (Ludvigsson et al. 2011). Based on the strength of these two associations between SNP and celiac disease on the one hand and between celiac disease and CAD on the other hand, we estimated the expected OR for each SNP on CAD.

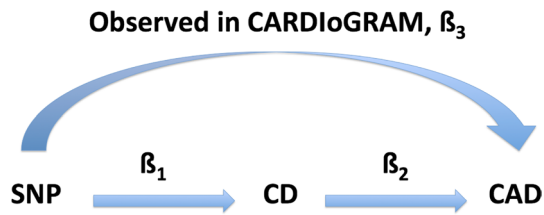


Fig. 1 Graphical display of how the observed and expected effect sizes for the association of BP-associated SNPs with CAD were calculated. The effect estimates quantifying the association between SNP and celiac disease (β_1) were obtained from the literature; the effect estimates for the association of celiac disease with CAD were estimated in a large Swedish population-based analysis (β_2) (Ludvigsson et al. 2011). The observed effect sizes (β_3) were obtained from the CARDIoGRAM database

In secondary analyses, we assessed whether any celiac disease-SNP reached study-wide statistical significance for CAD, adjusting for multiple testing using the Bonferroni method ($p = 0.05/41$ SNPs tested = 0.0012).

Power calculation

For each SNP, we calculated the statistical power to detect an association with CAD. For the power calculation, we used a power equation for unmatched studies with multiple controls per case (Schlesselman and Stolley 1982). We assumed the expected effects on CAD, the allele frequencies of each variant in the CARDIoGRAM controls, a significance level of 0.05, and the number of cases and controls from CARDIoGRAM (Supp. Table 1).

Results

By screening GWAS databases and the published literature, we identified a total of 41 loci associated with celiac disease at a genome-wide significant level ($p < 5 \times 10^{-08}$) in Caucasians (Dubois et al. 2010; Van Heel et al. 2007; Hunt et al. 2008; Östensson et al. 2013; Trynka et al. 2011). Three SNPs (rs12068671, rs61579022, rs79758729) of the initially identified SNPs were not represented in CARDIoGRAM, but we were able to identify respective proxies (rs10912292, rs11715698, rs11984075).

Association of celiac disease-associated SNPs with CAD

24 out of 41 celiac disease-related risk alleles revealed ORs for CAD < 1 in CARDIoGRAM (OR range 1.001–1.081) indicating a directionality consistent association for celiac disease and CAD (Fig. 2). The remaining 17 celiac disease-related alleles displayed ORs of either 1.0 or below 1 (range 0.951–0.988, Fig. 2). Thus, although we observed

a tendency towards a directionality consistent association with CAD for celiac disease-related risk alleles, the proportion (58 %) of SNPs with an OR > 1 failed to differ statistically from what could have been expected just by chance (50 %, $p = 0.069$). Four variants produced p values below the 5 % threshold, with one variant at the *HLA-DQA1* locus with opposite direction regarding its effect on celiac disease and CAD. Applying an adjustment for multiple testing to identify SNPs with a study-wide statistical significance association for CAD, only SNP rs653178 at the *SH2B3/ATXN2* locus remained statistically significantly associated with CAD ($p = 2.2 \times 10^{-6}$, OR for CAD 1.081).

The average statistical power of the 41 SNPs to detect an association with CAD was 78 % (range 41.3–100 %).

Comparison of expected and observed SNP effects on CAD

Based on (1) the association of each SNP with celiac disease and (2) the association between celiac disease and CAD as reported in the published literature (Ludvigsson et al. 2011), the celiac disease-associated alleles are expected to produce relative CAD risk increases between 1.8 % (*ARHGAP31* locus) and 40.4 % (*HLA-DQA1* locus) (Fig. 3).

Interestingly, these expected effects (please see above) were significantly greater than the effects actually observed in the CARDIoGRAM dataset ($p = 0.001$; Fig. 3).

Discussion

Although most epidemiological data suggest an increased risk for CAD in patients with celiac disease, it is not clear how this increased risk is mediated and whether celiac disease itself increases CAD risk. If that was the case, we would expect that genetic variants primarily associated with celiac disease also conferred an increased risk for CAD. Therefore, we evaluated celiac disease-related SNPs in a large meta-analytical dataset for CAD (CARDIoGRAM). We obtained two key results. First, slightly more celiac disease risk alleles than expected by chance (58 %) displayed an increased risk for CAD (OR > 1), but this difference failed to reach statistical significance. Second, the observed effects of celiac disease risk alleles on CAD were substantially smaller than the effect sizes expected based on published (genetic-) epidemiological data.

Despite some contradictory reports (Poddar et al. 2014; West et al. 2004), the majority of epidemiological data indicates a modest positive association between celiac disease and CAD (Emilsson et al. 2013a; Gajulapalli 2014; Ludvigsson et al. 2011; Viljamaa et al. 2006). A partially shared genetic architecture of CAD and celiac disease as

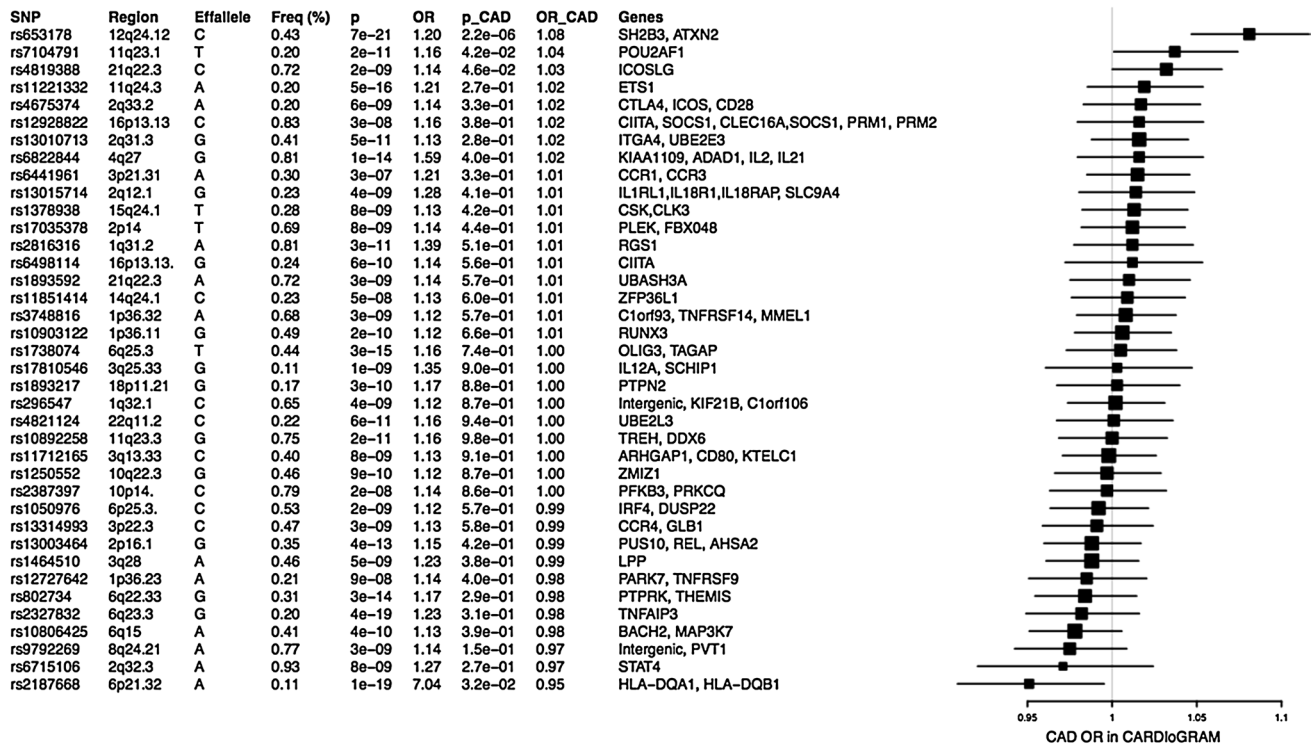
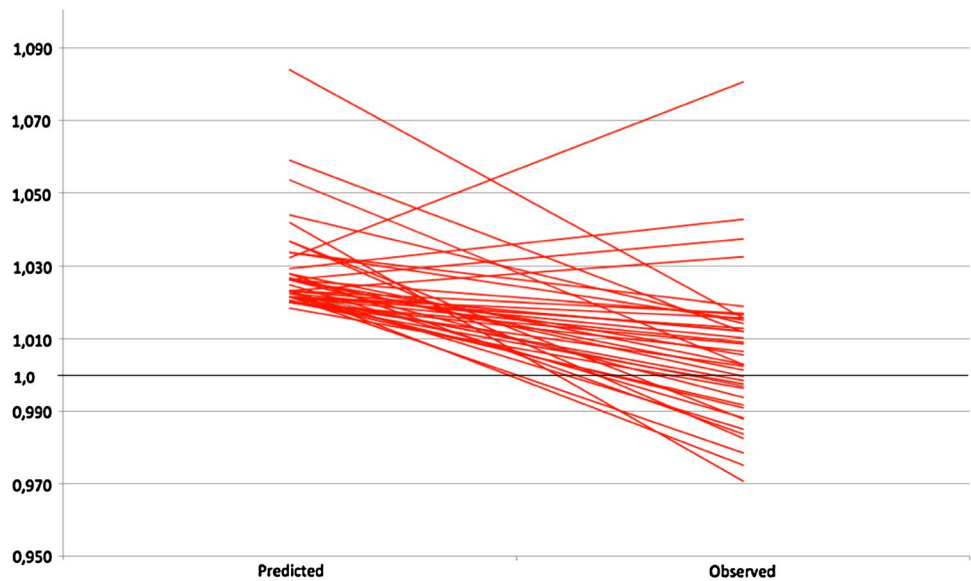


Fig. 2 Genes and respective lead SNPs (rs numbers) are listed. Forest plots display the associations of celiac disease-associated SNPs with CAD in CARDIoGRAM. Boxes represent the odds ratios (ORs)

and whiskers 95 % confidence intervals. Size of boxes proportional to inverse variance of ORs

Fig. 3 Bar plot comparing the predicted and observed effects on CAD. Each line represents one SNP test in our analysis [after exclusion of the HLA locus, which produced an estimated effect (OR) on CAD of 1, 4 vs. an observed effect of 0, 9]. The predicted effects are calculated based on the respective SNP effects on celiac disease (Dubois et al. 2010; Van Heel et al. 2007; Hunt et al. 2008; Östenson et al. 2013; Viljamaa et al. 2006) and the impact of celiac disease on CAD coming from epidemiological data (Ludvigsson et al. 2011). The observed effects were derived from the CARDIoGRAM dataset



an explanation for the co-occurrence of the two diseases is supported by the observation that first degree relatives of celiac disease patients are at higher risk of experiencing CAD compared to controls, although the absolute risk increase was rather modest (70/100.000) and of unclear clinical significance (Emilsson et al. 2014). About

one-third of the genes within the regions associated with CD are putatively linked to inflammatory pathways. However, none of CD SNPs related to inflammation showed signs of association in our large meta-analytical dataset for CAD (CARDIoGRAM), including data from 22,233 CAD cases and 64,762 controls. In fact, we observed no

statistically significant association with CAD for all alleles known to predispose to celiac disease. We observed a modest increase in the proportion of alleles associated with CAD (58 %) as compared to the proportion expected by chance (50 %), but this difference was not statistically significant. Our analyses do not support a causal contribution of celiac disease itself to CAD etiology and suggest that either other yet unidentified genetic variants contribute to the increased CAD risk in patients with celiac disease or that rather non-genetic risk factors foster the co-occurrence of both disease conditions. Potentially relevant non-genetic factors linking celiac disease and CAD include traditional CAD risk factors and malnutrition. It has been reported that patients with celiac disease have increased levels of CAD risk factors, including elevated LDL cholesterol or insulin resistance (Norsa et al. 2013), which could in part explain the increased CAD risk in celiac disease patients observed in clinical and population-based settings. However, the literature is not entirely consistent with some studies also reporting more favorable CAD risk profiles in patients with celiac disease as compared to controls (Emilsson et al. 2013b; Olén et al. 2009).

Furthermore, malnutrition might contribute to an increased CAD risk in patients with celiac disease. Clinical evidence indicates that malnutrition is relatively common among patients celiac disease (Barton et al. 2007). This malnutrition is characterized by weight loss, nutrient deficiencies and elevated levels of inflammatory markers, including interleukins and TNF α (Ferretti et al. 2012). Thus, a possible mechanism explaining the association between celiac disease and increased risk of CAD might be the presence of chronic inflammation, which is caused by the intake of gluten protein (Emilsson et al. 2013b).

Moreover, metabolic alterations, such as impaired functions of the gallbladder, pancreas, liver, and potentially overweight and obesity especially in patients who stick to the gluten-free diet might be an alternative explanation for the celiac disease-CAD-association (Farnetti et al. 2014).

Our analyses also indicate that the association between celiac disease and CAD as reported in the literature might be inflated. Indeed, the far largest population-based study from Sweden could not adjust for major confounders, including high blood pressure, lipids or smoking. Also, depression or the adherence to gluten-free diet, which might be relevant confounders were not taken into account, since they were not available (Lagro et al. 2011; Ludvigsson et al. 2011). This lack of adjustment could explain a potentially inflated measure of association between celiac disease and CAD (Lagro et al. 2011).

One genetic variant displayed a study-wise statistical significant association with CAD, rs653178 at the *SH2B3/ATXN2* locus. Of note, this locus not only associates with celiac disease, but also associates with multiple other

diseases like autoimmune disorders, hematopoietic traits or vascular pathologies (Auburger et al. 2014). Hence, it is unclear, which pathophysiological mechanisms actually promote the significant risk increase of CAD which has been seen in our analysis.

Strength and limitations

A strength of our analysis is the large size of our meta-analytical CARDIoGRAM database with GWAS data from 22,233 CAD patients and 64,762 controls. Furthermore, we studied all genetic variants currently known to be associated with celiac disease in a genome-wide significant fashion.

In conclusion, our genetic-epidemiological analyses provide no evidence that genetic variation associated with celiac disease also confers an increased risk for CAD. This observation does not support a causal contribution of celiac disease itself to CAD risk. Rather, non-genetic factors, including dietary or metabolic alterations in celiac disease might explain the co-occurrence of CAD and celiac disease. Furthermore, the strength of association between celiac disease and CAD observed in epidemiological studies might have been inflated due to significant residual confounding.

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