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The shared allelic architecture of adiponectin levels and coronary artery disease

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Abstract

Objective: A large body of epidemiologic data strongly suggests an association between excess adiposity and coronary artery disease (CAD). Low adiponectin levels, a hormone secreted only from adipocytes, have been associated with an increased risk of CAD in observational studies. However, these associations cannot clarify whether this relationship is causal or due to a shared set of causal factors or even confounding. Genome-wide association studies have identified common variants that influence adiponectin levels, providing valuable tools to examine the genetic relationship between adiponectin and CAD.

Methods: Using 145 genome wide significant SNPs for adiponectin from the ADIPOGen consortium ($n = 49,891$), we tested whether adiponectin-decreasing alleles influenced risk of CAD in the CARDIoGRAM consortium ($n = 85,274$).

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Conflict of interest statement

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.atherosclerosis.2013.03.034>.

Results: In single-SNP analysis, 5 variants among 145 SNPs were associated with increased risk of CAD after correcting for multiple testing ($P < 4.4 \times 10^{-4}$). Using a multi-SNP genotypic risk score to test whether adiponectin levels and CAD have a shared genetic etiology, we found that adiponectin-decreasing alleles increased risk of CAD ($P = 5.4 \times 10^{-7}$).

Conclusion: These findings demonstrate that adiponectin levels and CAD have a shared allelic architecture and provide rationale to undertake a Mendelian randomization studies to understand if this relationship is causal.

Keywords

Adiponectin; Coronary artery disease; Atherosclerosis; Gene; Association; SNP

1. Introduction

Coronary artery disease (CAD) is the leading cause of death in developed countries. ENREF_1 According to world health organization, CAD is responsible for approximately half of the 36 million deaths from non-communicable diseases [1]. Epidemiological studies have revealed numerous CAD risk factors such as obesity, dyslipidemia, hypertension, smoking and diabetes mellitus. Among these factors, obesity is one of the most prevalent causes of cardiovascular morbidity and mortality [2]. Excess body fat is associated with dysregulation of several bioactive factors produced from adipose tissue which may participate in the development of obesity-related diseases [3].

Adiponectin, a hormone produced predominantly by adipocytes, has anti-atherogenic and anti-inflammatory properties. Low circulating adiponectin levels have been linked to a range of important clinical parameters including blood glucose, indices of insulin resistance, proatherogenic dyslipidemia, risk of type 2 diabetes (T2D), stroke and CAD [4,5]. In a study of 225 male patients with documented CAD, compared with age-matched controls, lower plasma adiponectin levels ($<4.0 \mu\text{g/mL}$), were associated with a 2-fold higher prevalence of CAD, independent of established CAD risk factors [6]. Also, Dzieli ska et al. showed that plasma adiponectin levels were decreased in a group of 99 hypertensive men with CAD, as compared to normotensive healthy subjects [7]. Similarly, a nested case-control study among 18,225 male participants in the Health Professionals Follow-up Study revealed that after adjustment for common CAD risk factors, participants in the highest, compared with the lowest, quintile of circulating adiponectin levels had a significantly lower risk of MI (RR = 0.41; 95% CI: 0.24–0.70, $P < 0.001$) [5]. Lawlor et al. investigated the association of adiponectin with incidence of CAD in 4286 women who were randomly selected from 23 British towns between 1999 and 2001. Although adiponectin was associated with CAD risk factors in this study, adiponectin did not predict future risk of CAD [8]. Additional findings suggested that for each $1 \mu\text{g/mL}$ increase in plasma adiponectin level, there was an associated 3% risk reduction in CAD [9]. Lastly, a recent study demonstrated that plasma adiponectin levels in patients with acute coronary syndrome were significantly lower than those in patients with stable CAD [10]. Collectively these studies suggest that hypoadiponectinemia is a risk factor for development of atherosclerosis and CAD, underscoring the potential importance of this hormone.

Despite these associations, it is uncertain whether low adiponectin levels cause CAD. Genetic variants related to adiponectin levels can help us elucidate this relationship since they lie in the causal pathway and therefore their relationship with the outcome is likely not confounded by other risk factors. Further, since the temporal relationship between genetic variants and outcomes is clear, thereby excluding the possibility of reverse causation. Therefore, modern human genetics provides us with the opportunity to disentangle causal from non-causal associations between established risk factors including biomarkers such as adiponectin and CAD.

Variations in the gene encoding adiponectin (*ADIPOQ*) have been tested for their association with CAD. Two variants, rs2241766 (T+45G), rs1501299 (G+276T), have been assessed in several independent studies and a prospective analysis from Health Professionals follow-up study. While the rs1501299 variant showed evidence of association with CAD in Health Professionals Study [11] there no association was found in French/Swiss [12], Italian [13] and Japanese [14] studies. In addition, the rs2241766 variant was associated with CAD in the French/Swiss study [12] without showing evidence of association in Health Professional and Japanese studies [11,14]. Finally a coding variant, rs185847354, (I164T) had higher frequency among CAD cases in Japanese population [15]. Recent meta-analysis indicated a significant association of rs266729 (–11377C/G) but not rs2241766 or rs1501299 polymorphism with CAD among European and East Asian populations [16].

Several candidate and genome-wide association studies (GWAS) have shown pronounced associations between common polymorphisms in the *ADIPOQ*, *ARL15*, *CDH13* and *KNG1* and adiponectin levels [17–19]. Recently, in the largest multi-ethnic GWAS meta-analysis ($n = 45,981$) from ADIPOGen Consortium, we identified 10 novel loci for adiponectin levels and described their influence on risk of type 2 diabetes and metabolic traits [20].

In our ADIPOGen meta-analysis study, the coding and intronic variants in *STAB1* and *NT5DC2* were associated with weight to hip ratio (WHR) and high density lipoprotein cholesterol (HDL-C), while variants within 1 Mb of *TRIB1* were associated with all lipid traits. The coding and intronic variants in the locus on chromosome 12 harboring *ZNF664*, *CCDC92*, and *DNAH10* showed evidence of association with WHR, HDL-C, and TG. Finally, variants in the *PEPD* were associated with TG. [20]. This suggests that variants associated with adiponectin levels also correlated with components of the metabolic syndrome.

Given the lack of certainty regarding the nature of the relationship between adiponectin and CAD and the recent identification of replicated genetic determinants of adiponectin levels, we sought to determine whether the alleles that influence adiponectin levels also influence risk of CAD in the CARDIoGRAM consortium ($n = 85,274$).

2. Materials and methods

2.1. CAD samples

We used meta-analytic level data from the Coronary ARtery Disease Genome-wide Replication And Meta-Analysis (CARDIoGRAM) consortium. Details of the design of

CARDIoGRAM have been published previously [21]. Briefly, the CARDIoGRAM consortium combined GWAS data in individuals with European ancestry, including >22,000 cases with CAD, MI, or both and >60,000 controls, from 14 GWAS studies to understand the role of common genetic variation in CAD. The study was approved by correlated institutional review committees and that the subjects gave informed consent.

2.2. SNP selection

Through the ADIPOGen consortium we have recently conducted a meta-analysis of GWAS for adiponectin levels in European cohorts and in the joint analysis of discovery, in-silico and de-novo followup phases of study ($n = 39\,883$) identified 162 SNPs to be genomewide significant ($p < 5.0 \times 10^{-8}$) in their relationship with adiponectin levels [20]. (Table S1). These results include the previously described associations with adiponectin at *ADIPOQ* and *KNG1* on chromosome 3, and *CDH13* on chromosome 16. These analysis also identified novel loci on chromosome 1, 6, 8, 12, 16, and 19. Details of genotyping methods and quality control criteria have been described previously [20,21].

2.3. Statistical analysis

Single-SNP analyses: We employed the Single Nucleotide Polymorphism Spectral Decomposition (SNPSpD) method that developed by Nyholt D [22]. This method corrects the multiple testing based on linkage disequilibrium (LD) using spectral decomposition matrices of pairwise LD between SNPs. Using this method, 145 SNPs were estimated to be equivalent to 113 independent statistical tests due to LD for their association. So we employed a Bonferroni-corrected threshold of $\alpha = 4.4 \times 10^{-4}$ (where $4.4 \times 10^{-4} = 0.05/113$) to define the threshold of association for any individual SNP association with CAD.

Multi-SNP Genotyping Risk Score: Using the 145 SNPs which were genome-wide significant for their relationship with adiponectin levels in cohorts of European ancestry from the ADIPOGen consortium, we selected LD-independent adiponectin associated alleles by LD pruning the set of genome-wide significant adiponectin SNPs with an LD threshold of $r^2 \leq 0.05$ in the HapMap CEU population. Since many SNPs from the same independent blocks were associated with adiponectin, we selected the SNP from the LD block that explained the most variance in adiponectin levels. Next, we approximated the effect of the multi-SNP genetic risk score by calculating the combined effect of LD-independent adiponectin risk alleles on the trait of interest. This is determined as “ a ” in the below”,

$$a = \frac{\sum (\beta_i / \text{Se}_i^2)}{\sum 1/\text{Se}_i^2}$$

here β_i is the effect of the adiponectin-lowering alleles of a given LD-independent set of adiponectin SNPs, and Se_i is its standard error, as derived from consortium-level meta-analytic data for ADIPOGen. The weighted sum of the individual SNP coefficients, weighted by the estimates from the ADIPOGen data, leads not only to an estimate of the average combined allelic effect, but also to an approximate estimate of the model R^2 (when scaled by the inverse of the total meta-analysis sample size) from a multivariate regression

model containing these SNPs. Therefore, estimates of single SNP effects, obtained from the meta-analysis, can be used to obtain estimates of their joint effects. We have described this method in further detail elsewhere[20].

3. Results

145 out of 162 SNPs were available in CARDIoGRAM consortium results (Table S2). SNPSpD method identified that there were 113 statistically independent SNPs among the 145 SNPs. 49 of the 145 variants had p-values less than 0.05 for their association with CAD in the CARDIoGRAM consortium. However, only 5 variants remained significantly associated with CAD after correction for multiple testing ($P < 4.4 \times 10^{-4}$) (Table 1, Table S3). These SNPs (rs2954026, rs7846466, rs2954032, rs2954033, rs2980859) are located in a locus on chromosome 8 near *TRIB1* (40 kb from the gene). The per-allele odds ratios for CAD risk for each of these significant variants at *TRIB1* ranged from 1.05 to 1.06.

Next, we derived a multi-SNP genotypic risk score based on genome-wide significant SNPs from ADIPOGen Consortium and tested the association of this risk score with risk of CAD in the CARDIoGRAM consortium. The score included genotype information at 17 of the 145 SNPs representing independent LD blocks (Table S2). The multi-SNP genotypic risk score was associated with increased risk for CAD ($\beta = 0.021$, $p = 5.4 \times 10^{-7}$), where β is the average additive effect of adiponectin-decreasing risk alleles on the log odds ratio (OR = 1.02, 95% CI (1.013–1.030)) for CAD. These results remained significant after removing *TRIB1* locus SNPs ($\beta = 0.019$, $p = 2.68 \times 10^{-5}$).

4. Discussion

While CAD risk is associated with lower adiponectin levels in observational studies it is unclear if this is due to a direct role of adiponectin, the factors influencing adiponectin levels, or unmeasured confounders. Using 145 genome-wide significant SNPs for adiponectin levels, we demonstrate that adiponectin decreasing alleles are, on average, associated with an increased risk of CAD, and that variants near *TRIB1* are associated with both traits. These findings suggest that either adiponectin levels, or the genetic factors influencing adiponectin levels, impact on risk of CAD.

After accounting for multiple testing we identified five variants near the *TRIB1* that were associated with CAD and adiponectin levels. While this highlights the importance of this locus, the multi-SNP allelic risk score remained associated with CAD even after excluding this locus. *TRIB1* is located on chromosome 8 and encodes a G protein-coupled receptor-induced protein that interacts with Mitogen-activated protein MAP kinases and regulates the activation of MAP kinases [23]. MAP kinases signaling regulates the proliferation and chemotaxis of vascular smooth muscle cells. *TRIB1* expression was shown to be elevated in human atherosclerotic arteries [24]. Interestingly, several variants (rs2954029, rs2954021, rs17321515) in the *TRIB1* have been associated with HDL-C, LDL-C and CAD risk in European and Asian populations [25–27]. Two out of five SNPs (rs2954026, rs2954033) on chromosome 8 near *TRIB1* were also reported to be associated metabolic syndrome in the STAMPEED Consortium study [28]. Our findings are consistent with the finding from the

IBC 50K CAD Consortium that suggested an odd ratio of 1.06 for CAD risk with the variants in this gene [29].

Furthermore, functional studies in mice provided evidence that *TRIB1* play a role in lipoprotein metabolism in mice. Burkhardt et al. demonstrated that the overexpression of *trib1* reduced VLDL production that accordingly decreased the plasma triglyceride and cholesterol. Also *trib1*-knockout animals showed elevated levels of both triglycerides and cholesterol [30]. Their study revealed that *TRIB1* influences expression of lipogenic genes and lipogenesis in hepatocytes, with consequent effects on the plasma lipids and risk for CAD [30]. These findings provide evidence that a *TRIB1*-modulating agent might be novel pathway to target for management of dyslipidemia and prevention of CAD. One study investigated the relation between *TRIB1* polymorphisms and type 2 diabetes (T2DM) and related traits in Chinese population and revealed that no significant correlation with T2DM, while indicated the association with T2DM combined CAD [31].

We are not aware of any of functional studies interrogating the role of *TRIB1* in adiponectin metabolism. We postulate that *TRIB1* could either influence the expression of the *ADIPOQ* or other genes involved in production of adiponectin, or enhance the elimination of the adiponectin protein. The effect of *TRIB1* on adiponectin may also be through its effect on lipogenic genes and lipogenesis [30]. Moreover, the involvement of *TRIB1* in vascular biology of smooth muscle cells may effect adiponectin regulation through *CDH13*, a receptor for adiponectin expressed by endothelial smooth muscle. Despite the fact that *TRIB1* is a far weaker determinant of adiponectin compare to *ADIPOQ*, the stronger evidence of association of *TRIB1* with CAD might be through the synergistic effect of *TRIB1* on lipid traits and adiponectin and its subsequent involvement in atherosclerosis.

This study provides evidence of a shared allelic architecture between adiponectin and CAD, but does not constitute a Mendelian randomization study. This is because the study design employed cannot differentiate between SNPs that directly influence CAD through adiponectin levels and SNPs that influence CAD directly, but also influence adiponectin levels (i.e. pleiotropy). Thus, we caution that our results should not imply a causal relationship between adiponectin levels and CAD, as the effects of the SNPs influencing adiponectin may also influence CAD in pathways that are independent on adiponectin levels. Nonetheless, in aggregate, these findings suggest that at least some of the genetic variants influencing adiponectin also influence the risk of CAD.

In summary, our results provide direct evidence that a shared set of genetic factors exist that influences both adiponectin levels and CAD, suggesting that previous described epidemiologic relationships between decreased adiponectin levels and CAD are not due to unobserved confounding factors. These findings therefore provide rationale to undertake a Mendelian randomization to understand if the relationship between adiponectin and CAD is causal, or through shared pleiotropic factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

List of SNPs that were genome-wide significant in their relationship with adiponectin levels after correction for multiple testing in single-SNP analysis for CAD in CARDIoGRAM.

SNP	Chr/Pos ^a	EA/NEA ^b	Beta(SE)	P	n-samples	Closest gene ^c
rs2954026	8/126553708	T/G	0.0524(0.01)	0.00041	82,452	<i>TRIB1</i>
rs7846466	8/126554713	T/C	0.0524(0.01)	0.00040	82,446	<i>TRIB1</i>
rs2954032	8/126562574	A/G	0.0553(0.01)	0.0002	83,003	<i>TRIB1</i>
rs2954033	8/126562928	A/G	0.055(0.01)	0.0002	82,069	<i>TRIB1</i>
rs2980859	8/126568611	C/G	0.0586(0.02)	0.0001	80,115	<i>TRIB1</i>

^aPositions are relative to Human Genome NCBI Build 36.

^bEA: effect allele on CAD, NEA: non-effect allele.

^cWhen possible, plausible biological candidate genes have been listed; otherwise, the closest gene is designated.