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Genetic variants primarily associated with type 2 diabetes are related to coronary artery disease risk

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ABSTRACT

Background: The mechanisms underlying the association between diabetes and coronary artery disease (CAD) risk are unclear. We aimed to assess this association by studying genetic variants that have been shown to associate with type 2 diabetes (T2DM). If the association between diabetes and CAD is causal, we expected to observe an association of these variants with CAD as well.

Methods and results: We studied all genetic variants currently known to be associated with T2DM at a genome-wide significant level ($p < 5*10^{-8}$) in CARDIoGRAM, a genome-wide data-set of CAD including 22,233 CAD cases and 64,762 controls. Out of the 44 published T2DM SNPs 10 were significantly associated with CAD in CARDIoGRAM (OR>1, $p < 0.05$), more than expected by chance ($p = 5.0*10^{-5}$). Considering all 44 SNPs, the average CAD risk observed per individual T2DM risk allele was 1.0076 (95% confidence interval (CI), 0.9973–1.0180). Such average risk increase was significantly lower than the increase expected based on i) the published effects of the SNPs on T2DM risk and ii) the effect of T2DM on CAD risk as observed in the Framingham Heart Study, which suggested a risk of 1.067 per allele ($p = 7.2*10^{-10}$ vs. the observed effect). Studying two risk scores based on risk alleles of the diabetes SNPs,

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one score using individual level data in 9856 subjects, and the second score on average effects of reported beta-coefficients from the entire CARDIoGRAM data-set, we again observed a significant - yet smaller than expected - association with CAD.
Conclusions: Our data indicate that an association between type 2 diabetes related SNPs and CAD exists. However, the effects on CAD risk appear to be by far lower than what would be expected based on the effects of risk alleles on T2DM and the effect of T2DM on CAD in the epidemiological setting.

1. Introduction

Type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) are strongly associated conditions [1]. As a consequence, guidelines suggest that all patients with T2DM should be screened for CAD and, *vice versa*, all patients with CAD should be screened for T2DM [2]. Although diabetics carry a 2- and 3-fold higher probability to present with incident CAD [2,3] there is an ongoing debate whether T2DM is a causal factor. Interestingly, prevalent CAD also associated with an increased probability of incident T2DM [4]. This may be explained by the fact that even impaired glucose tolerance, or prediabetes, increases the risk of CAD resulting in clinically evident coronary events even before T2DM can be diagnosed [5]. However, the variable order in which the two diseases manifest raises doubt whether the association between T2DM and CAD is confounded rather than causal. Indeed, hypothetically T2DM and CAD could both be precipitated in parallel by common preceding factors such as a sedentary life style, an inadequate diet, obesity or others [6]. Observational studies, whether cross-sectional or longitudinal, are not able to fully exclude these and other confounders in the complex etiology of both T2DM and CAD [7]. Here we utilized genetic information to further study the commonly held view that the observed association between T2DM and CAD is due to a causal relationship.

Specifically, we tested if single nucleotide polymorphisms (SNPs) that affect T2DM risk also associate with the risk of an individual developing CAD. Such risk increase, if present, would be expected to be independent of exogenous environmental factors, since these confounders are expected to be distributed evenly in the respective genotype groups [8]. Thus, if T2DM SNPs were also found to be associated with increased CAD risk, this analysis based on genetic information would support the evidence of T2DM as a causal risk factor for CAD.

A series of large-scale genomewide association studies (GWAS) have reported that 44 SNPs are associated with T2DM in Caucasians with a genomewide level of significance ($p < 5 \times 10^{-8}$) [9–16]. In the present analysis, we assessed whether the respective T2DM associated risk alleles also associate with an increased risk for CAD. We used data from the CARDIoGRAM Consortium, which has meta-analyzed genomewide data from 14 studies, including 22,233 cases with CAD and 64,762 controls [17,18]. We compared the quantitative effects of T2DM SNPs on CAD risk as observed in CARDIoGRAM with those that could be expected based on the reported effects of these SNPs on diabetes risk (in the published literature) and the effect of diabetes on CAD risk in the Framingham Heart Study.

2. Methods

2.1. SNP selection

We systematically searched the literature including NHGRI GWAS Catalog (http://www.genome.gov/gwastudies/; *access date: 09/15/2012)* for SNPs with genomewide significant ($p < 5*10^{-8}$) associations with T2DM in Caucasians by using the terms "genomewide, GWAS, type 2 diabetes" [9–16]. For loci reported to be associated with T2DM, we searched for the respective SNPs in the CARDIoGRAM database.

If the SNPs did not pass quality control in CARDIoGRAM we identified proxy-SNPs using the SNAP (SNP Annotation and Proxy Search)-tool by searching with a r^2-threshold of 0.8 and a distance limit of 500 BPs [19]. The identified proxy-SNPs were then tested for association with CAD in CARDIoGRAM.

3. Study samples

3.1. CARDIoGRAM consortium

Details about the CARDIoGRAM Consortium have been reported elsewhere [18]. In brief, this consortium combined genomewide association data on CAD from several studies and consortia: CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) [20]; CADomics [18]; ADVANCE (Atherosclerotic Disease VAscular functioN and genetiC Epidemiology study) [21]; deCODE CAD study [22]; LURIC (Ludwigshafen Risk and Cardiovascular Health Study) [23]/AtheroRemo 1 and 2; MIGen (Myocardial Infarction Genetics Consortium) [24]; MedStar [25]; Ottawa Heart Genomics Study (OHGS) [26]; PennCATH [25]; the Wellcome Trust Case Control Consortium (WTCCC) (27; 28); and the German Myocardial Infarction Family Studies (GerMIFS) I, II, and III (KORA) [28–30].

A detailed description of probands (Cases/Controls) in the participating studies is presented in the supplementary data (Supplementary Table 1).

3.2. German MI family study (GerMIFS) I and II and WTCCC

Individual level data from the German MI Family Studies (GerMIFS) I and II and from WTCCC [28–30], which both participated in the CARDIoGRAM Consortium, were used to generate a genetic risk score as detailed below. All CAD cases were characterized by i) premature myocardial infarction (before the age of 60 years) and ii) > 1 first-degree relative with an MI/CAD before the age of 70 years (in most cases a sibling) within in the GerMIFS I and II. CAD was defined as having documented coronary bypass surgery or percutaneous coronary intervention (PCI) [27–31]. All patients recruited, were also characterized as having survived with CAD for long enough to be diagnosed, recruited and studied. CAD within the WTCCC study was defined as having a validated myocardial infarction, a history of PCI, coronary bypass surgery or angina with a positive noninvasive testing before the age of 66. Conversely, the control group was defined as having no known CAD up to the age at which they were recruited and studied.

3.3. Framingham Heart Study

The Framingham Study is a large prospective cohort study of the determinants of cardiovascular disease, that includes several thousand participants, from three generations [32–34]. Pooled