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Recessive protective effect of ADIPOQ rs1501299 on cardiovascular diseases with type 2 diabetes: A meta-analysis

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ABSTRACT

The association between a common variant of the ADIPOQ gene rs1501299 (+276G>T) and cardiovascular diseases (CVDs) outcomes has been reported with many studies. However, the evidence is insufficient for strong conclusions regarding CVDs and ADIPOQ rs15011299 (+276G>T). We performed a meta-analysis about the association between ADIPOQ rs1501299 (+276G>T) and CVDs risk using a predefined protocol, including 15 published studies with 5868 cases and 10,744 controls. The pooled data suggested a recessive protective effect of ADIPOQ rs1501299 (+276G>T) on CVDs for type 2 diabetes (T2D) population: the TT homozygote individuals had a reduced risk of developing CVDs compared to the carriers of G allele (OR = 0.74, 95% confidence interval (CI): 0.58, 0.94; $p = 0.013$). But there is still not enough evidence to indicate the association of the ADIPOQ rs1501299 (+276G>T) and the development of cardiovascular diseases (CVDs) outcomes in general population. In conclusion, our meta-analysis suggested that the ADIPOQ rs1501299 (+276G>T) polymorphism is a low-risk factor for the development of CVDs with T2D, but the association of this polymorphism with the susceptibility to CVDs in other populations remains unknown. It could be presumed that the ADIPOQ rs1501299 (+276G>T) be a potential cause of susceptibility to CVDs in persons with T2D, and it gives a new opportunity to investigate the mechanisms of CVDs susceptibility in T2D patients.

1. Introduction

Adiponectin (ACRP30, GBP28), a new hormone of the C1q/TNF superfamily, is predominantly derived from white adipose tissue and is abundant in human serum. Previous studies demonstrated that adiponectin could reduce the risk of type 2 diabetes (T2D), improve insulin sensitivity and regulate other biological processes. Recent evidence indicated that adiponectin has cardiovascular protection effects through metabolic regulation, vascular protection, anti-atherosclerosis, anti-inflammatory and anti-ischemia (Ouchi et al., 1999; Nanasato and Murohara, 2010; Lau et al., 2011). Adiponectin circulates in the blood in higher-order structural forms and at a relatively high concentration compared with the other peptide hormones. Several clinical studies reported that adiponectin levels were lower in patients with clinical manifestations of cardiovascular diseases (CVDs) than in age- and BMI (body mass index)-adjusted control subjects (El-Menyar et al., 2009; Persson et al., 2010b). Hypoadiponectinemia is also associated with disorders related to CVDs, such as diabetes, hypertension, metabolic syndrome (MS) and dyslipidemia (Okamoto, 2011; Vanhala et al., 2011).

The gene coding for adiponectin, previously called "adipose most abundant gene transcript 1" (AMP1) or "adipocyte C1q and collagen domain-containing" (ACDC) (OMIM 605441), is officially designated as ADIPOQ by the Human Genome Organization. It is located on chromosome 3q27 including 3 exons and 2 introns and spanning 16 kb of genomic sequence. Genome-wide scan and genome-scan meta-analyses have demonstrated that this region might contain genes relating to CVDs susceptibility, suggesting that ADIPOQ might be a candidate gene associated with susceptibility to CVDs and related diseases (Francke et al., 2001; Chiodini and Lewis, 2003). In the past decade, several single nucleotide polymorphisms (SNPs) of the ADIPOQ gene have been identified. Some SNPs were reported to be associated with hypoadiponectinemia or the abnormal function of adiponectin. Many molecular epidemiological studies focusing on the association between ADIPOQ variants and the risk of CVDs have been conducted since the initial studies by Ohashi's group and Lacquemant's group in 2004, which reported the possible role of some SNPs as genetic markers of CVDs in general population and T2D population, respectively (Lacquemant et al., 2004; Ohashi et al., 2004). However, the evidence remains insufficient to draw significant conclusions

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because of the small effect of these SNPs on the susceptibility to CVDs and the relatively small sample size in each study. To summarize the published data, we conducted a meta-analysis from all eligible studies to assess the association between the ADIPOQ rs1501299 (+276G>T) SNP and the risk of CVDs.

2. Materials and methods

2.1. Search strategy

We conducted a comprehensive search in the electronic databases of PubMed, EMBASE and Science Citation Index Expanded. We considered CVDs as coronary heart disease (disease of the blood vessels supplying the heart muscle) and cerebrovascular disease (disease of the blood vessels supplying the brain) and searched all papers published before April 30, 2011. The search terms for PubMed were as follows: (adiponectin or APM1 or acrp30 or gbp28 or ACDC or ADIPOQ) and (SNP* or "single nucleotide polymorphism*" or "genetic variant*" or "gene variation" or gene variant*) and ("coronary artery disease" or CAD or "coronary heart disease" or CHD or "coronary disease" or "heart disease" or "cardiovascular disease" or CVD or "ischemic heart disease" or IHD or "myocardial infarct" or "myocardial ischemia" or "myocardial infarction" or MI or angina or "acute coronary syndrome" or ACS or cerebrovascular or stroke). We searched the other databases listed above using similar search terms. Searching was performed in duplicate by two independent reviewers (Sun and C. Wei) and not limited by publication year or the English language. All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of relevant studies were hand-searched to find additional eligible studies. When more than one of the same sample was included in several publications, only the most recent or complete study was used in this meta-analysis. Our systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000).

2.2. Eligibility criteria

Eligible studies included case-control, cross-sectional, and cohort studies that investigated the association between the ADIPOQ rs1501299 (+276G>T) SNP and CVDs outcomes. The inclusion criteria were as follows: (1) the study provided cases of CVDs and control subjects without CVDs with a diagnosis based on angiographic studies or established clinical criteria; (2) the study provided information on the genotype frequency and the use of validated molecular methods for genotyping; and (3) the study included sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (95% CI). In studies with overlapping cases or controls, the most recent and/or the largest study with extractable data was included in our meta-analysis.

2.3. Data extraction

The same two reviewers collected data independently by using a standardized data extraction form. Disagreements were resolved by consensus and by consulting a third author (Tong). For each included study, the following data were collected: title, first author, publication year, country, ethnicity, study design, definition and number of cases and controls, sex distribution and mean age, genotyping methods, genotype and allele distributions (where data were not given, they were calculated from the corresponding genotype frequencies of the case and control groups).

2.4. Quality score assessment

The same two reviewers assessed the quality of each study independently by assigning a quality score using a standardized extraction form. Quality assessment scores were modified based on the scoring systems by Thakkinstian (2005a) and Persson et al. (2010a). The total scores ranged from 0 to 15 (Supplementary material 1).

2.5. Statistical analysis

Data analyses were performed according to Thakkinstian's method, as follows (Thakkinstian et al., 2005b). First, Hardy–Weinberg equilibrium (HWE) was calculated in our meta-analysis. We used data from control groups only in studies with case-control design and data from the entire group when another study design was used. The HWE was evaluated by the chi-square test or an exact test by using the genhwi command in Stata 10.0. Studies deviating from HWE were excluded from our meta-analysis.

Next, heterogeneity was checked, and if present, possible causes were explored. Data from each study were extracted as the number of subjects with each genotype (GG, GT, and TT) in the case and control groups. The gene effects of each study were defined as OR1, OR2, and OR3 for TT vs. GG, GT vs. GG, and TT vs. GT, respectively. These ORs were assessed separately for heterogeneity using the Q statistic, and the I^2 statistic was used to estimate heterogeneity quantitatively. If there was no significant heterogeneity in the three pairwise comparisons, then the gene effect was estimated and next steps were performed. Otherwise, possible causes of heterogeneity were explored, and stratification analysis was performed.

If no significant heterogeneity was present, regression analysis was used to pool data and to determine the gene effect. A logistic regression approach proposed for molecular association studies was used to estimate the gene effect. If there was a significant gene effect, the pairwise group differences were used to 'dictate' the most appropriate genetic model as follows:

1. If $OR1 = OR3 \neq 1$ and $OR2 = 1$, then a recessive model is suggested.
2. If $OR1 = OR2 \neq 1$ and $OR3 = 1$, then a dominant model is suggested.
3. If $OR2 = 1/OR3 \neq 1$ and $OR1 = 1$, then a complete overdominant model is suggested.
4. If $OR1 > OR2 > 1$ and $OR1 > OR3 > 1$ (or $OR1 < OR2 < 1$ and $OR1 < OR3 < 1$), then a codominant model is suggested.

The most appropriate genetic model was used to collapse the three genotypes into two groups (except for the codominant model), and the data was pooled again. The pooled OR was calculated by the inverse variance method, and the significance of the pooled OR was tested by Z statistic.

Sensitivity analysis was performed to assess the stability of the results by excluding a single study in the meta-analysis each time to reflect the influence of the individual data on the pooled OR. Cumulative meta-analyses were conducted through an assortment of studies by both publication year and sample size.

Finally, publication bias was assessed qualitatively by constructing funnel plots and quantitatively by using Begg's test and Egger's test (Begg and Mazumdar, 1994; Egger et al., 1997).

All statistical analyses were performed using Stata statistical software (version 10.1; Stata Corporation, College Station, Texas). Two-sided P values less than 0.05 were considered statistically significant, except for tests of heterogeneity where a level of 0.10 was used.