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Research paper

Impacts of common variants in *ALDH2* on coronary artery disease patients

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ABSTRACT

Genome-wide association studies (GWAS) have identified Aldehyde dehydrogenase 2 (*ALDH2*) as a susceptibility locus for coronary artery disease (CAD) previously. However, the impacts of common variants in this gene on CAD and its outcomes have not been extensively studied. This study explored the association between the Tagging SNPs in *ALDH2* and CAD as well as its main outcomes. Six common variants in ALDH2 were selected as tagging SNPs and two cohorts containing 7296 individuals were genotyped to investigate the impacts of *ALDH2* on CAD and its main outcomes. The results show that the variant rs671 in *ALDH2* is associated with an increased risk of CAD in southern Chinese (OR = 1.26, 95%CI: 1.07–1.48, $p = 0.004$), while not in northern Chinese (OR = 1.00, 95%CI: 0.86–1.50, $p = 0.94$). Meanwhile, we find that rs671 genotypes may not influence the outcomes of CAD (HR = 1.11, 95%CI: 0.892–1.38, $p = 0.346$). Additionally, we also tested the effect of rs671 genotype on CAD severity, while no significant association was found between them. In the subgroup analysis, the results revealed that rs671 were significantly associated with CAD (OR = 1.24, 95%CI: 1.11–1.38, $p < 0.001$) in non-alcoholic subjects. Overall, our findings indicate that the associations between rs671 in ALDH2 and CAD are regional disparity, and rs671 genotypes may not influence the main outcomes of CAD.

1. Introduction

Coronary artery disease (CAD) has been the leading cause of death and disability worldwide (Lozano et al., 2012). It's estimated that CAD killed 12.9 million people during the past decades (Lloyd-Jones et al., 2010). So it's important for us to elucidate the mechanisms underlying it. To date, multiple factors, especially genetic factors are thought involved in the development and progression of CAD (Ganesh et al., 2013). Genome-wide association study (GWAS) has been a useful tool in finding hereditary loci in complex disease during the past years (McPherson et al., 2007). Thus far, more than 40 genomic loci have been identified involved in the pathogenesis of CAD by GWAS (Lu et al., 2012; Lee et al., 2013). One of them was aldehyde dehydrogenase 2 (*ALDH2*) (Takeuchi et al., 2012). The *ALDH2* gene composes of 13 exons. In exon 12 position 1510, there is a polymorphism rs671. It's a G-to-A missense mutation, which leads the glutamate replaced by lysine in codon 504 (Glu504Lys) (Ohsawa et al., 2003). Several studies have reported the association between rs671 genotypes and CAD (Takeuchi et al., 2012; Lee et al., 2013). However, the impact of this polymorphism in *ALDH2* on vascular outcomes in patients with cardiovascular disease were rarely reported. Meanwhile, other polymorphisms in this gene were rarely observed. In this study, we investigated the association between common variants in *ALDH2* and CAD. In addition, we tested the impacts of rs671 on vascular outcomes in cardiovascular disease patients.

2. Methods

2.1. Study populations

Two cohorts were included in the study. The initial cohort comprises 1920 CAD patients and 1920 ethnically matched controls. The cases were consecutively recruited from Tongji Hospital in Wuhan (Hubei, People's Republic of China). The detailed inclusion criteria has been reported previously(Cui et al., 2014). Subjects having >50% luminal narrowing in one or more vessel by coronary angiography, myocardial infarction history or received coronary artery bypass graft were selected as cases. Patients with cardiomyopathy, valvular heart disease and genetic arrhythmia were excluded from the study. The healthy subjects

Abbreviations: GWAS, genome-wide association studies; ALDH2, aldehyde dehydrogenase 2; CAD, coronary artery disease; 4-HNE, 4-hydroxy-2-nonenal; MAF, minor allele frequency; HWE, Hardy Weinberg equilibrium.

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were recruited from two communities in Wuhan. For further analysis, subjects using antidiabetes medication or lipid-lowering medication were excluded from controls. To confirm the credibility of our results, we also conduct a replication study comprising 1536 CAD subjects and 1920 healthy participants for the significant mutation. Both the case and control subjects were consecutively recruited from the Second Hospital of Hebei Medical University in Shijiazhuang (Hebei, People's Republic of China) between January 2012 and July 2013. The inclusion criteria followed the same as the initial cohort. In detail, controls were recruited from the Physical Examination Center, and cases were recruited from Department of Cardiology in Second Hospital of Hebei Medical University. Subjects with valvular heart disease, cardiomyopathy, congenital heart disease, and renal or hepatic disease were excluded from this study. Written informed consent was obtained from all participants and the study was approved by the institutional ethics committees of local participating hospitals. The patients of the Tongji cohort were followed up by telephone or visit. We define myocardial infarction, stroke, heart failure and coronary death during the follow up as the main outcomes.

2.2. Tagging SNP and genotyping

Haploview version 4.1 (Informer Technologies, Inc.) was used to select tagging SNPs. The genotype data available from the HapMap database for the Chinese Han population was used for selecting tagging SNPs, as shown in Fig. 1. The *ALDH2* gene covers the region on chromosome 12 spanning a distance of approximately 55 kb (ranging from 110,684 kb to 110,739 kb). Six tagging SNPs were selected for tagging SNPs, as shown in Table 2. These 6 SNPs constitute a minimal set of tagging SNPs necessary to capture (with $r^2 > 0.75$) all 16 common SNPs (minor allele frequency >0.05) in this region.

Genomic DNA was extracted from peripheral blood leukocytes as previously reported(Liu et al., 2015). The *ALDH2* polymorphisms were genotyped by Taqman fluorescent allelic discrimination assay with the ABI 7900HT Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Specific Taqman probes and primers were designed by ABI Primer Expression 3.0 software and synthesized by Shanghai GeneCore BioTechnologies Co. Ltd., China. Allelic discrimination were called automatically by using the Sequence Detection Systems 2.4 software (Applied Biosystems). The details of amplification reactions and genotyping have been described in our previous study (Ding et al., 2010). To confirm the quality of our genotyping, approximately 10% of samples were re-genotyped. The concordance rate of these two methods is 100%.

2.3. Statistical analysis

SPSS 19.0 (SPSS Inc., Chicago, Illinois, USA) and Stata 11.0 software (StataCorp, College Station, Texas, USA) were used for statistical analyses. The statistical significance for deviations from Hardy Weinberg Equilibrium (HWE) was determined using chi-square test. Continuous variables are reported as mean ± standard deviation (SD) and compared with *t* test. Categorical variables were expressed as counts and percentages, and chi-square tests were used to compare these variables

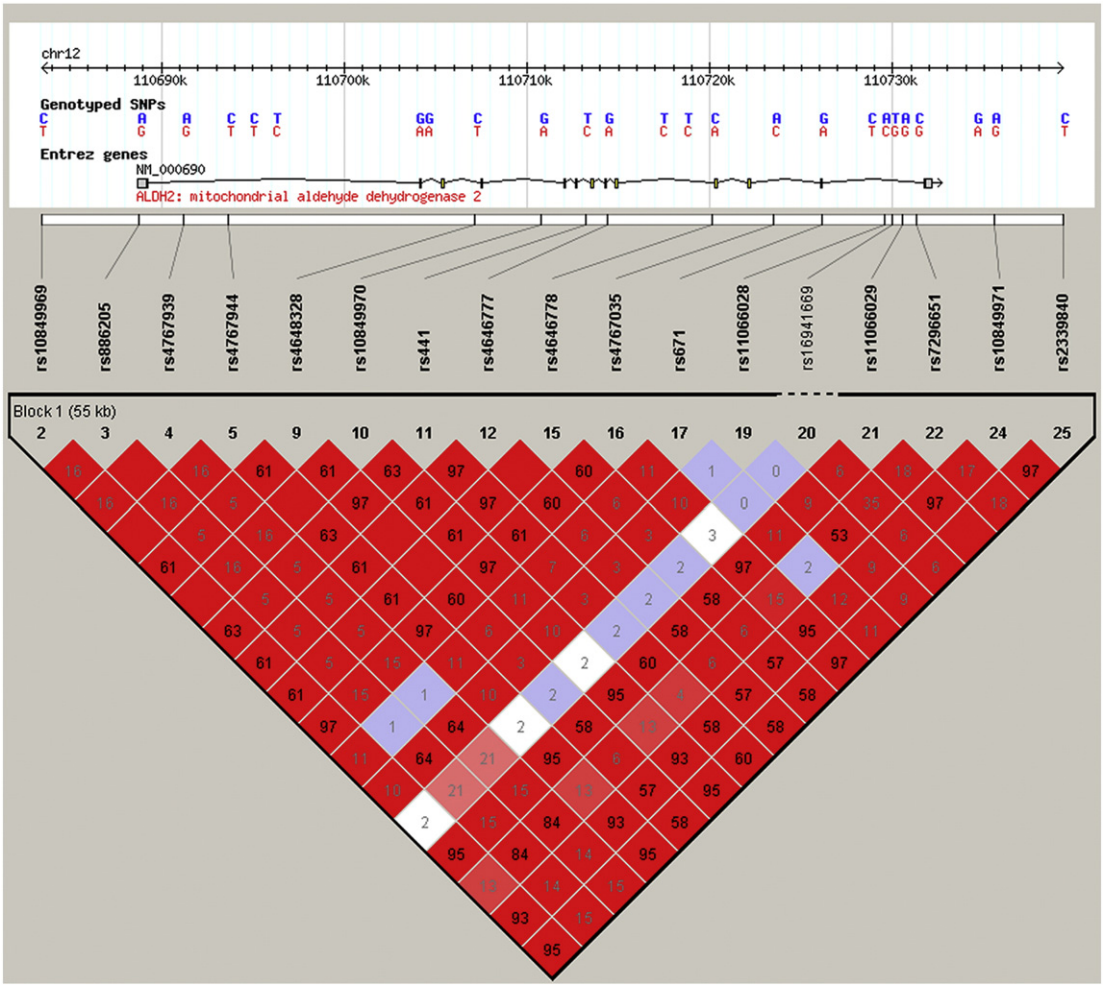

Fig. 1. Haploview linkage disequilibrium (LD) of the ALDH2 gene region. The number within each box indicates the r^2 value. Regions of high LD are shown in dark red. Regions of low LD are shown in white.