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Methylenetetrahydrofolate reductase C677T and methionine synthase A2756G gene polymorphisms and associated risk of cardiovascular diseases: A study from Jammu region

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ABSTRACT

Aim: Potent risk factors at both genetic and non-genetic levels are accountable for susceptibility and instigation of different cardiovascular phenotypes. Recently, homocysteine is being identified as an important predictor for cardiovascular diseases. Homocysteine remethylation plays a key role in the synthesis of methionine and S-adenosine methionine. Methylenetetrahydrofolate reductase (MTHFR) and methionine synthase (MTR) genes are known to regulate the homocysteine remethylation reaction and higher homocysteine level is significantly associated with diverse cardiovascular phenotypes. In this context, we aimed to carry out a study on the association of MTHFR (C677T) and MTR (A2756G) gene polymorphism with CVD in population of Jammu region of J&K state.

Materials and methods: A total of 435 individuals were enrolled (195 CVD patients and 240 controls) for the case–control study. Genotyping of MTHFR C677T and MTR A2756G gene polymorphism was done by PCR-RFLP technique. Biochemical parameters were estimated by biochemical analyser.

Results: Metabolic variables such as serum LDL-C, TC and TG were significantly higher in patients ($p < 0.0001$), whereas serum HDL-C was higher in controls. Majority of the patients were having history of hypertension (57.44%; $p < 0.0001$) as a concomitant condition. The evaluation of genetic association showed that, MTHFR C6877T (OR: 8.89, 95% CI: 2.01–39.40) and MTR A2756G (OR: 1.48, 95% CI: 1.09–2.00) polymorphisms associated with higher risk of CVD.

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Conclusion: The present study reveals significant differences in nongenetic variables among patients and control as well as association of gene polymorphisms with CVD risk.

1. Introduction

Notwithstanding the immense advancement and sophistication in healthcare system, the challenge to check the incidence of cardiovascular diseases (CVDs) still remains, be it a developed nation like the USA or a developing country like India. It is a matter of great concern that CVDs alone would soon be the single largest cause of mortality accounting for more than a third of all deaths worldwide.[1] Besides well established risk factors such as hypertension (HTN), diabetes mellitus (DM), obesity, smoking, male gender, dyslipidemia, sedentary lifestyle and family history,[2–5] genetic alterations in the genes controlling homocysteine and folate metabolism are also linked to onset of CVDs.[6,7] Several investigators have implicated elevated plasma homocysteine as an independent marker for atherosclerotic cardiovascular condition.[8–11] Homocysteine and folate metabolism is dependent on couple of genes performing their specific role, but two genes namely MTR and MTHFR genes are considered critical genes for development of diseased cardiovascular phenotypes particularly congenital heart diseases[12,13] and coronary artery diseases.[14–16] MTHFR enzyme is a co-factor for conversion of 5,10-methylenetetrahydrolate to 5-methyltetrahydrofolate. It has been demonstrated that C677T polymorphism in exon 4 of MTHFR gene reduces enzyme activity, which may be a plausible reason for elevated concentration of plasma homocysteine.[17–21] MTR is engaged in dual performance of both demethylation of 5-methyltetrahydrofolate to tetrahydrofolate and also, remethylation of homocysteine to methionine by utilizing methyl group donated by 5-methyltetrahydrofolate. A common polymorphism in the MTR gene (A2756G) is associated with hyperhomocystenemia and DNA hypomethylation.[22–24] The distribution of MTHFR and MTR gene SNPs project a higher degree of heterogeneity not among worldwide populations[25–28] but a transient difference was observed in allelic distribution among different Indian populations due to diverse ethnicity.[29,30] The state of Jammu & Kashmir represents diverse cultural and genetic heritage belonging to Kashmiri (Kashmir), Dogra (Jammu) and Ladakhi populations (Ladakh). The ethnicity, genetic makeup, basic lifestyle and dietic pattern of an individual can greatly influence the onset and pathogenesis of disease. The lack of any molecular level study in context to CVD, targeting the populations of Jammu, called for undertaking the research work documented herein. We have attempted to assess link of MTHFR (C677T) and MTR (A2756G) gene variation and risk of CVD in populace of Jammu region of J&K state.

2. Materials and methods

2.1. Study population

The study population comprised of 195 CVD cases (men = 128; women = 67) and 240 healthy controls (men = 145; women = 95), who were genetically unrelated and belonging to Jammu region of Jammu & Kashmir state. Eligible cases were patients with major CVD phenotypes encompassing coronary artery disease, acquired arrhythmia (associated with atherosclerotic coronary condition) and myocardial infarction (including acute coronary syndrome).

2.2. Ethical approval

The present study design was duly approved by Animal and Human Experimentation Ethical Committee (AHEEC), University of Jammu, Jammu and Kashmir, India. Each study participant was made aware of the nature and scope of the study. Data and blood collection from study individuals was effected after having their informed written consent.

2.3. Data collection and clinical evaluation

Non-genetic data including age, dwelling, age of onset and duration of disease, history of HTN/DM, habit of smoking/alcohol intake, sedentary lifestyle, family history, diet pattern, anthropometric (body mass index and waist hip ratio) and physiometric variables (SBP, DBP, PR and PP) were recorded in pre-designed health datasheet from each study participant.

2.3.1. Demographic profile

The dwelling pattern of the study participants was divided into urban (who had the advantage of instant access to urbane facilities), sub-urban (who dwelled at a distance) and rural (who had remote access to urbane settlements) areas.

2.3.2. Behavioral determinants

Smokers were categorized as current smoker (who smokes one or more cigarette/tobacco per day), ex-smoker (person with former smoking habit for at least 1 year) and non-smoker (person who never smoked). Alcohol intake was assessed in three categories as: current alcoholics (person who drinks per day or week), former alcoholics (subjects with previous history of alcohol intake) and non-alcoholics (person who never drunk). Physical activity was assessed as performers (person involved in any significant bodily activity like walking/jogging/exercise as a minimum of 30 min) and sedentary (person not involved in any bodily exercise).