Meta Gene 15 (2018) 16–22

Contents lists available at ScienceDirect

Meta Gene

journal homepage: www.elsevier.com/locate/mgene

Association of Mef2a gene polymorphisms in early onset of coronary artery disease of south Indian cohort

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ARTICLE INFO

Keywords:
Atherosclerosis
CAD
Mef2A
Early onset
Myocardial infarction

ABSTRACT

Myocyte enhancer factor-2A (MEF2A), encoding a member of the MEF2 family of transcription factors, has been identified for primary CAD and MI without other accompanying clinical feature. It plays a role in vascular ontogeny and shows its predominant expression in the coronary artery endothelium. In the present study, we sought to evaluate the possible role of Mef2A polymorphisms as a risk determinant of CAD.A total of 300 angiographically documented cases and 300 healthy controls were recruited for the study. Polymorphisms of Mef2A 279 C > T in exon 8 and 452 G > T, 481 A > G in exon 11 were determined by PCR-RFLP method. The Mef2a 279 C > T variation and 452 G > T was found to be significantly associated with CAD ($p < 0.001$ & $p < 0.001$). The 'CT' and 'TT' genotype was found to be predominant in CAD with two & single fold increased risk to CAD and the association being statistically significant. However we did not find significant association of 481 A > G polymorphism with CAD in addition haplotype analysis revealed that T-G-A and C-T-A haplotype was found to be about three & single fold higher in CAD than controls with the association being statistically significant ($p < 0.0001$) & ($p < 0.04$) conferring risk towards CAD. Further MLR analysis revealed that Family History, Diet, Alcoholism, LDL and Triglycerides Levels were associated independently with CAD ($p < 0.01$) Since Mef2a is highly expressed in endothelium the mutation in this gene would reduce the activation activity of MEF2A. Here we found significantly a greater frequency of 279Leu and 452 Gly among patients with myocardial infarction and this allele could be a genetic risk factor for myocardial infarction in our population.

1. Introduction

Coronary artery disease (CAD) a multifactorial disorder involves both environmental and genetic risk components in the etiopathogenesis of the disease. It is caused by atherosclerotic occlusion of the coronary arteries, wherein, the underlying pathology of CAD begins early in life and its evolution usually occurs slowly over decades, while the symptoms and signs of coronary artery disease are noted in the advanced state of disease (Libby et al., 2002).

Atherosclerotic process begins with the disruption of endothelial function due to the accumulation of lipoprotein droplets in the intima of the coronary vessels. The endothelium of the coronary artery plays a protective role and prevents the arteries from damage by blood elements such as platelets and monocytes. Defective endothelium leads to infiltration of inflammatory particles such as LDLs, monocytes, and macrophages leading to atherosclerosis (Heitzer et al., 2001; DP et al., 2004).

The primary risk factors which are modifiable include high blood cholesterol levels, cigarette smoking, obesity, hypertension and diabetes. Family history of CAD, age and genetic factors are some of the other non modifiable risk factors (Yusuf et al., 2004; Broeckel et al., 2002).

According to recent WHO reports, Indian subcontinent has seen a substantial increase in the prevalence of coronary artery disease (CAD) in young men (20–40 years) and women (20–50 years). Asian Indians < 40 years of age had a 15-fold higher rate of CAD compared to Chinese and a 10-fold higher rate compared to Malays. The shift in the prevalence to younger adults however remains elusive; nonetheless, it may be well attributed to sedentary life style at a very juvenile age (Enas et al., 2001; Enas et al., 2011).

Recent advances in genetic approaches to understanding CAD involve genome-wide linkage and large-scale GWAS studies as core

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http://dx.doi.org/10.1016/j.mgene.2017.10.001
Received 12 June 2017; Received in revised form 8 September 2017; Accepted 3 October 2017
Available online 04 October 2017

human genetics strategies. These have been complemented by comparative genomic studies The genes identified through these combined approaches have diverse functions viz. as transcription factors that are implicated in vasculogenesis (*MEF2A*) signaling molecules involved in inflammation (*LTA*), innate (*TLR4*) and adaptive (*MHC2TA*) immunity, and novel carrier proteins like apolipoproteins (*APOA5*), as well as genes for which the physiological roles are as yet to be identified.

The Myocyte enhancer factor-2 (MEF2) families consists of four members, designated as MEF2A, MEF2B, MEF2C, and MEF2D. The Mef2A is a protein that in humans is encoded by the *MEF2A* gene and located on chromosome 15q26. The MEF2A protein is highly expressed in the endothelium of coronary artery and has been shown to play a pivotal role in morphogenesis and myogenesis of cardiac and smooth muscle cells (Bhagavatula et al., 2004).

MEF 2 also participates in Ca signals and mediates CAD Gene Expression where in increased intracellular Ca^{2+} results in Calmodulin CaM kinases activation. Mutations/deletions in MEF2A will alter the expression of a subset of genes and thus reprogram the transcriptional profile in the endothelium, leading to malfunction endothelium which is susceptible to the infiltration of inflammatory particles such as LDLs, monocytes, and macrophages. These macrophages further play a central role in lipid accumulation, secretion of cytokines, release of growth factors and thereby promotes additional accumulation of smooth muscle cells (SMCs) which leads to disruption of fibrous cap and formation of plaques and atherosclerosis (Fig. 1) (Passier et al., 2000; Kolodziejczyk et al., 1999; Wu et al., 2000; Blaeser et al., 2000; McKinsey and Olson, 2005).

Recent report by Wang et al. (2003) indicated the Mef2A gene as the positional candidate responsible in CAD where in 21 bp nucleotide deletion eliminates seven amino acids from the c-terminus of mef2a (Wang et al., 2003) and according to Bhagavatula et al. (2004) a seven amino acid deletion in exon 11 of Mef2A, reduces the transcriptional activity of MEF2A by a loss-of-function mechanism (Bhagavatula et al., 2004).

According to Gonzalez et al. (2006) screening of exons 7 and 11 in a large cohort of Spain identified P279L gene polymorphisms which significantly lead to reduce Mef2A transcription activity. Other studies negated the role of MEF2A in CAD while others confirmed its influential role (Gonzalez et al., 2006).

Recently Elhawari et al. (2010) studied the association of MEF2A gene single-nucleotide polymorphisms (SNP), of exon 11 namely, rs325400 G > T and rs34851361 A > G, with CAD as a susceptible gene. According to documented medical literature, there are no published reports mentioning the Mef2A gene polymorphisms in relation to CAD especially in south Indian population. Hence the present study was aimed to evaluate an association of Mef2A Gene Exon 8 1250 C > T (P279L, rs121918529), Mef2A Exon 11 452 G > T (rs325400) and Mef2A Exon 11 481 A > G (rs34851361) in clinical presentation of CAD.

2. Materials & methods

2.1. Study population

A total of 300 (20–40 yrs) angiographically confirmed myocardial infarction patients were recruited from Department of Cardiology,

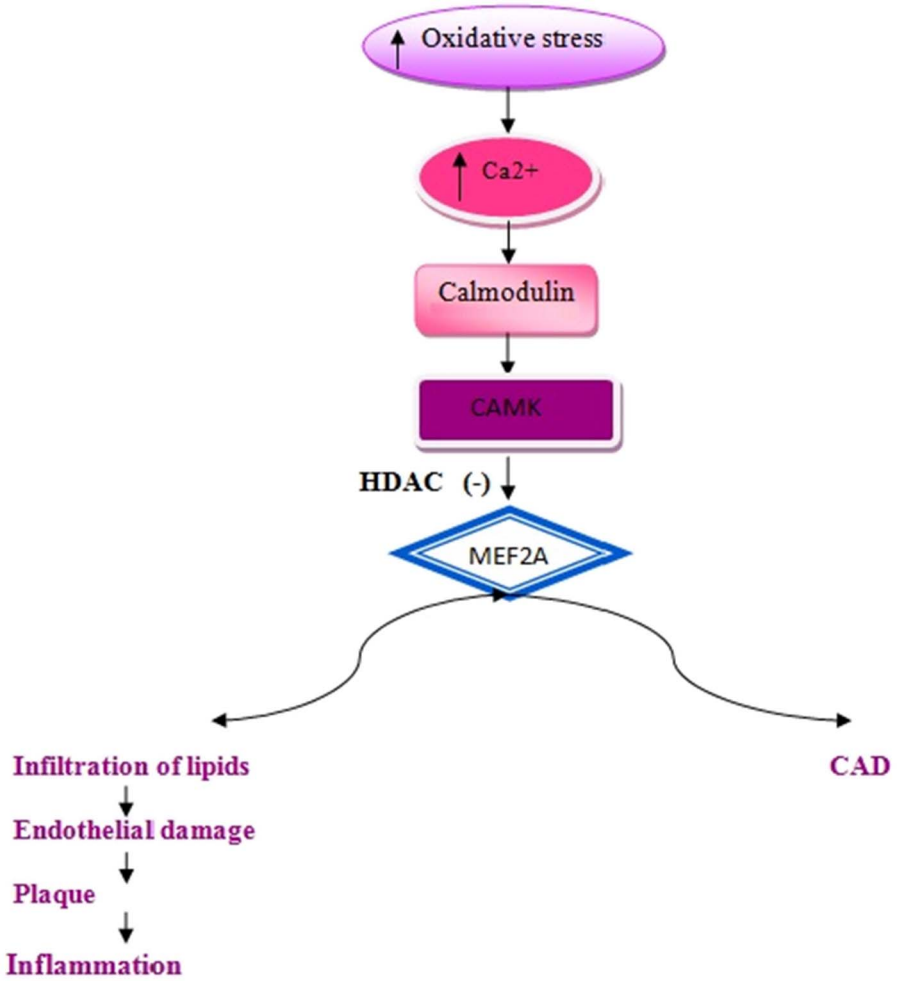

Fig. 1. MEF 2 participates in Ca signals to mediate CAD gene expression. Increased stress increases intracellular calcium concentration and activates calmodulin, which, in turn, activate CaM kinases. Activated CaMKs activate MEF2-regulated transcription by phosphorylating histone deacetylases (HDACs), which repress MEF2 transactivation, resulting in HDAC release from MEF2 and export of HDACs from the nucleus.