Cytochrome2J2 (CYP2J2) Gene Polymorphism in Coronary Artery Disease

Thesis

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Marwa Elazab Mahmoud

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List of Abbreviations

Abbreviations	Full term
AA	*Arachidonic acid.*
ACE	*Angiotensin converting enzyme.*
ACS	*Acute coronary syndrome.*
AMI	*Acute myocardial infarction.*
ANOVA	*Analysis of variance.*
AP-1	*Activator protein-1.*
ARDS	*Acute respiratory distress syndrome.*
AT-1	*Angiotensin II type 1.*
BMI	*Body mass index.*
bp	*Base pair.*
BUN	*Blood urea nitrogen.*
CAD	*Coronary artery disease.*
CD14 receptor	*Cluster of differentiation 14 receptor .*
CD40L	*Cluster of differentiation 40 ligand.*
CK	*Creatine kinase.*
CK-MB	*Creatine kinase MB fraction.*
CNS	*Central nervous system.*
COX	*Cyclooxygenase.*
CRP	*C- reactive protein.*
CT	*Computed tomography.*
cTnC	*Cardic troponin C.*
cTnI	*Cardic troponin I.*
cTnT	*Cardic troponin T.*
CYP	*Cytochrome.*
ddNTPs	*Dideoxynucleotides triphosphate.*
DHETs	*Dihydroxyeicosatetraenoic acids.*
DNA	*Deoxyribonucleic acid.*
dNTPs	*Deoxynucleotide Triphosphates.*
ECG	*Electrocardiogram.*

List of Abbreviations (Cont...)

Abbreviations	Full term
EDTA K3	*Tri-potassium ethylene di-amine- tetra-acetic acid.*
EETs	*Epoxyeicosatrienoic acids.*
eNOS.....	*Endothelial nitric oxide synthase.*
EOA	*Epoxyoctadecenoic acid.*
EPA.....	*Eicosapentaenoic acid.*
ESC/ACC.....	*European Society of Cardiology and the American College of Cardiology.*
FFA.....	*Free fatty acid.*
g	*Gravity.*
HDL-C	*High density lipoprotein Cholesterol.*
HepG2.....	*Hepatoma G2.*
HETEs	*Hydroxy-eicosatetraenoic acids.*
hsCRP.....	*high Sensitivity C-Reactive Protein.*
ICAM-1	*Intercellular adhesion molecule 1.*
IL-6	*Interleukin – 6.*
IQR	*Interquartile range.*
kb	*kilo base pair.*
kDa.....	*Kilodalton .*
LA	*Linolenic acid.*
LDL-C.....	*Low density lipoprotein cholesterol.*
let-7b	*Lethal 7b.*
LOX.....	*Lipoxygenase.*
LTs.....	*Leukotrienes.*
MALDI-TOF.....	*Matrix assisted laser desorption ionization time of flight.*
$\bar{x}$	*Mean.*
miRNAs	*MicroRNAs.*
MMPs.....	*Matrix metalloproteinases.*

List of Abbreviations (Cont...)

Abbreviations	Full term
MPO	*Myeloperoxidase.*
mRNA	*Messanger ribonucleic acid.*
MS	*Mass spectrometry.*
NF-κB	*Nuclear factor- κB.*
NO	*Nitric oxide.*
P	*Probability.*
PCR	*Polymerase chain reaction.*
PCR-RFLP	*Polymerase chain reaction and restriction fragment length polymorphism.*
PGs	*Prostaglandins.*
PLGF	*Placental growth factor.*
PUFAs	*Polyunsaturated fatty acids.*
RPM	*Revolutions per minute.*
Rs	*Reference sequence*
sCD40L	*Soluble CD40 ligand.*
SD	*Standard deviation.*
sEH	*Soluble epoxide hydrolase .*
SNPs	*Single nucleotide polymorphisms.*
Sp1	*Specificity protein 1.*
T2DM	*Type 2 Diabetes Mellitus.*
TC	*Total cholesterol.*
TG	*Triglycerides.*
TNF-α	*Tumor necrosis factor α*
TXs	*Thromboxanes.*
3` UTR	*3 prime untranslated region.*
WHO	*World Health Organization.*
Xa	*Active factor X .*
μL	*Microliter.*

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INTRODUCTION

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide ***(Bangalore and Messerli, 2006).*** Although CAD mortality rates worldwide have declined over the past four decades, CAD remains responsible for about one-third or more of all deaths in individuals over age 35 ***(Nichols et al., 2014).***

In Egypt, according to World Health Organization (WHO) regional office report, there is an increased prevalence of coronary heart disease which is responsible for about 23.14% of all deaths among Egyptians ***(Mendis et al., 2014).***

Acute cardiovascular events are thought to be ultimately caused largely by an inflammation-mediated destabilization and rupture of atherosclerotic lesions ***(Stoll and Bendszus, 2006).*** It is also generally accepted that coronary artery disease is a complex polygenic disease resulting from the interaction between genetic variation and environmental factors ***(Flossmann et al., 2013).*** There are some traditional factors that increase the risk of coronary artery disease such as hypertension and smoking, but genetic risk factors, suggested by evidence from inheritance-based studies, also contribute to a predisposition to coronary artery disease ***(Choi, 2015).***

CYP2J2 is a member of the cytochrome P450 (CYP) family of monooxygenases. In humans, it is the sole member of the CYP2J subfamily ***(Ma et al., 2009).*** Specifically, CYP2J2 is an epoxygenase that catalyzes epoxide formation at the site

of a carbon–carbon double bond in the substrate, as other CYP epoxygenases do, such as CYP2C8 and CYP2C9 ***(Spiecker et al., 2010).***

The CYP2J2 is abundantly expressed in coronary artery endothelial and smooth muscle cells and in cardiac myocytes. Other tissues, including the liver, kidneys, lungs, pancreas and gastrointestinal tract also express CYP2J2 ***(Wu et al., 2012).***

Arachidonic acid is metabolized in endothelial cells by cytochrome P450 epoxygenases into four epoxyeicosatrienoic acids (EETs; 5, 6-EET, 8, 9-EET, 11, 12-EET and 14, 15-EET) ***(Node et al., 2011).*** Accumulating evidence indicates that CYP epoxygenase-derived EETs exert diverse cardiovascular protective effects including antiapoptotic effects in endothelial cells, anti-inflammatory effects by inhibiting endothelial nuclear factor-κB (NF-κB), antiangiogenic effects and upregulation of endothelial nitric oxide synthase (eNOS) expression and activity, all of which suggest a potential anti-atheroscelerotic effects of CYP epoxygenase-derived EETs that may be beneficial against coronary artery disease ***(Oltman et al., 2013).***

A large degree of inter-individual variation in CYP2J2 expression has been observed. Among the factors known to be associated with different human cytochrome P450 gene expression are genetic polymorphisms ***(Wolf et al., 2010).*** In CYP2J2, the G-50T (CYP2J2*7) (rs890293) polymorphism in the proximal promoter disrupts specificity protein 1 (Sp1) transcription factor binding site and leads to reduced CYP2J2 transcription ***(Campbell et al., 2014).***

Aim of the Work

The aim of the present study is to investigate the association between G-50T (CYP2J2*7) (rs890293) gene polymorphism and ischemic coronary artery disease.

CORONARY ARTERY DISEASE

A. Introduction:

Coronary artery disease (CAD) is the commonest cause of heart attacks, which occur when blood flow to the myocardium is interrupted ***(Antman et al., 2012)***. The clinical presentations of CAD include stable angina pectoris, acute coronary syndrome (unstable angina, myocardial infarction), heart failure and sudden death ***(Kastrup, 2013).***

B. Epidemiology of CAD:

Cardiovascular diseases cause more deaths per year than the next four leading causes of death combined (cancer, chronic lower respiratory diseases, accidents and diabetes mellitus) ***(Thom and Haase, 2010).***

CAD prevalence is increasing and is expected to become the dominant cause of mortality worldwide, reaching 23.4 million in 2030. CAD accounted for 30.8% deaths or 1 of every 3 deaths in the United States ***(Dariush et al., 2016).***

In Egypt, according to World Health Organization (WHO) regional office report, there is an increased prevalence of coronary heart disease which is responsible for about 23.14% of all deaths among Egyptians ***(Mendis et al., 2014).***

C. Risk Factors of CAD:

Risk factors for CAD are either modifiable by changing lifestyle, daily habits and by medical treatment, or non-modifiable risk factors, they cannot be altered through lifestyle habits as shown in Table (1) ***(Chogle and Chakravartye, 2009).***

Table (1): Risk factors of CAD

Modifiable	- Smoking - Hypertension - Dyslipidemia - Obesity - Metabolic syndrome and diabetes mellitus - Physical inactivity
Non Modifiable	- Age - Sex and Menopausal Status - Genetic predisposition and family history
Non-traditional	- Infections - Stress and depression - Homocysteine - Fibrinogen

(Apple et al., 2008)

1) Modifiable Risk Factors:

a) Smoking:

Smoking participates in the pathogenesis of coronary artery disease and sudden death by different mechanisms, including the promotion of atherosclerosis, the stimulation of coronary thrombosis and cardiac arrhythmias through reducing oxygen carrying capacity of the blood ***(Lavi et al., 2011).***