Association of CYP2J2 Gene Polymorphism with Ischemic Stroke

Thesis

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List of Abbreviations

Abb.	Full term
ASO	Allele specific oligonucleotide
ATO	Arsenic trioxide
ATP	Adenosine triphosphate
BMI	Body Mass Index
bp	Base pair
BP	Blood pressure
CAD	Coronary artery disease
CHE	Cholesterol esterase
CHO	Cholesterol oxidase
COX	Cyclooxygenase
CS	Cerebral stroke
CsA	Cyclosporine A
CT	Computed tomograohy
CYP	Cytochrome P450
CYP2J2	Cytochrome P 450 family 2 subfamily J member 2
ddNTPs	Dideoxynucleotides
DHA	Docosahexaenoic acid
DHETs	Dihydroxyeicosatetraenoic acids
DHOAs	Dihydroxyoctadecenoic acids
dNTPs	Deoxynucleotides
EDHF	Epithelium-derived hyperpolarizing factors
EDPs	Epoxydocosapentaenoic acids
EETs	Epoxyeicosatetraenoic acids
ELISA	Enzyme linked immunosorbent assay
EOA	Epoxyoctadecenoic acid
EPA	Eicosapentaenoic acid
FABP4	Fatty acid-binding protein 4
FABPs	Fatty acid-binding proteins

List of Abbreviations cont...

Abb.	Full term
FH	Family history
G6PD	Glucose-6-phosphate dehydrogenase
GFAP	Glial fibrillary acidic protein
GK	Glycerol kinase
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GPO	Glycerol phosphate oxidase
HDL-C	High density lipoprotein-cholesterol
HETEs	Hydroxyeicosatetraenoic acids
HK	Hexokinase
HRT	Hormonal replacement therapy
hs-CRP	High-sensitivity C-reactive protein
HTN	Hypertension
ICAM-1	Intercellular adhesion molecule-1
IQR	Interquartile range
IS	Ischemic stroke
LACI	Lacunar infarct
LC-MS	Liquid chromatography–mass spectrometry
LDL-C	Low density lipoproteins-cholesterol
LOC	Level of consciousness
LOX	Lipoxygenase
LTs	Leukotrienes
MADB	N, N-bis(4-sulfobutyl)-3,5-dimethylaniline, disodium salt
M-CSF	Macrophage colony-stimulating factor
$MgCl_2$	Magnesium chloride
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NIHSS	National institute of health stroke scale

List of Abbreviations cont...

Abb.	Full term
p	Probability
PACI	Partial anterior circulation infarct
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PGE2	Prostaglandin E_2
P-gp	P-glycoprotein
PGs	Prostaglandins
POCI	Posterior circulation infarct
POD	Peroxidase
PUFAs	Polyunsaturated fatty acids
PVD	Peripheral vascular disease
RXR	Retinoid X receptor
RBS	Random blood sugar
RFLP	Restriction fragment length polymorphism
SD	Standard deviation
SNPs	Single nucleotide polymorphisms
sEH	Soluble epoxide hydrolase
Sp1	Specificity protein-1
Tac	Tacrolimus
TACI	Total anterior circulation infarct
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
TXs	Thromboxanes
VCAM -1	Vascular cell adhesion molecules-1
WHO	World Health Organization

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INTRODUCTION

Cerebral stroke (CS) is one of the major causes of death and disability worldwide *(Bushueva et al., 2015)*. Ischemic stroke is the most common type of stroke in Egypt, as in other countries, accounting for 43% to 79% of all stroke types *(Khedr et al., 2013)*.

Stroke is regarded as a severe disorder with high morbidity and high mortality, which is a major healthcare problem and a serious economic burden worldwide. It claims over 6 million deaths each year worldwide. In Egyptian population, the overall prevalence of stroke is high, with crude prevalence rate 963 of 100,000 individuals of all ages and the disease caused the most mortality rate in all around country *(Abd-Allah and Moustafa, 2014)*.

Ischemic stroke (IS) occurs when the blood supply to the brain is interrupted or reduced. In 2013, the American Heart Association/American Stroke Association updated their endorsed definition of stroke to one that includes silent infarctions (inclusive of cerebral, spinal and retinal) and silent haemorrhages *(Sacco et al., 2013)*.

Increasing evidence indicated that is a complex clinical syndrome resulting from several risk factors, including age, hypertension, diabetes mellitus, smoking, and dyslipidaemia, which are important predictive factors for IS occurrence

(***Kamouchi et al., 2012).*** To date, many researches have been performed focusing on the relationship between genetic factors, such as single-nucleotide polymorphisms (SNPs) and susceptibility to IS (***Hsieh et al., 2012).***

Some studies have identified that the CYP2J2 -50G>T variant may increase the risk of IS, whereas others have not found an association between variation in CYP2J2 and stroke (***Liu et al., 2007).***

AIM OF THE WORK

The aim of this pilot study is to investigate the association of CYP2J2 gene polymorphism with increased risk of ischemic stroke in a group of Egyptian population retrieved from Ain Shams University Hospitals.

I- ISCHEMIC STROKE

A. <u>Definition:</u>

According to World Health Organization **(WHO),** stroke is a "neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours" *(WHO Media Center, 2014).* This can be due to ischemia caused by thrombosis, embolism or hemorrhage. Approximately 87 % of strokes are ischemic in nature; 10% are intra cerebral and 3% are subarachnoid haemorrhages *(Kaur et al., 2015).*

B. <u>Epidemiology:</u>

Cerebrovascular stroke is the most frequent cause of permanent disability in adults worldwide *(Donnan et al., 2008)*, the second most common cause of death (after ischemic heart diseases) and one of the leading causes of death in Egypt, according to the WHO *(WHO media center, 2014).*

Annually, 15 million people suffer a stroke worldwide. Of these, 5 millions are left permanently disabled. The WHO estimates that a stroke occurs every 5 seconds worldwide *(WHO Global burden of stroke, 2011).*

Globally, the average 30-day case fatality following first ischemic stroke is about 22.9%, with the exception of Japan (17%) and Italy (33%) *(Feigin et al., 2005).*

Ischemic stroke is the most common type of stroke in Egypt *(Khedr et al., 2013).*

C. Causes and Classifications of Acute Ischemic Stroke:

Ischemic stroke may occur because of a wide range of vascular diseases that lead to thromboembolism to the brain. Establishing the most likely cause is important because the cause of stroke influences both short-term and long-term prognoses and it affects treatment decisions, especially those related to prevention of recurrent events.

As a result, defining the subtype of ischemic stroke influences design of clinical trials and provides important information for epidemiological studies. Thus, the use of a validated subtype classification system that permits comparison of results is important in a broad range of research studies in stroke *(Ay et al., 2014).*

1. *The Trial of Organization 10172 in Acute Stroke Treatment Classification:*

It is based on clinical symptoms and results of further investigations. On this basis, a stroke is classified into 5 categories based on etiology; thrombosis or embolism due to atherosclerosis of a large artery, embolism of cardiac origin, occlusion of a small blood vessel, other determined cause and undetermined cause (no cause identified*) (Table 1) (Chung et al., 2014).*

Table (1): Subtypes of Ischemic Stroke, TOAST Classification

Large artery atherosclerosis	*Extracranial or intracranial disease*
Small artery occlusion (lacune)	
Cardioembolism	*Higher or lower risk cardiac lesions*
Other demonstrated cause	• No atherosclerotic vasculopathies • Prothrombotic disorders
Undetermined cause (cryptogenic)	• Incomplete evaluation for cause • Diagnostic studies were negative • ≥2 conflicting causes found

(Chung et al., 2014)

2. *The Oxford Community Stroke Project Classification (OCSP):*

It is a common clinical stroke classification tool, which categorizes stroke into 4 subtypes: total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI) and posterior circulation infarct (POCI). OCSP classification can predict the extent of the stroke, the area of the brain affected, the underlying cause, and the prognosis *(Asdaghi et al., 2011).*

D. Risk Factors of Acute Ischemic Stroke:

1. *Non-modifiable Risk Factors:*

a. *Age:*

Atherosclerosis increases with age, subsequently increasing the risk of ischemic stroke. The prevelance of stroke for individuals older than 80 years of age is approximately 27%, compared with 13% for individuals 60 to 79 years of age *(bastan et al., 2016).*

b. Sex:

Men have a higher risk for stroke (1.25 times that of women), but mortality is higher among women who account for three out of every five-stroke deaths; this may be due to the fact that men tend to get strokes at younger age and therefore are better able to survive the trauma *(Mosca et al., 2007).* Some risk factors for stroke apply only to women. Among these are pregnancy, childbirth, menopause and the treatment with hormonal replacement therapy (HRT) *(Del Zoppo, 2009).*

c. Ethnicity/Race:

Previous studies show that black patients have a higher incidence of stroke than white patients. The mechanisms of this association are poorly understood but might be related with genetic or nutritional factors *(Catalan Society of Neurology, 2011).*

d. Family history:

Family history of stroke in a first-degree relative increases the risk of suffering from an acute cerebrovascular event, this increased risk may be due to different mechanisms, including inherited predisposition, genetic transmission of susceptibility to stroke, familial-related lifestyle, cultural and environmental factors, or interactions between genes and environmental factors *(Arboix, 2015).*