

Evaluation of Renalase Gene Polymorphism in Egyptian Patients with Chronic Kidney Disease

Thesis

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بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا
عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

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List of Abbreviations

Abbrev.	Full Term
A.A	: Amino acid
AADC	: Aromatic L-amino acid decarboxylase
AC	: Adenyl cyclase
ACR	: Albumin/creatinine ratio
ADMA	: Asymmetric dimethyl-arginine
AER	: Albumin excretion rate
AGEs	: Advanced glycation end products
Ang II	: Angiotensin II
AO	: Amine oxidase
AR1A/B	: Adrenergic receptor 1 subtypes
ASP	: Aspartic acid
AT1	: Angiotensin-1
ATP	: Adenosine triphosphate
BMI	: Body mass index
Bp	: Base pair
BP	: Blood pressure
BUN	: Blood Urea Nitrogen
C3	: Complement 3
Camp	: Cyclic adenosine monophosphate
CATECHOL	: Catechdamines
CD14	: Clusters of differanations 14
CD56	: Clusters of differanations 56
CDC	: Centres for disease control and prevention
CHD	: Congestive heart disease
CHF	: Congestive heart failure
CIN	: Chronic interstitial nephritis
CKD	: Chronic kidney disease
CMV	: Cytomegalovirus.
CNS	: Central nervous system
COMT	: Carboxy-O-methyl transferase
CPO	: Glycerol phosphate oxidase
CRF	: Chronic renal failure
CT	: Computed tomography
CVD	: Cardiovascular disease
D1R	: Dopamine receptor type 1
DA	: Dopamine

List of Abbreviations (Cont.)

Abbrev.	Full Term
DAG	: 1,2-diacylglycerole
DAO	: Diamine oxidase
DBH	: Dopamine b hydroxylase
DBP	: Diastolic blood pressure
DHBS	: 3,5 dischloro, 2, hydroxyl benzene sulphuric acid
DM	: Diabetes mellitus
DN	: Diabetic nephropathy
DNA	: Deoxy ribonucleic acid
ECG	: Electrocardiography
Echo	: Echocardiography
ECM	: Extracellular matrix
EDTA	: Ethylene diamine tetra-acetic acid
eGFR	: Estimated glomerular filtration rate
EPO	: Erythropoietin
ESRD	: End-stage renal disease
ET	: Endothelin
FAD	: Flavin adenine dinucleotide
FBG	: Fasting blood glucose
FSGS	: Focal and segmental glomerulosclerosis
GFR	: Glomerular filtration rate
GK	: Glycerol kinase
GLDH	: Glutamate dehydrogenase
Glu	: Glutamic acid
Gq	: G protein stimulating phospholipase C activity
Gs	: G-protein-stimulating adenylyl cyclase activity
HD	: Hemodialysis
HDL-C	: High density lipoprotein-cholesterol.
HIV	: Human immunodeficiency virus
HTN	: Hypertension
IRB	: Institutional review board
IgA	: Immunoglobulin A
IgG	: Immunoglobulin G
IgM	: Immunoglobulin M
IP3	: Inositol 1,4,5-trisphosphate
ISE	: Ion-selective electrodes

List of Abbreviations (Cont.)

Abbrev.	Full Term
JNC7	: The seventh Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure
KDIGO	: Kidney Disease Improving Global Outcomes
KDOQI	: Kidney Disease Outcomes Quality Initiative
KDa	: Kilo Dalton
KEEP	: Kidney Early Evaluation Program
LAT2	: Type 2 L-amino acid transporter
LDL	: Low density lipoproteins
L-DOPA	: L-dihydroxyphenylalanine
LMW	: Low-molecular-weight
LV	: Left ventricle
LVH	: Left ventricular hypertrophy
MAO	: Monoamine oxidase
MAP	: Mean arterial pressure
MDRD	: Modification of diet in renal disease formula
MRI	: Magnetic resonance imaging
NA	: Nucleic acid
NADH	: Nicotinamide adenine dinucleotide
NAG	: N-acetyl- β -D-glucosaminidase
NE	: Norepinephrine
NHANES	: National Health and Nutrition Examination Survey.
NHE3	: Sodium hydrogen exchanger
NK	: Natural killer
NKF	: National kidney foundation
NO	: Nitric oxide
Npt2a	: Sodium phosphate co transporter
NSAIDS	: Non-steroidal anti-inflammatory drugs
OCT2	: Human organic cation transporter 2
PAD	: Peripheral arterial diseases
PCR	: Polymerase chain reaction
Pcr	: Plasma creatinine
PIP2	: Phosphatidyl inositol 4.5 biphosphate
PKA	: Protein kinase A
PKC	: Protein kinase C
PLC	: Phospholipase C

List of Abbreviations (Cont.)

Abbrev.	Full Term
PNMT	: Phenylethanolamine methyl transferase
RAAS	: Renin–angiotensin–aldosterone system
RBP	: Retinol-binding protein
RFLP-PCR	: Restriction fragment length polymorphism-polymerase chain reaction
RT	: Room temperature
SBP	: Systolic blood pressure
SDS-PAGE	: Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SNGFR	: Single nephron glomerular filtration rate
SNP	: Single nucleotide polymorphism
SNS	: Sympathetic nervous system
SSAO	: Semicarbazide-sensitive amine oxidase
T.Bil	: Total Bilirubin
TAE	: Tris-acetate EDTA buffer
TBE	: Tris-borate EDTA buffer
TBRI	: Theodor Bilharz Research Institute
TIF	: Tubulointerstitial fibrosis
TIN	: Tubulointerstitial nephritis
V	: Volume of urine
VLDL	: Very low density lipoprotein
WHO	: World health organization
WNK1	: Lysine deficient protein kinase 1gene mutation
WNK4	: Lysine deficient protein kinase 4gene mutation

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INTRODUCTION

Chronic kidney disease (CKD) is one of the most problematic diseases in Egypt. In the last decade, the nephrology community has focused its attention on the main causes of morbidity and mortality in CKD patients. Compared with the general population, patients with CKD have an unacceptably high risk for premature death, primarily as a result of cardiovascular disease (CVD) (*Go et al., 2004*).

Premature CVD, including hypertension, stroke, peripheral vascular disease, sudden death, coronary artery disease, and congestive heart failure, is a prevalent, notorious problem in patients with CKD. More cardiovascular disease is associated with more decline in kidney function, therefore, an aggressive management of specific cardiovascular risk factors is mandatory to prevent the development and progression of CVD (*Cheung et al., 2000*).

Hypertension is present in approximately 80% to 85% of patients with CKD (*Stompor et al., 2011*). Hypertension plays a key role in progressive deterioration of renal function and in the exceedingly high rate of cardiovascular events, which represent the primary cause of morbidity and mortality in these patients (*Straznicky et al., 2009*). Hypertension is a multifactorial disease and its pathogenesis is not yet fully understood (*Paulis and Unger, 2010*). Over the last few years

the genetic susceptibility to hypertension has been a special focus of attention and many candidate genes have been studied so far. The renalase pathway is a previously unknown mechanism for regulating cardiac function and blood pressure (*Jeunemaitre et al., 2007*).

Renalase is a novel flavin adenine dinucleotide-dependent amine oxidase that is secreted by the kidney. It circulates in the blood and modulates the cardiac function and systemic blood pressure. It metabolizes the circulating catecholamines. Low serum levels of renalase was observed in patients with chronic kidney disease which leads to impaired degradation of catecholamines with elevation of their circulating level causing excessive tension of the sympathetic nervous system. This may explain the frequent occurrence of hypertension among these patients (*Stec et al., 2011*). Blood renalase level is markedly reduced in patients with end-stage kidney disease (ESRD) (*Schlaich et al., 2009 and Farzaneh-Far et al., 2010*).

The human renalase gene resides on chromosome 10 at q23.33 and encodes a 342–amino acid protein with a calculated molecular mass of 38 kDa. Abnormalities in the circulating level of renalase are present in animal models of chronic kidney disease (CKD) with hypertension (*Li et al., 2008*). Two isolated single –nucleotide polymorphisms (SNPs) in the