Association of Endothelial Nitric Oxide Synthetase (eNOS) gene polymorphism with glaucoma in Egyptian patients

(Thesis)

Submitted for the partial fulfillment of
M.Sc. Degree in
CLINICAL & CHEMICAL PATHOLOGY
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2013

العلاقه بين تعدد أشكال جين (الإنزيم مخلق أكسيد النيتريك الغشائى) ومرضى المياه الزرقاء فى مصر

رسالة مقدمة
توطئة للحصول على درجة الماجستير
فى الباثولوجيا الإكلينيكية و الكيميائية

مقدمة من
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List of abbreviations

Abbrev.	Title
7-NI	7-nitroindazole
AACG	Acute angle-closure glaucoma
ACA	anti-cardiolipin antibody
AD	Alzheimer's disease
ADH	anti diuretic hormone
ADMA	asymmetric dimethylarginine
ANP	Atrial Natriuretic Peptide
BH4	tetrahydrobiopterin
CD ratio	cup-to-disc ratio
CHD	chronic heart disease
CYP1B1	Cytochrome P450 1B1
DAN	2, 3-diaminonaphthalene
DM	Diabetes mellitus
DN	diabetic nephropathy
EDHF	endothelium-derived hyperpolarizing factor
EDRF	Endothelial-Derived Relaxing Factor
EDTA	ethylene diamine tetra-acetate
eNOS	Endothelial Nitric oxide synthase
ESR	Electron spin resonance
FAAO	Foundation of the American Academy of Ophthalmology
$Fe(DETC)_2$	iron diethyl dithiocarbanate
FBG	fasting blood glucose
Hb	hemoglobin
ICE	Iridocorneal endothelial syndrome
IL1a	interleukin 1a
iNOS	inducible NOS
IOP	intraocular pressure
JOAG	juvenile open angle glaucoma
L-NA	NG-nitro-L-arginine
L-NAME	L-NA methylester
L-NIO	N-iminoethyl-L-ornithine
L-NMMA	NG-monomethyl- L-arginine
LTG	low tension glaucoma
µl	Micro liter

Mm Hg	Millimeter mercury
MMPs	matrix metalloproteinases
mV	millivolt
MYOC	Myocilin
NADPH	reduced nicotinamide adenine dinucleotide phosphate
nNOS	neuronal NOS
NO	Nitric oxide
NOS3	Nitric oxide synthase 3
NTG	Normal-tension glaucoma
NVG	Neovascular glaucoma
ONH	optic nerve head
OPA1	Optic Atrophy 1
OPTN	Optineurin
PACG	Primary angle-closure glaucoma
PCG	primary congenital glaucoma
PDS	Pigment dispersion syndrome
PGI2	prostaglandin I2
PI	peripheral iridotomy
POAG	Primary open-angle glaucoma
PPMD	Posterior polymorphous dystrophy
PCR	Polymerase chain reaction
PXF	Pseudoexfoliation
RGCs	retinal ganglion cells
SAS	Sleep apnea syndrome
TGF	tubuloglomerular feedback
TM	trabecular meshwork
VNTR	variable number tandem repeats

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Acknowledgment

First of all, I would like to thank **"Allah"** for his grace and mercy, and for giving me the effort to complete this work.

I would like to express my deep thanks and sincere gratitude to Prof. Dr. **Mohamed Mohamed Shehata**, Prof. of clinical & chemical pathology, Faculty of medicine, Cairo University. He kindly offered me his valuable meticulous scientific help, precious time, effort and constant support.

My deepest appreciation and thanks are offered to Prof. Dr., **Azza Khalil Amer**, Prof. of clinical & chemical pathology, Ophthalmology Research Institute, Scientific Research Academy, for her kind supervision, valuable suggestions, advices, and continuous support.

I am heartily thankful to dear Assist. Prof. Dr. **Gihan Abdel-Azim Refaat**, Assist. Prof. of clinical & chemical pathology, Ophthalmology Research Institute, Scientific Research Academy, for her encouragement, guidance and support from the initial to the final level which enabeled me to develop an understanding of the subject.

My sincere thanks to Dr. **Asmaa Ismaeel Ahmed**, lecturer of chemical & clinical pathology, Faculty of medicine, Cairo University, for her valuable advice, and continuous help and supervision.

To glaucoma patients, for whose benefit the present work was conducted, I wish it would help them a step forward.

Finally, I take this opportunity to express my profound gratitude to my beloved parents, my sincere husband for their moral support and patience during completion of this work.

Abstract

Glaucoma is a generic term for an etiologically heterogeneous but clinically similar dysfunction and death of retinal ganglion cells (RGCs) often associated with elevated intra ocular pressure. It is the leading neurodegenerative cause of blindness and the second leading cause of blindness worldwide after cataract.

Primary Open Angle Glaucoma (POAG) is a glaucoma with a visually open anterior chamber angle or drain (by gonioscopy), and without underlying secondary ocular disease. POAG is the most common of the glaucomas, accounting for up to 75% of all glaucoma.

The gene encoding *eNOS* (endothelial Nitric Oxide Synthase) is located on chromosome 7q35-36. It has been established that the VNTR (variable number tandem repeat) in the intron 4 of *eNOS* significantly influences the plasma NO levels. Retinal ganglion cell (RGC) degeneration in the glaucomatous optic nerve head of POAG patients clearly corresponds to excess plasma NO-mediated neurotoxicity.

In the current study, there is no significant association between eNOS 27 bp VNTR polymorphism which located in intron 4 and POAG in the Egyptian patients (p=0.139). However by exclusion of DM from the cases and the controls, we found a significant increase in bb genotype in the control group compared to glaucoma group (p=0.04). Also there was a significant increase in b allele in non diabetic control subjects compared to non diabetic glaucomatous patients (p=0.036).

Introduction & aim of the work

Glaucoma is a multifactor optic neuropathy characterized by apoptotic cell death of the retinal ganglion cells (RGCs) in the optic disc or retinal nerve fiber ***(Mckinnon et al., 2008).*** This irreversible retinal deterioration results in progressive visual field loss along with decreased contrast and color sensitivity ***(Mozaffarieh et al., 2008). (Quigley and Broman, 2006)*** have estimated that by the year 2010, approximately 60.5 million individuals will be affected by this disease, which causes bilateral blindness, and this number may rise to 79.6 million by the year 2020. Glaucoma is classified as a silent disease because patients usually do not have any signs and symptoms until the end stage, when considerable damage has been done to the eye ***(Coleman, 1999; Palimkar et al., 2001).*** Increased intraocular pressure (IOP) is an established risk factor of the disease, along with old age, race and refractive error ***(Kooner et al., 2008).*** In addition to these factors, vascular ***(Orzalesi et al., 2007),*** immunological ***(Bakalash et al., 2002)*** and neurotoxic ***(Hirooka and Shiraga, 2007)*** factors are also believed to cause glaucoma ***(Ayub et al., 2010).***

Wiggs, (2007) point to genetics as an additional risk factor for the disease. Different strategies used to understand the genetic risk factors have helped to define the molecular events responsible for some Mendelian forms of the disease. In addition, some of the chromosomal locations of the genes that are likely to be involved in common forms of glaucoma have also been identified ***(Ayub et al., 2010).***

Galassi et al., (2004) have shown that as a result of a variety of physiologic stresses, a highly conserved mechanism of gene regulation is activated. Stress or hypoxia in the tissues stimulates increased synthesis of Nitric oxide (NO), which results in an