Study of nitric oxide synthase (eNOS) gene polymorphisms in systemic lupus erythematosus and rheumatoid arthritis patients

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Abstract

Systemic Lupus Erythematosus and Rheumatoid Arthritis are chronic, multifactorial autoimmune disorders where many genes have been tested for carrying the risk of development or the progression of these diseases.

The aim of the present study was to detect the prevalence of endothelial nitric oxide synthase (eNOS) genetic polymorphisms [the 27-bp repeat in intron 4 and the SNP T-786C polymorphism in the promoter region] among Egyptian SLE and RA patients and to study the influence of these genetic polymorphisms on the clinical and laboratory features of these patients.

In this study no statistically significant association could be found between these genetic polymorphisms as risk factors of these two diseases or the clinical features of the patients specially lupus nephritis. But we could find an association between the T-786C genetic polymorphism and the extra-articular manifestations of RA.

Key words: endothelial nitric oxide synthase (eNOS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), PCR, RFLP.

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List of abbreviations

α	Alpha.
β	Beta.
γ	Gamma.
δ	Delta.
κ	Kappa.
λ	Lambda.
ζ	Zeta.
ACL	Anti cardiolipin.
ACPA	Anti cyclic citrullinated peptide.
ACR	American college of rheumatology.
ADAMTS	A Disintegrin And Metalloproteinase with Thrombospondin Motifs.
ADCC	Antibody-dependent cellular Cytotoxicity.
AECA	Anti endothelial cell antibody.
AFA	Anti Fillagrin antibody.
AIM	Absent in myeloma.
AKA	Anti keratin antibody.
AP	Activator protein
APF	Anti perinuclear factor.
ARA	American rheumatism association.
ARDS	Adult respiratory distress syndrome.
ATP	Adenosine triphosphate.
AVA	Anti vimentin antibody.
BAFF	B cell activating factor.

BCR	B cell receptor.
BLK	B lymphoid tyrosine kinase.
BLyS	B lymphocyte stimulator.
C3, C4…	Complement component 3…
CaMK	Calmodulin dependent kinase.
CBC	Complete blood count.
CCP	Cyclic citrullinated peptides.
CD	Cluster of differentiation.
CF	Citrullinated fibrin.
CHB	Congenital heart block.
CIA	Collagen induced arthritis.
CIE	Countercurrent immune electrophoresis.
COMP	Cartilage oligomeric matrix protein.
CRE	Cyclic AMP response element.
CREB	CRE binding protein.
CREM	CRE modulator.
CRP	C- reactive protein.
Csk	C-src tyrosine kinase.
CT	Computerized tomography.
CTLA	Cytotoxic T-lymphocyte associated protein.
DAS	Disease activity score.
DC	Dendritic cells.
DIP	Distal interphalangeal.
DMARDs	Disease modifying anti rheumatic drugs.
DN	Double negative.
DNA	Deoxyribonucleic acid.

ds-DNA	Double stranded DNA.
EBI3	Epstein Barr virus induced gene 3.
EBV	Epstein-Barr virus.
EF	Extra follicular.
EIA	Enzyme immunoassays.
Elf-1	E74-like factor 1 (ets domain transcription factor)
ELISA	Enzyme linked immunesorbant assay
ENA	Extractable nuclear antigens.
eNOS	Endothelial nitric oxide synthase.
EPO	Erythropoietin.
ESR	Erythrocyte sedimentation rate.
Fc	Fragment crystallizable .
FCGR	Fragment crystallizable gamma region.
FITC	Fluorescein isothiocyanate.
Foxp3	Forkhead box P3
FS	Felty's syndrome.
FSH	Follicle stimulating hormone.
GC	Germinal center.
G-CSF	Granulocyte colony stimulating factor.
GN	Glomerulonephritis.
GSH	Glutathione.
GWAS	Genome wide associated studies.
HLA	Human leucocytic antigen.
HMGB1	High mobility group box.
ICAM	Intercellular adhesion molecules.
ICOS	Inducible co-stimulatory molecule

ID	Immunodiffusion.
IFN	Interferon.
Ig	Immunoglobulin.
IIF	Indirect immune fluorescence.
IL	Interleukin
iNOS	Inducible nitric oxide synthase.
IP3	Inositol triphosphate.
IRF	Interferon regulatory factor.
ITGAM	Integrin alpha M.
ITGAX	Integrin alpha X.
JAK	Janus kinase.
KCS	Keratoconjunctivitis sicca.
LAT	Linker of activation of T cells.
LGL	Large granular lymphocytes.
LH	Luteinizing hormone.
LN	Lupus nephritis.
LT	Lymphotoxin.
Lyn	Tyrosine protein kinase.
Lyp	Lymphoid specific tyrosine phosphatase.
MBL	Mannose binding lectin.
MCAF	Monocyte chemotactic and activating factor.
MCP	Monocyte chemoattractant protein.
MCP	Metacarpophalangeal
MCV	Mutated citrullinated vimentin.
MHC	Major histocompatibility complex.
MHP	Mitochondrial hyper polarization.

MMP	Matrix metalloproteinase.
MRI	Magnetic resonance imaging.
MRL	Murphy Roths Large.
mRNA	Messenger RNA.
mTOR	Mammalian target of rapamycin.
MTP	Metatarsophalangeal
MTX	Methotrexate.
NAC	N-acetylcysteine.
NeF	Nephritic factor.
NFAT	Nuclear factor of activated T cells.
NFκB	Nuclear factor kappa B.
NK	Natural killer.
nNOS	Neuronal nitric oxide synthase.
NO	Nitric oxide.
NOD	Non obese diabetic.
NSAIDs	Non steroidal anti inflammatory drugs.
OPG	Osteoprotegerin.
PAD	Peptidyl arginine deiminase.
PAN	Polyarteritis nodosa.
PBMCs	Peripheral blood mononuclear cells.
PCR	Polymerase chain reaction.
PDCD	Programmed cell death.
PGM1	Phosphoglucomutase-1.
PIP	Proximal interphalangeal.
PRL	Prolactin.
PTPN22	Protein tyrosine phosphatase, non-receptor type 22

RA	Rheumatoid arthritis.
RANKL	Receptor activator of nuclear factor kappa B.
RANTES	Regulated upon Activation, Normal T-cell Expressed, and Secreted.
RF	Rheumatoid factor.
RFLP	Restriction fragment length polymorphism.
RNA	Ribonucleic acid
RNP	Ribonucleoprotein.
ROI	Reactive oxygen intermediates.
RORC	Related orphan receptor.
RPR	Rapid plasma reagin.
RUNX	Runt-related transcription factor.
SCID	Severe combined immunodeficiency.
SCY	Small inducible cytokine.
SE	Shared epitope.
SIG	Small inducible gene.
SLE	Systemic lupus erythematosus.
SLEDAI	SLE disease activity index.
Sm	Smith.
SNP	Single nucleotide polymorphism.
snRNP	Small nuclear ribonucleoprotein.
SS	Sjögren syndrome.
ss	Single stranded.
STAT	Signal transducer and activator of transcription.
Syk	Spleen tyrosine kinase.
TCR	T Cell Receptor.

TFH	T follicular helper.
TGF	Transforming growth factor.
TH	T helper.
TLR	Toll like receptor.
TNF	Tumor necrosis factor.
TRAF	Tumor necrosis factor associated protein
Treg	Regulatory T cells.
UH	Ubiquitinated histone.
UV	Ultra violet.
VDRL	Venereal disease research laboratory.
WHO	World Health Organization.
ZAP	Zeta associated protein.

Introduction

Nitric oxide (NO), is a potent endogenous vasodilator, is one of the most important biological molecules, which has a role in many biological systems. It acts as a trigger, mediator or effector to a variety of biological reactions and signal transduction pathways ***(Wang et al., 2000).***

NO synthesis is tightly regulated by nitric oxide synthases (NOS), which appear in three isoforms: neuronal (nNOS), inducible (iNOS) and endothelial (eNOS). Endothelial NOS (eNOS) is a 135-kda protein, encoded on chromosome 7q35-36, consisting of 26 exons and spanning a genomic region of 21kb.it is expressed primarily in endothelial cells and in low levels in platelets. NO produced by eNOS is considered to prevent smooth muscle cell proliferation, platelet adherence and neutrophil activation and adhesion. Although a small quantity of NO protects against the adhesion of leucocytes and platelets to the blood vessel wall as a protective and anti-inflammatory agent, larger amounts of NO released by cells in response to cytokines can destroy host tissues, impair cellular responses and exert an immunomodulatory role that modifies the course of diseases such as SLE by affecting functions of lymphocytes and macrophages ***(Heeringa et al., 1998).***

Systemic lupus erythematosus (SLE) is a prototype of human autoimmune diseases and is a disorder with generalized autoimmunity of unknown aetiology, characterized by multisystemic organ involvement, polyclonal B cell activation and the production of autoantibodies. Although the aetiology of SLE is not known now, several genetic factors affected by environmental agents may contribute to the development or severity of SLE.