Glucocorticoid Receptor Gene Bcl1 Polymorphism in Rheumatoid Arthritis

Thesis
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Rania Salah Eldin Morsy Seddek

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List of Abbreviations

ACPA	:	Anti–citrullinated peptide antibodies
ACR	:	The American College of Rheumatology
AKA	:	Antikeratin antibodies
Anti-Sa	:	Anti-Savoie
APF	:	Targeting pro-filaggrin
ARMS	:	Amplification Refractory Mutation System
ASH	:	Allele-specific oligonucleotide hybridization
ASO	:	Allelic-specific oligonucleotides
bDMARDs	:	biological agents
BMI	:	Branch Migration Inhibition
bp	:	base pair
CarP	:	Anti-carbamylated protein
CBC	:	Complete Blood Counts
CI	:	Confidence intervals
cis-eQTL	:	cis-expression quantitative trait loci
COX-2	:	Cyclooxygenase type 2
CRP	:	C reactive protein
csDMARDs	:	Conventional sDMARDs
CSF1R	:	Colony-stimulating factor 1 receptor;
CVS	:	Cardiovascular system
DAS	:	Disease activity score
DBD	:	DNA-binding domain
ddNTP	:	di-deoxynucleotide
DMARDs	:	Disease modifying antirheumatic drugs
DNA	:	Deoxyribonucleic acid
EBV	:	Epstein–Barr virus
EDTA	:	Ethylene diamine tetra acetic acid
ELISA	:	Enzyme-linked immunosorbent assay
ESR	:	Erythrocyte Sedimentation Rate
EULAR	:	European League Against Rheumatism
FLSs	:	Fibroblast-like synoviocytes
FRET	:	Fluorescence resonance energy transfer
GCs	:	Glucocorticoids

List of Abbreviations (Cont.)

GR	:	Glucocorticoid receptor
GREs	:	GCs responsive elements
GWAS	:	Genome-wide association studies
HLA	:	Human Leukocyte Antigen
HPA	:	Hypothalamic pituitary adrenal gland
HSP	:	Heat shock proteins
ICAM-1	:	Intercellular adhesion molecule-1
IL-1Ra	:	IL-1 receptor antagonist
IL-6	:	Interleukin-6
JAKs	:	Janus kinases
LAK	:	Lymphokine-activated killer
LBD	:	Ligand-binding domain
MBs	:	Molecular beacons
M-CSF	:	Macrophage colony-stimulating factor
MM	:	Mismatch
MMP	:	Matrix metalloproteinase;
MRI	:	Magnetic resonance imaging
mRNA	:	messenger Ribonucleic acid
NK	:	Natural killer
NLS	:	Nuclear localization sequences
NO	:	Nitric oxide
NSAIDs	:	Nonsteroidal anti-inflammatory drugs
NTD	:	N-terminal regulatory domain
OLA	:	Oligonucleotide ligation assay
OR	:	Odds ratios
PAD	:	Peptidylarginine deiminase
PCR	:	Polymerase chain reaction
PDGFR	:	Platelet-derived growth factor receptor;
PGE2	:	Prostaglandin-E2
PM	:	Perfect-match
PTPN	:	Protein tyrosine phosphatase non-receptor 22
RA	:	Rheumatoid arthritis

List of Abbreviations (Cont.)

RANKL	:	Receptor activator for nuclear factor $_{\kappa}$B ligand
RFLP	:	Restriction fragment length polymorphisms
RNA	:	Ribonucleic acid
SD	:	Standard deviation
SNP	:	Single-nucleotide polymorphism
SSCP	:	Single-Strand Conformation Polymorphism
TCR	:	T-cell receptor
TGF	:	Transforming growth factor
TH1	:	T helper 1
TLR	:	Toll-like receptor
TNF	:	Tumour necrosis factor
TNF	:	Tumor necrosis factor
tsDMARD	:	Targeted sDMARD
US	:	Ultrasound
VAS	:	Visual analogue scale

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease attacking mainly synovial joints leading to their destruction ***(Rhen et al., 2005 and Aydeniz et al., 2011)***.

One of the principal lines of the treatment of rheumatoid arthritis (RA) is glucocorticoids. The latter should bind to glucocorticoid receptors to exert their action ***(Chatzikyriakidou et al., 2009 and Koper et al., 2014).***

A great variability among subjects have been reported regarding sensitivity to glucocorticoids treatment. This variability may be attributed to polymorphism of glucocorticoid receptors ***(Koper et al., 2014)***.

Aim of the Work

The aim of this study is to investigate glucocorticoid receptor (GR) gene Bcl1 polymorphism in rheumatoid arthritis (RA) patients and healthy control subjects.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease primarily affects the synovial joints, resulting in pain, deformity and eventual functional limitation, causing substantial morbidity and accelerated mortality ***(Cush et al., 2008).***

A) Epidemiology:

RA is a common chronic disease that affects about 1% of the world population ***(Saxena et al., 2017).*** Prevalence of RA also varies according to geographical area and population and is more prevalent in developed countries ***(Andrade et al., 2017).***

RA occurs at twice the rate in women compared with men, with a prevalence of 1.06% in women (as a percentage of the total population) compared with 0.61% in men ***(Nayak and Sheth, 2017).*** The lifetime risk of RA in adults is 3.6 percent (1 in 28) for women and 1.7 percent (1 in 59) for men ***(Amalraj et al., 2017).***The incidence of RA increases with increasing age in most populations until about the eighth decade of life, when it declines ***(Silman et al., 2009 and Saxena et al., 2017).***

B) Etiology & Risk Factors:

The underlying cause of most rheumatic diseases is unknown. However, several risk factors have been identified ***(Lahiri et al., 2012).***

1) Genetic Factors:

Genetic risks for RA have been acknowledged for a number of years and genome-wide association study (meta-) analyses have identified various RA-associated genes, such as HLA-DRB1, PADI4, PTPN22, TNFAIP3, STAT4and CCR6 ***(Okada et al., 2014)***.

2) Hormonal Factors:

Hormonal factors, such as estrogen, have been hypothesized to be of importance for disease development ***(Wallenius et al., 2010).*** A higher incidence of RA is seen among women compared to men across all ages and the highest incidence among women has been reported between 55 and 64 years of age, during the peri- or postmenopausal stage ***(Humphreys et al., 2013).*** Generally, estrogens, in particular 17-β estradiol (E2) and prolactin, act as enhancers at least of humoral immunity, and testosterone and progesterone as natural immunosuppressants ***(Ortona et al., 2016).***

3) Environmental Factors:

a. Infections:

Clearly, no single microorganism is responsible for the development of RA. Evidence supporting a role for parvovirus B19 includes the presence of viral DNA in the synovial fluid, synovial cells, and/or synovial tissue of RA patients ***(Tobon et al., 2010).*** EBV RNA has been identified in B cells in synovial tissue from RA patients ***(Meron et al., 2010).*** Sera from RA patients contain high titres of Epstein–

Barr virus (EBV) antigens and of antibodies to latent and replicative EBV antigens ***(Darborg et al., 2013)***. The most suspected candidate is Porphyromonas gingivalis, a bacterium that causes periodontitis, which is associated with RA ***(Kharlamova et al., 2016).***

b. Smoking:

The relationship between smoking and RA is strongest among people who are anticitrullinated protein/peptide antibodies (ACPA-positive), a maker of auto-immune activity ***(Scott et al., 2010).*** The hypothesis that tobacco smoke (and other environmental exposures to the lungs, such as silica) can lead to a mucosal immune response giving rise to ACPA production has been supported by studies using high-resolution imaging techniques of the lungs, as well as by analysis of immune cells and autoantibodies in sputum and bronchial alveolar lavage from subjects at risk of developing RA ***(Willis et al., 2013 and Catrina et al., 2014).***

One of the most important findings from epidemiological and risk factor studies of RA is the interaction between the HLA shared-epitope and smoking. In a population-based case–control study, the risk of developing RF-positive RA was substantially higher in smokers carrying two copies of shared-epitope genes (RR, 15.7) than in smokers with no copies of shared-epitope genes (RR, 2.4) ***(Costenbader et al., 2008).***

c. Diet:

Diet has been evaluated in several studies for its role in the management of established RA ***(Hagen et al., 2009).***