GENETIC SUSCEPTIBILITY TO PSORIASIS: A GENOME WIDE ASSOCIATION STUDY IN EGYPTIAN PSORIATIC PATIENTS

Thesis

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CONTENTS

LIST OF FIGURES

LIST OF TABLES

List of Abbreviations

APC	Antigen presenting cells
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BAG6	Bcl2 Associated Gene-6
CASP	Collaborative Association Study of Psoriasis
CD	Cluster of differentiation
CHISQ	Chi Square
CI	Confidence Interval
CLA	Lymphocyte-associated antigen
CNV	Copy number variation
CsA	Cyclosporine A
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DC	Dendritic cell
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
EMEA	European Medicines Agency
FDA	Food and Drud Administration
GWAS	Genome Wide Association Study
HLA	Human leukocytic antigen
ICAM-1	Intercellular adhesion molecule 1
IFN	Interferon
IL	Interleukin
JAK	Janus associated kinase
Kg	Kilogram
LFA	Lymphocyte function-associated antigen
LILRB1	Leukocyte Immunoglobulin-Like Receptor,

	Subfamily B Member 1
MAP3K	Mitogen Activated Protein Kinase Kinase Kinase
mg	Milligram
MHC	Major histocompatibility complex
MICA	MHC Class I Polypeptide-Related Sequence A
MICB	MHC Class I Polypeptide-Related Sequence B
MICB	MHC Class I Polypeptide-Related Sequence B
MTX	Methotrexate
Nb-UVB	Narrowband ultraviolet B
NCR	Natural Cytotoxicity triggering Receptor
NK	Natural killer
OR	Odds Ratio
PASI	Psoriasis Area Severity Index
PCR	Polymerase Chain Reaction
PsA	Psoriatic Arthritis
PSGL-1	P-selectin glycoprotein ligand-1
PUVA	Psoralen with UV-A
RAR	Retenoic acid receptor
SCC	Squamous cell carcinoma
SD	Standard Deviation
SLC22A4	Solute Carrier family 22, subfamily A member 4
SLC9A4	Solute Carrier family 9, subfamily A member 4
SLC9A8	Solute Carrier family 9, subfamily A member 8
SNPs	Single Nucleotide Polymorphisms
STAT	Signal Transducer and Activator of Transcription
TCM	Cell central memory T cell
TCR	T cell receptor

TE	Effector T cell
TEM	Effector memory T
TGF	Transforming Growth Factor
Th	T helper
TNF-α	Tumor Necrosis Factor-alpha
TRIM40	Tripartite Motif Containing 40
USP34	Ubiquitin Specific Peptidase
UV-A	Ultra-Violet-A
VDR	Vitamin D Receptor
VEGF	Vascular Endothelial Growth Factor
VLA-4	Very Late Antigen-4
µl	Microliter

Abstract

Genome wide association studies have been performed in Psoriasis in several ethnic groups but never in Egyptians. The objective of this study is to determine the genetic susceptibility in Egyptian psoriasis patients. Blood samples from 339 Egyptian patients were withdrawn and more than 200,000 SNP's were scanned using microarray Techniques. HLA Cw*06 and other novel susceptibility Loci were found to be positively associated with psoriasis.

Key words:
Psoriasis – SNP's- GWAS-microarray

INTRODUCTION

Psoriasis vulgaris is a common chronic inflammatory skin disease with a prevalence of ~2%–3% in white populations ***(Lomholt, 1963; Nevitt and Hutchinson, 1996).*** The hallmarks of psoriasis are a clonal T cell expansion and infiltration of the epidermis, as well as a benign hyperproliferation of keratinocytes. Clinically, the disease is characterized by erythematous, scaly plaques, and it may be associated with severe arthritis ***(Lee et al., 2000).***

The multifactorial etiology of psoriasis is well established. Although environmental factors, such as streptococcal infections ***(Boehncke et al. 1997)***, have been shown to affect the onset of the disease, family studies clearly indicate that psoriasis has a strong genetic component ***(Abele et al. 1963; Farber et al. 1974; Brandrup et al. 1978).*** The genes responsible for susceptibility to psoriasis have not yet been identified ***(Lee et al., 2000).***

The inheritance of psoriasis is complex; this complexity arises because variations in the phenotypic expression of the disease, genetic heterogeneity, and interactions either between genetic factors and the environment or among genes do not allow a simple correlation of the disease phenotype with the genotypic constitution ***(Lander and Schork 1994)***. It is noteworthy that only two psoriasis-susceptibility loci, PSORS1 and PSORS2, have been confirmed in replication studies ***(Lee et al., 2000).***

In the last decade, numerous genome wide scans using linkage analysis on multiply affected families have elucidated eight other replicated susceptibility loci *(PSORS2–9)* as reviewed by ***Capon and colleagues (2004)***. Follow up sequencing and fine mapping within these susceptibility loci have, to date, yielded few candidate genes with biologic relevance to psoriasis pathophysiology ***(Duffin and Kreuger, 2009)***.

Early genome-wide linkage studies of psoriasis have focused on segregation of microsatellite markers in families; however, the only locus consistently identified resided in the major histocompatibility complex. Subsequently, several groups mapped this locus to the vicinity of HLA-C ***(Elder et al., 2010).***

Genetic susceptibility evidence is supported by familial clustering of the disease ***(Lomholt, 1976)***, increased concordance among monozygotic twins ***(Brandrup et al., 1982)*** and the repeatedly confirmed association with HLA-Cw6 ***(Nair et al., 2006)*** - However, only 60–65% of individuals with psoriasis carry this risk variant and 15% of individuals without psoriasis carry HLA-Cw6 ***(Gudjonsson et al., 2006)*** - lending support to the widely held belief that other common genetic variants contribute to psoriasis susceptibility ***(Duffin and Kreuger, 2008)***.

More recently, the development of millions of single-nucleotide polymorphisms, coupled with the development of high-throughput genotyping platforms and a comprehensive map of human haplotypes, has made possible a

genome-wide association approach using cases and controls rather than families ***(Elder et al., 2010)***.

AIM OF WORK

Little is known about the genetic elements influencing the course of the disease in different ethnic groups. In our study we plan to address this issue by conducting a Genome Wide Association Study (GWAS) in a large cohort of Egyptian patients suffering from psoriasis.

EPIDEMIOLOGY AND GENETICS OF PSORIASIS

Definition of Psoriasis:

Psoriasis vulgaris is a genetic, systemic, inflammatory, chronic disorder, which can be altered by environmental factors. It may be associated with other inflammatory disorders such as psoriatic arthritis, inflammatory bowel disease, and coronary artery disease. It is characterized by scaly, erythematous patches, papules, and plaques that are often pruritic ***(Menter et al., 2008)***.

Psoriasis is important to the clinician because it is common and has treatment implications beyond the care of skin lesions. It is important to the physician-scientist because it serves as a model for studies of mechanisms of chronic inflammation. ***(Nestle et al., 2009)***.

In recent years, substantial advances have been made in elucidating the molecular mechanisms of psoriasis. However, major issues remain unresolved, including the primary nature of the disease as an epithelial or immunologic disorder, the autoimmune cause of the inflammatory process, the relevance of cutaneous versus systemic factors, and the role of genetic versus environmental influences on disease initiation, progression, and response to therapy ***(Nestle et al., 2009)***.

Epidemiology of psoriasis:

- **Prevalence** :

Psoriasis is found worldwide, although its frequency varies widely among different ethnic groups. According to published reports, prevalence in different populations varies from 0% to 11.8% ***(Farber and Nall, 1998)***. Many confounding variables must be considered when considering these data, most particularly the method of ascertainment *(clinic-based or population based, examination-based, or questionnaire-based)* ***(Christophers, 2001)***. Nevertheless, examination of available population-based studies reveals prevalences ranging from 0.2% to 4.8 % ***(Gudjonsson and Elder, 2007)***.

Published estimates of the prevalence of psoriatic arthritis (PsA) vary widely, between 0.04% and 0.4 % ***(Gladman, 1997) (Gudjonsson and Elder, 2007)***.

- **Sex Ratio:**

Although some studies find minor deviations, psoriasis is equally common in males and females. Several studies have reported an earlier age of onset in females, but this is not universally observed. ***(Farber and Nall, 1998)***. There is no evidence for morphological differences in psoriasis between males and females ***(Gudjonsson and Elder, 2007)***.

- **Age at onset:**

Several authors have discussed the difficulties associated with accurate assessment of age at onset in psoriasis. Nevertheless, as noted by ***Lomholt (1963)***, age at onset is a very important piece of epidemiological information ***(Gudjonsson and Elder, 2007)***.

Psoriasis may first appear at any age. It is most likely to appear between the ages of 15 and 30 years but ranges from birth to the eighth or ninth decade. There