INTERLEUKIN-18 GENE POLYMORPHISM IN EGYPTIAN ASTHMATIC CHILDREN

Thesis submitted for partial fulfillment of master degree in Pediatrics

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2012

ABSTRACT

Asthma is a multifactorial respiratory disease determined by interactions of multiple disease susceptibility genes and environmental factors**.** IL-18 is an important cytokine for initiating and perpetuating the catabolic and inflammatory response in allegic asthma**.** A number of SNPs that influence IL-18 production are found in the gene promoter region**.**

The aim of this study was to investigate the association of IL-18 -607 C/A promoter polymorphism with asthma and whether this polymorphism influenced the severity of asthma in affected children. The influence of this promoter gene polymorphism on total serum IgE level in studied subjects was investigated.

This study included 40 asthmatic children, subdivided into four groups according to different degrees of asthma severity, and 20 healthy subjects were included as control group.

Key Words:

Definition of Asthma, Incidence and Prevalence of Asthma, Etiology of Asthma, Pathogenesis of Asthma, Gene Polymorphism in Asthma, Diagnosis of Asthma, Asthma Classification, Asthma Management and Prevention, Cytokines and Bronchial Asthma, Interleukin-18.

Acknowledgements

First of all, I would like to thank ***GOD,*** *who gave me the power by his abundant grace to produce this piece of work.*

I would like to express my appreciation and sincere gratitude to ***Prof. Dr. Hala Hamdi Shaaban,*** *Professor of Pediatrics, Faculty of Medicine, Cairo University, who enriched the study with her experience and knowledge, and provided me with her valuable instructions, sincere help and support.*

I am very grateful to ***Dr. Abeer Mohamed Mohy,*** *Assistant Professor of Clincal and Chemical Pathololgy, Faculty of Medicine, Cairo University, not only for her kind assistance, support, but also for her patience with constant guidance and effort.*

Sincere thanks to ***Dr. Abdel Rahman Ahmed Abdel Razek,*** *Lecturer of Pediatrics, Faculty of Medicine, Cairo University, for his help and encouragement throughout this work.*

I will always be grateful to my parents, my sister, and my husband for all their love, support and understanding.

To all patients, for whose benefit the present study was conducted, I wish it would help you a step forward.

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List of abbreviations

AEC	Absolute eosinophilic count
AHR	Airway hyper-responsiveness
AMP	Adenosine 5'-monophosphate
APCS	antigen presenting cells
ASCIA	Australasian Society of Clinical Immunology and Allergy
ASM	Airway smooth muscle
BAL	Broncho-alveolar lavage
CBC	Complete blood count
CCL	CC chemokine
CCR	CC chemokine receptor
CD	Cluster of differentiation antigen
COPD	Chronic obstructive pulmonary disease
CVA	Cough variant asthma
CXCL	CXC chemokine
CXCR	CXC chemokine receptor
DNA	Deoxyribonucleic Acid
EDTA	Ethylenediaminetetra-acetic acid
EGF	Epidermal growth factor
EIA	Exercise-induced asthma
ELISA	Enzyme-linked immunosorbant assay
FEF	Forced expiratory flow
FEV1	Forced expiratory volume in one second
FeNO	Fractional exhaled nitrous oxide
FVC	Forced vital capacity

GERD	Gastroesophageal reflux disease
GINA	Global initiative for asthma program
GM-CSF	Granulocyte macrophage –colony stimulating factor
GWAS	Genome-wide association studies
HB	Hemoglobin
HRCT	High resolution computed tomography
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
INF-γ	Interferon-gamma
LABA	Long-acting beta2-agonist
LTE4	Leukotriene E4
LTRAs	Leukotrienes receptor antagonists
MBP	Major basic protein
MDC	Monocyte-derived chemokines
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung and Blood Institute
NGF	Nerve growth factor
NO	Nitric oxide
PAF	Platelet-activating factor
PCR	Polymerase chain reaction
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PLT	Platelet
RADS	Reactive airways dysfunction syndrome
RAST	RadioAllergoSorbent Test

RFLP	Restriction fragment length polymorphism
RSV	Respiratory syncytial virus
SABA	Short-acting beta2-agonist
SCF	Stem cell factor
SFC	Salmeterol/fluticasone propionate combination
SNP	Single-nucleotide polymorphism
SPT	Skin prick testing
SVT	Supraventricular tachycardia
TARC	Thymus and activation-regulated chemokine
TGF-β	Transforming growth factor beta
Th1	T-helper 1
Th2	T- helper 2
TLC	Total leucocytic count
TMG	Tetramethylguanidine
TNF	Tumor necrosis factor
TSLP	Thymic stromal lymphopoietin
VEGF	Vascular endothelial growth factor
WHO	World health organization

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INTRODUCTION

Asthma is a syndrome characterized by intermittent narrowing of the small airways of the lung, with subsequent airflow obstruction and symptoms of wheeze, cough and breathlessness. An important characteristic of asthma is airways hyper-responsiveness, which is the exaggerated narrowing of the airways in response to provocative agents **(Settin et al., 2008).**

As a chronic inflammatory disease, many of the researches related to asthma has been focused on pro-inflammatory mechanisms, advances have been made in defining mechanisms that control inflammation and induce immune tolerance to specific antigens **(Gern and Seroogy, 2005).**

Recently, new insights in the pathogenesis of asthma suggest the role of lymphocytes; airway inflammation in asthma may represent a loss of normal balance between two "opposing "populations of T-helper (Th) lymphocytes**.** Two types of Th lymphocytes have been characterized**:** Th1 and Th2**.** Th1 cells produce interleukin (IL)-2 and interferon (IFN)-gamma which are critical in cellular defense mechanisms and promote proinflammatory immune reaction in response to infection**.** Th2, in contrast, generates a family of cytokines (IL-4, IL-5, IL-6, IL-9, and IL-13) that can mediate allergic inflammation and promote antibody dependent immune response**.** As a result, there is a great interest in using cytokines as markers of human immune function **(Sharma, 2010).**

Inerleukin-18(IL-18) is unique cytokine that enhances innate immunity and both Th-1and Th-2 driven immune responses **(Abdel Naser et al., 2009**), it was originally described as interferon-gamma releasing factor, but has a different mechanism of action to IL-12 **(Barnes, 2001**), where it was recently found to act in synergy with IL-12 to promote the development of Th2 immune response by induction of IL-13. So, according to its role in regulation of Th1/Th2 balance, IL-18 is considered as a candidate asthma susceptibility gene **(Lachheb et al., 2007).**

For the past few years, studies were made to determine the gene loci predisposing to asthma and other atopic disorders & by the completion of the human Genome Project, analysis of single-nucleotide polymorphisms (SNP) has become the newest approach in the detection and localization of the genetic determinants of the human disease **(Li et al., 2009).**

Based on these studies, it was found that cytokine gene polymorphism could affect the serum levels of cytokines by influencing transcriptional regulation **(Amirzargar et al., 2009).**

AIM OF WORK

The aim of the present study is to investigate whether the presence of IL-18-607 C/A polymorphism was associated with asthma (or atopy) and whether this polymorphism influenced the severity of asthma in affected children. We examine also the relationship between the IL-18 gene polymorphism and the serum total IgE level.

DEFINITION OF ASTHMA

Asthma is a chronic inflammatory disorder of the airways characterized by an obstruction of airflow, which may be completely or partially reversed with or without specific therapy. In susceptible individuals, airway inflammation may cause recurrent or persistent bronchospasm, which causes symptoms including wheezing, breathlessness, chest tightness, and cough, particularly at night or after exercise **(Sharma, 2010).** Airway inflammation is associated with airway hyper reactivity or bronchial hyper responsiveness (BHR), which is defined as the inherent tendency of the airways to narrow in response to various stimuli (eg, environmental allergens and irritants) **(NHLBI, 2007).**

Although the cause of childhood asthma has not been determined, contemporary research implicates a combination of environmental exposures and inherent biological and genetic vulnerabilities **(Liu et al., 2007)**