



# Molecular Characterization of Tumor Necrosis Factor-Alpha Gene in Bronchial Asthmatic Children

*Thesis*

**Submitted for the Fulfillment of PhD  
in Childhood Studies Child Health and Nutrition  
Department of Medical Studies**

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2012**



## Acknowledgment

*First and above all, I pray thanking God for his blessing and giving me the effort to complete and achieve this work.*

*I would like to express my deep gratitude, thanks, and respect to **Prof. Dr. Ehab M. Eid** Professor of Public Health, Institute of Postgraduate Childhood Studies, Ain Shams University for granting me the privilege of working under his supervision and for his great encouragement and unfailing tender advice throughout this work and throughout my career.*

*I would like to express my thanks and admiration to **Prof. Dr. Howaida Elgebaly**, Professor of Pediatrics, Institute of Postgraduate Childhood Studies, Ain Shams University for her supervision, suggesting this valuable point of research, continues encouragement, beneficial remarks and kind advises during the whole work.*

*I wish to express my deep thanks and utmost gratitude to **Dr. Nasser A. Elhawary**, Professor of Genetics, Faculty of Medicine, Medical Genetics Center, Ain Shams University for his guidance, advice and fruitful suggestions without which this work would have never been accomplished.*

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**Manal Fawzy**



# التوصيف الجزيئي لجين معادل التنكرز الورمي ألفا في الأطفال المصابين بالربو الشعبي

رسالة  
مقدمة للحصول على درجة دكتوراه الفلسفة  
في دراسات الطفولة  
قسم الدراسات الطبية

مقدمة من  
الطبيبة/ منال فوزي ذكرى  
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## List of Abbreviations

<b>ALI</b>	Acute lung injury
<b>AP-1</b>	Activator protein one
<b>ARDS</b>	Acute respiratory disease syndrome
<b>ASK1</b>	Apoptosin single regulating kinase 1
<b>BHR</b>	Bronchial hyper responsiveness
<b>BT</b>	Bronchial thermoplasty
<b>CB</b>	Chronic brouchitis
<b>CFC</b>	Chlorofluorocarbon
<b>COPD</b>	Chronic obstruction pulmonary disease
<b>CSGA</b>	Collaborative study on the genetics of asthma
<b>CTLA4</b>	Cytotoxic T lymphocyte antigen-4
<b>DPI</b>	Dry-powder inhaler
<b>EPR-3</b>	Expert panel report III
<b>FADD</b>	Fas-associated death domain
<b>FEF<sub>25-75</sub></b>	Forced expiratory flow over 25-75% of the FVC
<b>FeNo</b>	Fractional exhaled nitric oxide
<b>FEV1</b>	Forced expiratory volume in one second
<b>FRC</b>	Functional residual capacity
<b>FVC</b>	Forced vital capacity
<b>GER</b>	Gastroesophageal reflux
<b>GINA</b>	Global initiative for asthma
<b>GM-CSF</b>	Granulocyte-macrophage colony-stimulating factor
<b>HFA</b>	Hydrofluoroalkane
<b>ICAM-1</b>	Intracelleular adhesion molecule one

<b>ICS</b>	Inhaled corticosteroids
<b>IgE</b>	Immunoglobulin E
<b>IL-4</b>	Interleukin 4
<b>IL4R</b>	Interleukin 4 receptor antagonist
<b>IL-5</b>	Interleukin 5
<b>ILIRN</b>	Interleukin one receptor antagonist
<b>LPS</b>	Lypopoly saccharide
<b>LTA</b>	Lymphotoxin-a
<b>LTC4S</b>	Leukotriene C4 synthase
<b>MAPK</b>	Mitogen-activated protein kinase
<b>MDCs</b>	Macrophage-derived chemokines
<b>MDI</b>	Metered dose inhaler
<b>MHC</b>	Major histocompatibility complex
<b>MIP</b>	Macrophage inflammatory protein
<b>NF-KB</b>	Nuclear factor kappa B
<b>NHLB</b>	National heart, lung and blood institute of health
<b>NIH</b>	National Institutes of Health
<b>NOS1</b>	Nitric oxide synthase 1 gene
<b>PDGF-B</b>	Platelet driven growth factor-B
<b>PEFR</b>	Peak expiratory flow rate
<b>RAGE</b>	Receptor for advanced glycation end products
<b>RIP</b>	Receptor-interacting protein
<b>RSV</b>	Respiratory syncytial virus
<b>RV</b>	Residual volume
<b>SNPs</b>	Single-nucleotide polymorphisms
<b>SPINK5</b>	Serine protease inhibitor kazal type 5

<b>STA-6</b>	Singal transducer and activator of transcription 6 gene
<b>TACE</b>	TNF alpha converting enzyme
<b>TAKCs</b>	Thymus and activation regulated chemokines
<b>TGF</b>	Transforming growth factor
<b>Th 2</b>	T-helper type 2
<b>TLC</b>	Total lung capacity
<b>TNF-<math>\alpha</math></b>	Tumor necrosis factors-alpha
<b>TNF-<math>\beta</math></b>	Tumor necrosis factors-beta
<b>TNF-R1</b>	TNF-receptor one
<b>TNF-R2</b>	TNF-receptor two
<b>TRADD</b>	TNF-receptor associated death domain
<b>URTI</b>	Upper respiratory tract infection
<b>VCAM-1</b>	Vascular cell adhesion molecule one

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## Introduction

Asthma (MIM # 600807) is a common respiratory disease characterized by variable air flow obstruction, inflammation of the airways and bronchial hyper responsiveness (BHR). Asthma is recognized as T-helper type 2 (Th2) disease with a particular profile of cytokine release, including interleukin 4 (IL4) and interleukin 5 (IL5). Increasing evidence indicates that cytokines are also associated with inflammatory response that characterizes human asthma. One such mediator is tumor necrosis factor-alpha (TNF- $\alpha$ ) (*Thomas et al., 1996*) that has been shown to induce airway hyper reactivity (*Lin et al., 2002*).

The genetic evidence in the etiology of asthma, the mode of inheritance is complex and not yet fully understood (*Ober and Moffatt, 2000*). It is likely that several genes, each with moderate-to-major effects, act together with environmental exposures to determine an individual's overall risk of development of asthma. The Collaborative Study on the Genetics of Asthma (CSGA) is a multicenter collaborative study supported by the National Heart, Lung and Blood Institute of the National Institutes of Health (NHLBI/NIH), whose purpose is to identify important loci that contribute to the development of asthma and asthma-associated phenotypes. Different frequencies of asthma-susceptibility genes in each ethnic

population provided the strongest evidence for linkage at 6p21 in the European American population, at 11q21 in the African American population, and at 1p32 in the Hispanic population (*Xu et al., 2001*). Further evidence for linkage has been investigated at 5q31, 8p23, 12q22, and 15q13 loci (*Noguchi et al., 1997; Gao et al., 2006*).

TNFA and TNFB (namely as lymphotoxin- $\alpha$ , LTA) genes belongs to TNF gene super family located with in human major histocompatibility complex (MHC) (6p21) in a region repeatedly linked to asthma (*Shin et al., 2004*). More common polymorphisms in the promoter of TNFA ( $-1031C>T$ ,  $-863C>A$ , and  $-857C>T$ ) have been identified (*Moffatt and Cookson, 1997*). The TNF position  $-308$  and LTA polymorphisms have essentially influenced TNF transcription and secretion respectively (*Beghe et al., 2004; Gao et al., 2006*). A number of independent studies have indicated an association of the TNF $\alpha$   $-308G>A$  promoter polymorphism with the risk of asthma (*Moffatt and Cookson, 1997; Shin et al., 2004; Aoki et al., 2006*).

It is noteworthy that little work has been made concerning the association between one single nucleotide polymorphism (SNP; LTA  $+252A>G$ ) (*Elhawary and Kamal, 2006*) and the asthmatic cases. In this study, we will performed