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

Thesis

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التوصيف الجزيئى لجين معامل التنكرز الورمي ألفـــا في الأطفال المصابين بالربو الشعبي

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مقدمة للحصول على درجة دكتوراه الفلسفة
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List of Abbreviations

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

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

STA-6	Singal transducer and activator of transcription 6 gene
TACE	TNF alpha converting enzyme
TAKCs	Thymus and activation regulated chemokines
TGF	Transforming growth factor
Th 2	T-helper type 2
TLC	Total lung capacity
TNF-α	Tumor necrosis factors-alpha
TNF-β	Tumor necrosis factors-beta
TNF-R1	TNF-receptor one
TNF-R2	TNF-receptor two
TRADD	TNF-receptor associated death domain
URTI	Upper respiratory tract infection
VCAM-1	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-α) ***(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 lymhotoxin-α, LTA) genes belongs to TNF gene super family located with in human major histocomtability 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 TNFα −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