Assessment of CYP1A1 (MspI) Gene Polymorphism in Patients with Chronic Obstructive Pulmonary Disease

Thesis

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By

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List of Abbreviations

Abb.	Full term
A	*Adenine*
AATD	*Alpha 1 antitrypsin deficiency*
AGER	*Advanced glycosylation end product-specific receptor*
AHR	*Aryl hydrocarbon cytosolic receptor*
AIP	*AHR interacting protein*
ALL	*Acute lymphocytic leukemia*
AML	*Acute myeloid leukemia*
ARNT	*Aryl hydrocarbon receptor nuclear translocator*
AS	*Allele specific*
C	*Cytosine*
CAD	*Coronary artery disease*
CBR	*Cytochrome b5 reductase*
CDF	*Childhood disadvantage factors*
CHRNA3/5	*Cholinergic nicotine receptor alpha 3/5*
COPD	*Chronic obstructive pulmonary disease*
CVD	*Cardiovascular disease*
CYP	*Cytochrome P45O enzymes*
CYP1A1	*Cytochrome P 450 family 1 superfamily A member 1*
FAM13A	*Family with sequence similarity 13,member A*
FEV1	*Forced expiratory volume in fisrt second*
FVC	*Forced vital capacity*
G	*Guanine*
GOLD	*Global initiative for chronic obstructive lung disease*
HHIP	*Hedhog-interacting protein*
HSP90	*Heat shock protein*
IREB 2	*Iron regulatory binding protein 2*
M1	*MspI polymorphism*

List of Abbreviations cont...

Abb.	Full term
m1	*T Allele*
m2	*C Allele*
M2	*IIe462Val polymorphism*
M3	*T3205C polymorphism*
M4	*Thr461Asn polymorphism*
MALDI-TOF	*Matrix assisted laser desorption ionization time of flight.*
NFI	*Nuclear factor 1*
Nk	*Nuclear factor*
PAH	*Polyaromatic hydrocarbons*
PCR	*Polymerase chain reaction*
PHAHS	*Polyhalogenated aromatic hydrocarbons*
POR	*Cytochrome p450 oxireductase*
RAR	*Retinoic acid receptor*
RARE	*Retinoic acid responsive element*
RFLP	*Restriction fragment length polymorphism*
SERPINA1	*Serpin family A member 1*
SMRT	*Silencing mediator for retinoid and thyroid receptors*
SNP	*Single nucleotide polymorphism*
T	*Thymine*
TH1	*T- Helper 1*
TH2	*T-Helper 2*
VEGF	*Vascular endothelial growth factor*
XREs	*Xenobiotic response elements*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The block in the airflow in COPD is caused by inflammation in the airway causing a combination of obstructive bronchitis and parenchymal destruction (emphysema), which differs from one individual to the other ***(Harju et al., 2015).***

Chronic obstructive pulmonary disease is a major cause of illness worldwide and it is increasing substantially representing a socioeconomic burden. According to a study conducted by ***Pelegrino et al. in (2013),*** 12 million people were affected by this disease worldwide. The Global Burden of Disease Study indicated that COPD will be ranked as the third most leading cause of death worldwide by 2020 ***(Muka et al., 2015).***

The common risk factors for COPD are tobacco smoking (with approximately 10 % of smokers developing COPD), occupational dusts and exposure to chemicals. Although smoking is considered the most important risk factor for developing COPD, studies have described a significant prevalence of the disease among non-smokers, suggesting the influence of genetic factors on COPD susceptibility ***(Steiling et al., 2013).***

Oxidative stress plays a vital role in the pathogenesis of various lung disorders, either by causing direct injury to lungs or by involving in the process of inflammation at molecular level. Oxidant/antioxidant imbalance occurs in COPD and in smokers. Free radicals released from cigarette smoke can trigger structural changes in lipid perioxidation, which can impair the function of membrane and the activity of its receptor and enzymes, disturbing the membrane permeability ***(Ford et al., 2014).***

Cytochrome P450 1A1 (CYP1A1) is a protein of cytochrome p450 family which plays a key role in activation of polycyclic aromatic hydrocarbons (PAH) which are present in cigarette smoke and air pollution and considered as carcinogenic. Its aromatic hydrocarbon hydroxylase which catalyzes the first oxidative step in the metabolism of PAH, releasing reactive intermediates so- products, which are significantly more toxic than their parent compounds. CYP450 genes are highly polymorphic with mutations that cause increased, decreased, altered or no enzyme activity ***(Zhou et al., 2016).***

There are many single nucleotide polymorphisms (SNP) involving the CYP1A1 gene, one of them is *CYP1A1* MspI (rs4646903) polymorphism, in which the thymine (T) is substituted by cytosine (C) at 3801 nucleotide in the 3′non-coding region of *CYP1A1* gene, which may be associated with an increased enzyme activity, subsequently altering lung function and increasing susceptibility to COPD ***(Yang et al., 2014).***

AIM OF THE WORK

The aim of the present study is to evaluate the role of Cytochrome P450 1A1 (CYP1A1 MspI) (3801 T/C) gene polymorphism in the development of Chronic Obstructive Pulmonary Disease (COPD) by PCR-RFLP.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, which is usually caused by significant exposure to noxious particles or gases. The chronic airflow limitation that is a significant characteristic of COPD is caused by a mixture of obstructive bronchitis (a condition of increased swelling and mucus production in the airways) and emphysema (a condition that involves damage to the walls of the alveoli of the lung) ***(James et al., 2017).***

Currently, COPD is listed as the fourth leading cause of death in the world, but it is projected to be the 3rd leading cause of death by 2020. More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally. This increase in COPD-related mortality has mainly been driven by the expanding epidemic of smoking, reduced mortality from other common causes of death (e.g., ischemic heart disease, infectious diseases), the aging of the world's population, and scarcity of effective therapies ***(Allinson et al., 2016).***

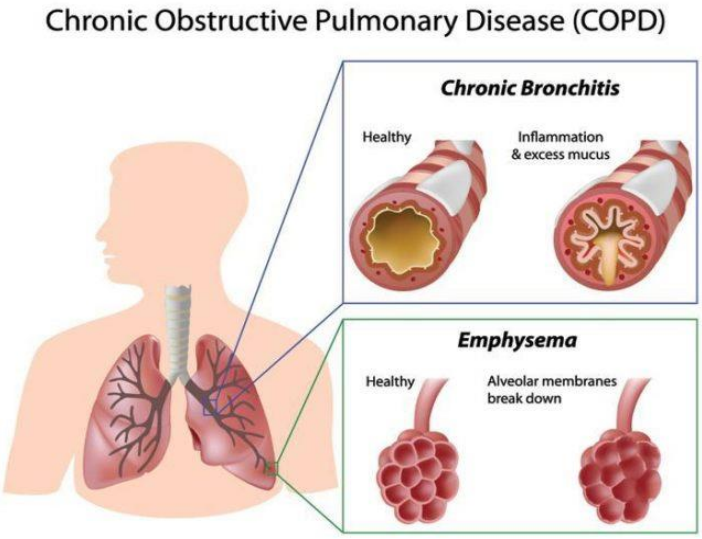

Figure (1): Pathological changes occurs in COPD ***(Norbert et al., 2017).***

A. Epidmiology of COPD:

According to the Burden of Obstructive Lung Diseases programme (BOLD), estimated number of COPD cases was 384 million in 2010, with a global prevalence of 11.7%. There are around three million deaths annually as a result of increasing prevalence of smoking in developing countries, and aging populations in high-income countries. The prevalence of COPD is expected to rise over the next 30 years, so that by 2030 there may be over 4.5 million deaths annually related to this disease ***(Obaseki et al., 2016).***

In Egypt, the prevelance rate of COPD was 6.6%. The highest prevelance was among people above 60 years old (9.2%). Male gender is more affected than females, urban areas prevelance was (7.6%) while in rural areas was (6.3 %).

Highest prevelance was in retired population (10 %) followed by worker (7.1 %). As regard smoking habbits, the prevelance was high in ex-smokers (16.3%) followed by current smokers (8.6%) ***(Mohamed et al., 2016).***

B. Risk Factors for COPD:

1. Genetic Factors:

Complex diseases, including COPD, are caused by the interaction of environmental factors and genetic susceptibility. Many studies focused on association between genetic variations within candidate genes and COPD -related phenotypes:

a. Cholinergic nicotine receptor alpha 3/5 (CHRNA3/5):

They are subunits of the nicotine cholinergic receptor, located on chromosome 15q25. The proteins are responsive to nicotine and are upregulated during chronic tobacco exposure. The *CHRNA3/5* locus is associated with emphysema and lung cancer ***(Lao et al., 2015)***.

b. Iron regulatory binding protein 2 (IREB2):

It is a protein that binds iron-responsive elements (IREs). It is located on chromosome 15q25, maintaing cellular iron metabolism, and is regulated in response to oxygen and iron supply ***(Zumbrennen et al., 2014)***.

The IREB2 expression is higher in the lung tissue of COPD cases with high level of iron, causing abnormal iron