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Open Access Journal of Pulmonary & Respiratory Sciences

Alpha-1 Antitrypsin Genotypes in Patients with Chronic Obstructive Pulmonary Disease

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Editorial

Volume 3 Issue 1

Received Date: June 19, 2018

Published Date: June 27, 2018

DOI: 10.23880/oajprs-16000119

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Alpha-1 antitrypsin (AAT), a proteinase inhibitor produced by the SERPINA1 gene that protects the pulmonary alveoli and other connective tissues in the lungs against the destructive effects of neutrophil elastase and other proteases. SERPINA gene is known to be associated with COPD. The main evidence of this is the development of pulmonary emphysema in humans. Additionally, AAT also has immunomodulatory functions that make it a natural anti-inflammatory molecule. AAT is the most abundant protease inhibitor in human serum with average of 149mg/dL in normal persons. The amount of serum AAT is directly related to the patient's genotype. Approximately, 2% to 3% of patients with chronic obstructive pulmonary disease (COPD) generally have severe deficiency of this protein. The AAT or SERPINA1 gene is passed on by simple Mendelian inheritance in an autosomal codominant pattern and is characterized by its extensive polymorphism with more than 100 allelic variants. The most common variant in the most severe AAT deficiency is the Z allele. When SERPINA1 gene has not been purposefully removed from some genetic association analyses and was included as one of the studied loci by including known AAT-deficient patients, the MZ genotype is found to be associated with COPD and COPD progression in some open-ended genome-wide association studies.

Some of the longitudinal studies are limited by short interval follow-up with 2-3 years, and contribute to their negative results. In the several previous studies with following-up of 6 to more than 21 years revealed that pulmonary function was more decline in MZ genotype persons compared to the MM genotype group, for examples, 20- 40mL more yearly FEV1 decline, more FEV1/FVC decline, annual FEV1 decline of 75mL in MZ group versus 53mL in MM persons, annual forced expiratory flow decline at 25%-75% of FVC(FEF25-75 %) of 108.2mL/second/year in persistent smoking MZ group versus 66.8mL/second/year in persistent smoking MM individuals, but some studies demonstrated no difference in respiratory symptoms. The longest study (over 21 years) as we know conducted by Dahl et al showed that the frequency of alleles did not significantly differ from that predicted by Hardy-Weinberg equilibrium. After adjusting for sex, age, tobacco consumption and FEV1 at the study entry, MZ persons had 50% more incidence of COPD, as well as more chance of hospital admission and death from COPD, when compared to MM group. However, there was a statistical difference in the annual FEV1 decline in MZ group compared to MM subjects with mean difference of only 4mL. Surprisingly, when grouping was based on smoking status, the FEV1 decline was similar among MZ and MM populations. When considering the nonsmokers, the difference in annual FEV1 decline was worse by 7mL every year among MZ population (20+/-2.9mL) compared to MM subjects (13+/-0.7mL). A previous study revealed that frequency of rapid FEV1 decline (-154+/-3mL/year) among MZ smoking persons compared to smokers that did not rapid decline (+15+/-2mL/year). Current smoking MZ persons who had a family history of COPD had rapid decline in pulmonary function with pronounced association (odds ratio of 9.7).

The international guidelines recommend measuring AAT levels in all symptomatic adults with persistent air

flow obstruction on spirometry and in young pulmonary-emphysema patients (aged 45 years or below) or non-smokers. Due to largely unrecognition of AAT deficiency among physicians, some studies demonstrated the long intervals between the first symptom and the definitive diagnosis (6.3-7.2 years). Approximately, 44% of patients with AAT deficiency reported that they had seen at least 3 physicians before receiving a confirmed diagnosis of AAT deficiency.

In conclusion, initial serum AAT level measuring by dried blood spot testing and subsequent genotyping will be a simply and satisfactory initial approach to a screening program for severe AAT deficiency, as a definitive diagnosis.