**DNAH5, A Possible Genetic Marker in Diagnosing Connective Tissue Disease-Associate Interstitial Lung Disease (CTD-ILD)**

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**Abstract**

Connective Tissue Disease-associate Interstitial Lung Disease (CTD-ILD) treatment depends on early accurate diagnosis. We hereby report a case of a 66-year-old man who has been diagnosed with CTD-ILD according to his High Resolution Computed Tomography (HRCT) and symptoms. In the meantime, we find axonemal dynein heavy chain gene 5 (DNAH5) variants in his Whole-Exome Sequence (WES). We wonder if DNAH5 is a biomarker of CTD-ILD.

**Introduction**

Interstitial Lung Disease (ILD) manifests as diffuse parenchymal lung disorders with various degrees of inflammation and fibrosis [1,2]. Noticeably, approximately 20% ILD are CTD-ILD [3]. Connective Tissue Diseases (CTDs), such as Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SSC) and polymyositis/Dermatomyositis (PM/DM) and so on, are the main triggers of ILD; in the meanwhile, ILD is the largest killer in patients with CTD [4]. In addition, a significantly better prognosis of CTD-ILD is presented comparing to other kind of ILD like Idiopathic Interstitial Pneumonia (IPF) [5,6]. Nevertheless, in clinical practice, ILD usually can be the first manifestation of a CTD-ILD, with extrapulmonary symptoms appearing years later, which are likely delaying treatment [6]. Therefore, early diagnosis and better classification of CTD-ILD are crucial [7].

We consider that find a biomarker may help. DNAH5 variants frequently contribute to Primary Ciliary Dyskinesia (PCD), which characterized by recurrent inflection in the upper and lower airway and bronchiectasis with the clinical presentations of respiratory distress in term neonates, recurrent oto-sinopulmonary infections, bronchiectasis, situs inversus and/or heterotaxy, and male infertility [8-10]. DNAH5 can also cause small airway obstruction and develop hyperinflation resulting in Chronic Obstructive Pulmonary Disease (COPD) [11]. We report a case of a CTD-ILD patient with DNAH5 mutation, wondering if DNAH5 mutation involves in CTD-ILD.

**Case Presentation**

In October 2019, a 66-year-old male with a smoking history of 360 pack-years was admitted for rapid progression of dyspnea and dry cough for last two months. He has been diagnosed to be a case of ILD on basis of HRCT with no obvious symptoms for five years. On physical examination, erythema keratodes were observed on his upper limbs and light Velcro rales at bilateral low lobes. But no Clubbed- finger, no Raynaud, and no morning stiffness. Immunological and serological results showed anti-KU-antibody, anti-Signal Recognition Particle (anti-SRP) Antibody and Antinuclear Antibody (ANA) were positive. Laboratory investigations suggested serum Immunoglobulin G (IgG) was 17.3 g/L (normal level 7 g/L to 16 g/L), Immunoglobulin E (IgE) was 230 IU/mL (normal level 20-200 IU/mL), relatively at high level. Thoracic HRCT showed distributions of the pulmonary fibrosis were diffuse bilaterally and symmetrical (Figure 1). Additionally, the level of Krebs von Lungen (KL)-6 in his blood significantly increased 1180 U/mL, normal range 0 U/mL-500 U/mL. His SpO2 maintained at 95% to 97% range either at the rest or at exertion. Pulmonary function test revealed dispersion function decreased slightly. The result of 6 Minutes Walking Test (6-MWT) was 661 m. The patient was diagnosed with CTD-ILD. Of note, a WES analysis followed by Sanger sequencing identified a heterozygous missense mutation (c.2047C>T) of DNAH5. After a week of oral prednisone 20 mg/day and quetiapine 200 mg/day for treatment, he’d relieved from dyspnea and dry cough.
DNAH5, which encodes Outer Dynein Arm (ODA) components, has been proven clearly to be the PCD disease-causing gene and leads to a total deficiency of ODA and its function when it mutates [9,19,20]. ODA functions as a force-generating protein of respiratory cilia with ATPase activity [11]. In PCD patients, respiratory cilia do not move normally, which brings out that mucus and debris in airway can’t be incompletely cleared, leading to repeated sinusitis, bronchiectasis, chronic otorhinolaryngological dysfunction of the pulmonary and upper respiratory tract [15]. Horizonal Computed Tomography (HRCT) shows distribution of the pulmonary fibrosis were diffuse bilaterally and symmetrical. A novel oncogenic driver in human lung squamous cell carcinoma [25]; these results suggest DNAH5 variants significantly influence the structure and function of pulmonary. Herein, although further investigation is warranted to confirm the connection of DNAH5 and CTD-ILD, our case provides a new vision and idea to predict the occurrence of ILD in CTD patients as to improve prognosis.

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