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Case Report
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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 den Lungen (KL)-6 in his blood significantly increased 1180 U/mL, normal range 0 U/m L-500 U/m L). His SpO_2 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 sequence 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.

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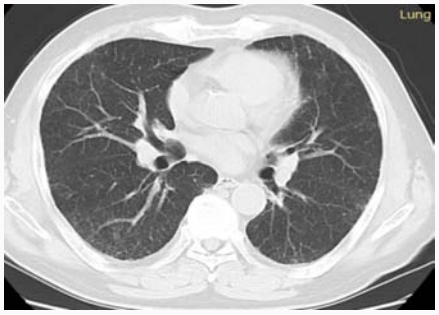

Figure 1: High Resolution Computed Tomography (HRCT) shows distribution of the pulmonary fibrosis were diffuse bilaterally and symmetrical.

Discussion

ILD is a group of heterogeneous diseases distinguished by fibrosis or inflammation of the pulmonary parenchyma [12]. Existing major categories of ILD include environmental exposures related ILD, CTD-ILD, sarcoidosis, and IPF [12-14]. Meanwhile, CTD-ILD frequently occurs in identified CTD patients (SSc, RA, PM/DM, SLE and so on) or Interstitial Pneumonia with Autoimmune Features (IPAF) patients [15]. According to Angelo et al. [6] there are different histological patterns in CTD-ILD, consisting of Non-Specific Interstitial Pneumonia (NSIP), Organizing Pneumonia (OP), usual Interstitial Pneumonia (UIP), Lymphocytic Interstitial Pneumonia (LIP) and Diffuse Alveolar Damage (DAD). Furthermore, the prevalence, diagnostic criterion, clinical presentations and treatment of CTD-ILD are varied by CTD types. Since the heterogeneity of diseases, there is no specific management guideline of CTD-ILD until now. For some acute and subacute CTD-ILD patients, rapidly progressive ILD may be the first or only manifestation of an underlying CTD with poor prognosis, so treatment is always earlier than definite diagnose of CTD [16]. All CTD patients are at risk of ILD, however, the necessity of targeting underlying ILD in CTD-ILD patients with immunosuppressive therapy lacks unified expert consensus [17]. Whether occult or probable forms of CTD-ILD are associated with a better outcome is uncertain. Therefore, prior ascertainment will help a lot. In daily clinical work, we are used to combining auto-antibodies, laboratory abnormalities, histopathology and HRCT image with symptoms or clinical features to diagnose CTD-ILD. But this method is short of specificity to guide treatment scheme, just like our above case. Collectively, find a stable biomarker, which suggests that common and rare genetic variants may play a significant role, may contribute to overcome the limitations [18].

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 cleaned, leading to repeated sinopulmonary infection and small airway obstruction [21,22]. Hence, *DNAH5*-mutation patients may suffer from manifestations of PCD, for instance, bronchiectasis, chronic sinusitis, chronic oto-sino-pulmonary diverse and even respiratory failure caused by irreversible lung damage [23,24]. According to Lee et al. [11] *DNAH5* variants may contribute to develop hyperinflation in patients with COPD, with Residual Volume (RV) and RV/Total Lung Capacity (TLC) ratio [11]. Besides, it was confirmed that TRA2B-*DNAH5* fusion becomes 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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