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Whole-exome sequencing identified novel *DNAH5* homozygous variants in two consanguineous families with primary ciliary dyskinesia

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To the Editor: Primary ciliary dyskinesia (PCD) is a rare autosomal recessive inherited disease characterized by dysfunction of the motile cilia. *DNAH5*, the most frequently mutated gene in PCD, encodes a heavy chain of the ciliary outer dynein arms (ODAs). Herein, we report two patients with Kartagener syndrome (sinusitis, bronchiectasis, and situs inversus) in two consanguineous families carrying two novel homozygous *DNAH5* variants [Supplementary Figures 1A and 1B, http://links.lww.com/CM9/B598].

Patient I was a 30-year-old male. He had recurrent respiratory infections since childhood and had visited our outpatient respiratory clinic. Lung function tests showed obstructive impairment (forced expiratory volume in one second to forced vital capacity ratio [FEV_1/FVC] was 65.96% after bronchodilator administration). His nasal nitric oxide (nNO) concentration was significantly lower than normal: 10.8 nL/min (normal >77 nL/min). Computed tomography (CT) showed sinusitis, bronchiectasis, and situs inversus [Figure 1A and Supplementary Figures 1C and 1E, http://links.lww.com/CM9/B598]. The results suggested that the patient may have PCD; therefore, we performed whole-exome sequencing for him. A novel homozygous variant, c. 7979A >G (p. Asn2660Ser), in *DNAH5* (NM_001369.3) was identified [Figure 1B]. Although the variant is located in exon 48, the splicing prediction software (Varseak, https://varseak.bio/index.php) analysis suggested that this variant may cause abnormal splicing. We extracted RNA from the airway mucosa of the patient and validated its splicing effect (r.7977_8012del, p.Asn2660_Val2671del) [Figures 1C and 1D]. High-speed video analysis (HSVA) showed immotile cilia of the patient [Supplementary Video 1, http://links.lww.com/CM9/B640], and electron microscopy of the cilia showed a significant ODA defect [Figure 1E]. Based on these results, the patient was diagnosed with PCD. Although the patient had one son, we performed a routine semen analysis to verify whether the variant affected reproductive function, and found that the patient's sperm morphology and motility were normal [Figure 1F].

Patient II was a 48-year-old man who had experienced recurrent coughing for more than 40 years. The lung function test showed obstructive impairment (FEV_1/FVC was 69.96% after bronchodilator administration) and restrictive ventilation dysfunction (FEV_1 percent predicted [FEV_1 pred%] of 42.9%). The patient's nNO was 2.4 nL/min. CT also showed sinusitis, bronchiectasis, and situs inversus [Figure 1A, Supplementary Figures 1D and 1F, http://links.lww.com/CM9/B598]. Whole-exome sequencing revealed a homozygous variant in exon37 of *DNAH5*, c.6086G > A (p.Gly2029Asp) [Figure 1B]. The patient had two offspring and refused any other PCD-related examinations.

PCD is an inherited genetic motile ciliopathy that may present as Kartagener syndrome (sinusitis, bronchiectasis, and situs inversus). To date, more than 50 genes have been found to be related to PCD.[1] PCD is hetergenous and most pathogenic genes have autosomal recessive inheritance, many patients with PCD are found in consanguineous families. *DNAH5* is one of the most common PCD-associated genes. Dynein axonemal heavy chain 5 (DNAH5) is an important component of the ODAs of cilia. Mutations in *DNAH5* cause defects in the ODAs of the cilia, leading to cilia movement dysfunction and resulting in PCD symptoms such as sinusitis, bronchiectasis, and situs inversus.[2] According to guidelines, genetic testing, immunofluorescence, nNO measurement, HSVA, and transmission electron micros-

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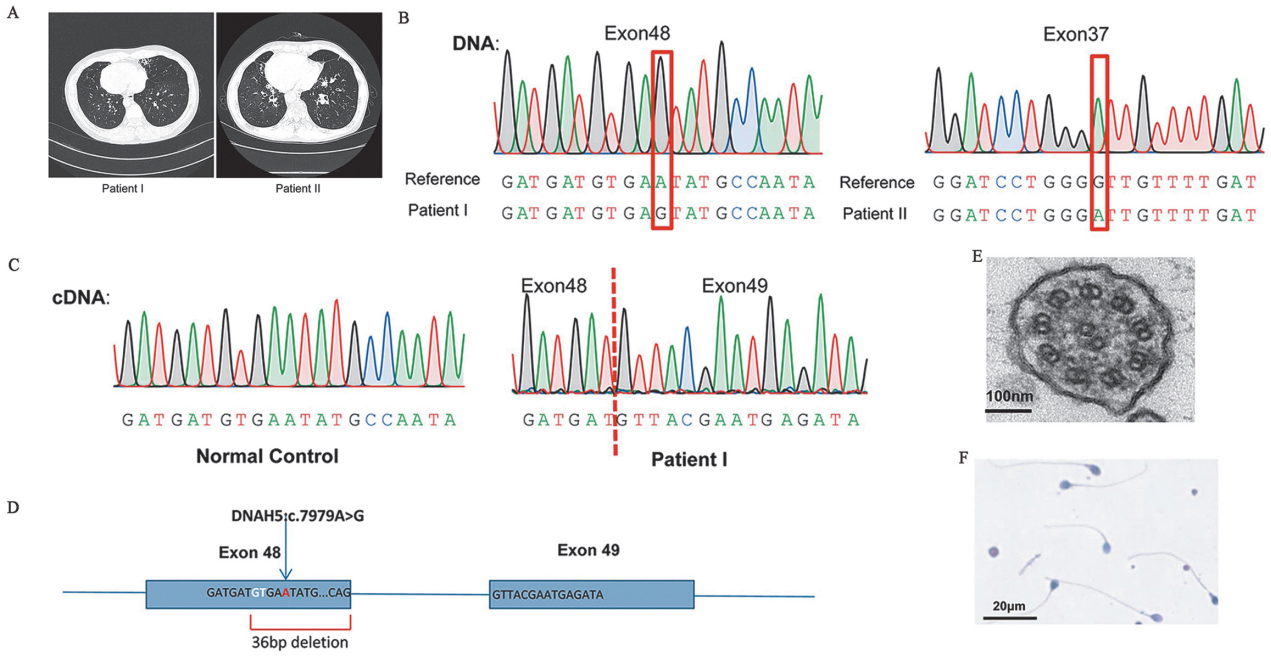

Figure 1: (A) The CT scan of patients showed bronchiectasis and situs inversus. (B) The result of the Sanger sequencing for two patients. (C) The cDNA sequence of patient I and normal control. (D) The variant c.7979A>G caused a 36-bp deletion of *DNAH5* RNA. (E) Transmission electron microscopy showed an outer dynein arm defect of the patient's cilia. (F) Sperm morphology and motility are normal in Patient I. cDNA: Complementary DNA; CT: computed tomography; DNAH5: Dynein axonemal heavy chain 5.

copy (TEM) are important diagnostic methods for PCD.[3] In our Patient I, the results of nNO, HSVA, TEM, and genetic testing confirmed the diagnosis of PCD. Patient II had significantly reduced nNO levels and a homozygous variant of *DNAH5*, which also suggested a diagnosis of PCD.

Infertility is a common symptom of PCD due to the dysfunction of sperm flagella. However, in the previous literature, it is rare to see patients with *DNAH5* variants with infertility problems. Consistent with most of the *DNAH5* cases reported previously, both of our patients had offspring without assisted reproductive technology. Routine semen analysis is the most common way to assess male reproductive function; however, many factors affect this examination.[4] Accidental semen routine abnormalities are common in healthy individuals, and repeated experiments are important in determining infertility.

Whole-exome sequencing is a popular objective method to identify inherited diseases, especially PCD. With the development of sequencing technology and cost reduction, genetic testing is becoming an important method for PCD diagnosis in bronchiectasis patients.[5] Measurement of nNO is an acceptable non-invasive examination for most patients. Most patients with PCD have low levels of nNO. Immunofluorescence, HSVA, and TEM are important examinations for PCD diagnosis that can directly detect defects in the cilia. As these examinations require invasive access to the respiratory mucosa, many patients do not accept them. Furthermore, not all hospitals are equipped with relevant examination equipment, increasing the difficulty of diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patients consent forms. In the form, the patients have given consent for their images and other clinical information to be reported in the journal.

Conflicts of interest

None.

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