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Case Report

Severe bronchiectasis and chronic rhinosinusitis due to homozygous *WFDC2* Variants: The first three cases reported from Japan

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ABSTRACT

We report three cases of bronchiectasis caused by homozygous *WFDC2* variants. The ages at diagnosis of bronchiectasis were 18, 24, and 16 years, and all patients had a history of chronic sinusitis since childhood. Despite low nasal nitric oxide levels, the radiologic features resembled those of cystic fibrosis, characterized by bronchiectasis predominantly in the upper lobes. All patients experienced frequent exacerbations and respiratory dysfunction, even with long-term macrolide therapy. Consequently, two of the three patients required lung transplantation. Considering the possibility of founder mutations, *WFDC2* variants should be included in diagnostic panels for patients with sinopulmonary disease in Asian populations.

1. Introduction

Refractory chronic airway disease that usually presents with bronchiectasis and chronic rhinosinusitis has historically caused significant clinical and diagnostic challenges due to diverse etiologies and overlapping clinical presentations [1–3]. Over the past decade, next-generation sequencing technology has significantly contributed to understanding several diseases, such as primary ciliary dyskinesia (PCD), primary immunodeficiency, and cystic fibrosis (CF) [4–7]. However, cases with undiagnosed conditions persist, and these cases often present low levels of nasal nitric oxide (nNO) and are preliminarily diagnosed as probable PCD in Japanese settings where CF is rare [8].

WAP four-disulfide core domain 2 (*WFDC2*) variants have recently emerged as a novel cause of severe sinopulmonary disease. It is expressed predominantly in secretory cells of the respiratory epithelium and submucosal glands, and defects in its expression result in deficient antibacterial activity and antiprotease activity [9]. In the original study by Dougherty GW et al., *WFDC2* mutations were shown to resemble CF rather than PCD, presenting nasal polyps and upper lobe predominant bronchiectasis [10].

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A recent study from Korea highlighted a founder mutation of *WFDC2* in the population, with findings similar to those of the original study [11]. Previously, we identified a founder mutation in dynein regulatory complex subunit 1 (*DRC1*) as a possible cause of PCD in Japan and Korea [12], prompting further investigation to identify the same *WFDC2* mutation in our cohort of patients with sinopulmonary disease who remained undiagnosed with PCD or CF.

This case series presents the first three novel cases of *WFDC2*-associated severe sinopulmonary disease in Japan. Through detailed clinical analysis and screening of genetic variants in the entire coding region of *WFDC2* (Fig. 1), we aimed to elucidate the phenotypic spectrum of *WFDC2* variants in Japanese patients, contributing to improved awareness and management of this condition.

2. Case series

2.1. Case 1 (DBC-19804)

A 31-year-old woman was referred to the outpatient clinic for evaluation of PCD. She did not experience any episodes of neonatal respiratory distress (NRD). The patient had undergone surgical treatment for sinusitis at the age of 9 and had been diagnosed with sinopulmonary disease at the age of 18 on the basis of her clinical history of sinusitis and bronchiectasis. She stopped visiting the previous hospital at the age of 27 but restarted long-term macrolide therapy at the age of 31 after being treated for pneumonia. She was not married and did not have a history of smoking. Consanguinity was not noted. No family history was reported except for sinusitis in her grandmother.

Various evaluations were performed at the outpatient clinic. The pulmonary function test revealed a mixed impairment pattern (VC 1.68 L, percent predicted VC 57.3 %, FEV_1 1.15 L, percent predicted FEV_1 66.5 %). A chest computed tomography (CT) scan revealed diffuse bronchiectasis predominantly in the upper lobes and centrilobular shadows in both lung fields (Fig. 2A). The sinus CT scan demonstrated hypoplasia in the maxillary sinus, as well as fluid retention and mucosal thickening in all sinuses (Fig. 2B). Mucoid *Pseudomonas aeruginosa* was repeatedly isolated from sputum cultures.

For the PCD diagnostic test, the nNO level was low at 15.5 nL/min, but electron microscopy revealed a normal ciliary ultrastructure, and no pathogenic variants were identified in our PCD-causative gene panel [13]. Additionally, no cystic fibrosis transmembrane conductance regulator (*CFTR*) mutations were detected. Coding exons (exons 1–3 of NM_006103.4) of *WFDC2* were amplified by PCR from genomic DNA, and Sanger sequencing of the PCR products revealed a homozygous missense variant, NM_006103.4:c.291C>G (p.Cys97Trp), which has a minor allele frequency of 0.000734 in the Japanese population (ToMMo 60KJPN) (https://jmorp.megabank.tohoku.ac.jp/) (Fig. 2C).

For treatment, patients routinely practice airway clearance techniques (ACT), including the active cycle of breathing technique (ACBT) and oscillating positive expiratory pressure (OPEP), along with long-term macrolide therapy. She was referred to a specialized center for lung transplantation.

2.2. Case 2 (DBC-21410)

A 42-year-old woman was referred to our hospital for the treatment of severe bronchiectasis. She did not experience unexplained

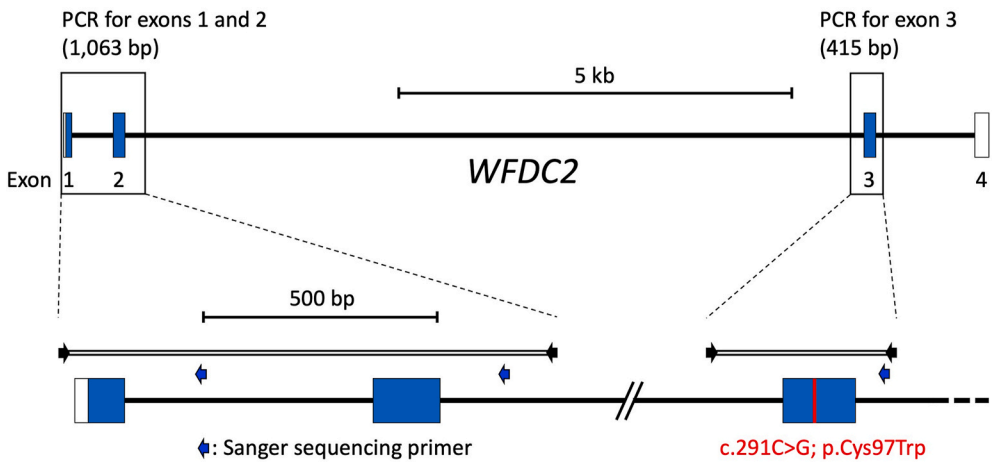

Fig. 1. PCR amplification and Sanger sequencing of the *WFDC2* coding region.
The nucleotide sequence of the entire *WFDC2* coding region (indicated by blue boxes) was analyzed using PCR-direct Sanger sequencing. Exons 1 and 2 were amplified from genomic DNA by PCR with primers 5′-GCGGTTAAATCCCCGCACCTGAGC-3′ and 5′-AGCCCGTCATGCACCAGAGACTCG-3′, and the PCD product (1063 bp) was sequenced using primers 5′-CTCTCCACCTCCAGCACATTGGAC-3′ and 5′-ACTGACGGATCTGGTTTCAACCGC-3′. Exon 3 was amplified with primers 5′-GATCTTCCTGGGCCTCCTGAGAGC-3′ and 5′- CTAACCTCCCTTCACCTCCGCCTG-3′, and the PCR product (415 bp) was sequenced using the primer 5′-CCGCCTGGGTGACGTTTTCTCCTG-3′. A red vertical line in exon 3 marks the position of the variant NM_006103.4:c.291C>G (p.Cys97Trp).

NRD at birth. The patient had been diagnosed with bronchiectasis when she was 24 years old. Since then, she has undergone long-term macrolide therapy. She has also received multiple courses of oral and intravenous antibiotics to treat bronchiectasis exacerbations. She was also diagnosed with bronchial asthma a few months after birth. Additionally, she had undergone surgical treatment for chronic sinusitis three times, but detailed information about these procedures was unavailable. She had no history of smoking. The patient was married but had no children. There was no consanguinity. She reported a family history of respiratory disease in her grandfather, but specific details were not available.

On admission, carbapenem-resistant *P. aeruginosa* was isolated from her sputum culture, whereas mycobacteria were negative. Pulmonary function tests revealed obstructive impairment (VC 2.66 L, percent predicted VC 82.6 %; FEV_1 1.28 L, percent predicted FEV_1 52.0 %). Chest CT scans revealed diffuse bronchiectasis predominantly in the right upper lobe (Fig. 2A). Sinus CT revealed dense opacities in the maxillary sinus and sphenoid sinus and hypoplasia in the maxillary sinus, likely due to past surgical procedures. Additionally, the frontal sinus was aplastic (Fig. 2B). Arterial blood gas analysis revealed slight increases in carbon dioxide levels (pH 7.420, pO2 90.2 mmHg, pCO2 47.2 mmHg, HCO3 28.3 mmol/L, BE 3.3 mmol/L). The immunoglobulin levels were within normal ranges (IgG 2358 mg/dL, IgA 219 mg/dL, IgM 95 mg/dL). The 6-min walking test revealed a distance of 381 m, with the lowest oxygen saturation level of 92 %.

For the PCD diagnostic test, the nNO level was low at 10.2 nL/min, but electron microscopy revealed a normal ciliary ultrastructure. No pathogenic variants were identified in PCD-associated genes or in *CFTR* gene. PCR and Sanger sequencing of the genomic DNA revealed the same homozygous missense variant of *WFDC2* (p.Cys97Trp) (Fig. 2C).

For the treatment plan, we prioritized intensive ACT and rehabilitation and proposed lung transplantation as a definitive intervention. Additionally, voriconazole (VRCZ) was prescribed to treat chronic *Aspergillus* pulmonary disease on the basis of *Aspergillus fumigatus* isolation and corresponding radiological findings. During her admission, no exacerbations occurred, and she successfully underwent lung transplantation at a specialized center three months after admission.

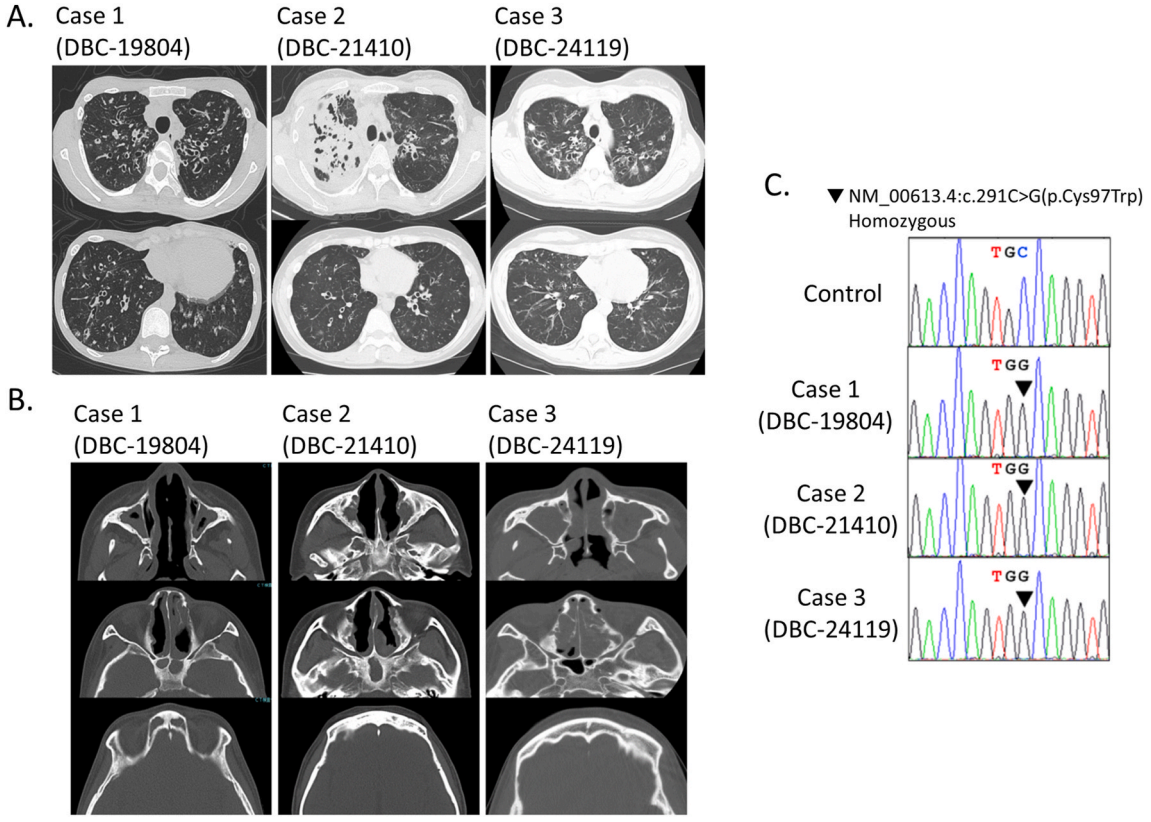

Fig. 2. (A) Chest computed tomography revealed diffuse bronchiectasis, predominantly in the upper lobe.
(B) Sinus computed tomography revealed severe sinusitis, characterized by fluid retention and mucosal thickening in all sinuses, as well as hypoplasia or aplasia.
(C) Electropherograms of Sanger sequencing of *WFDC2* gene.
The electropherogram generated by Sanger sequencing identified a single peak of G nucleotide in all three cases at C-nucleotide position in the control sample, which was homozygous/hemizygous missense variant NM_006103.4:c.291C>G (p.Cys97Trp). The black triangle indicates the position of the variant. Although hemizygosity in the affected individual could not be completely ruled out, the presence of a large deletion with a high allele frequency is unlikely in the Japanese population.

2.3. Case 3 (DBC-24119)

A 34-year-old woman was referred to the outpatient clinic for evaluation of PCD. She had no history of NRD at birth. The patient underwent surgery for chronic sinusitis at the age of 10. At the age of 16, she was hospitalized due to hemoptysis and was subsequently diagnosed with bronchiectasis. Since then, she has been receiving long-term macrolide therapy. Her medical history was notable only for sinopulmonary disease, and she did not have a history of smoking. There was no history of consanguinity in her parents. Her older brother was also diagnosed with bronchiectasis, but neither her parents nor her younger brother had any respiratory diseases. It was unclear whether she was infertile.

When she was referred to the outpatient clinic, she underwent various evaluations. Her blood test results revealed no evidence of a specific cause of bronchiectasis: immunoglobulin levels were within the normal range (IgG 2064 mg/dL, IgA 537 mg/dL, IgM 148 mg/dL, and IgE 48 IU/mL), and *A. fumigatus*-specific IgE was negative. Pulmonary function tests revealed a mixed impairment pattern (VC 1.95 L, percent predicted VC 55.9 %, FEV_1 1.90 L, percent predicted FEV_1 39.4 %). Her chest CT scans revealed diffuse bronchiectasis, predominantly in the upper lobes and proximal airways. Cystic bronchiectasis was observed in her upper lobes, whereas cylindrical bronchiectasis, mucus plugging, and multiple centrilobular nodules were observed in her lower lobes (Fig. 2A). Sinus CT scans revealed aplasia of the frontal sinus (Fig. 2B). Mucoid *P. aeruginosa* and methicillin-sensitive *Staphylococcus aureus* were cultured from her sputum samples.

For the PCD diagnostic test, the nNO level was low at 48.9 nL/min. Electron microscopy revealed a normal ciliary ultrastructure. There were no pathogenic variants in PCD-associated genes or *CFTR* gene. PCR and Sanger sequencing of the genomic DNA revealed the same homozygous missense variant of *WFDC2* (p.Cys97Trp) (Fig. 2C).

For treatment, she continued long-term macrolide therapy. We introduced ACT and recommended routine vaccinations.

3. Discussion

In the present study, as hypothesized, *WFDC2* variants (c.291C>G; p.Cys97Trp; homozygous) were identified in our cohort, suggesting that this variant may be the founder mutation in Japanese patients, as it is in Korean patients. All patients exhibited similar clinical phenotypes, including chronic rhinosinusitis, chronic *P. aeruginosa* infection, low nNO levels, upper lobe predominant bronchiectasis resembling CF, and severe respiratory dysfunction. These findings align with previously reported cases. This is the first report on nNO levels in Asian patients with *WFDC2*-related bronchiectasis. Importantly, while long-term macrolide therapy was introduced, all patients underwent multiple courses of antibiotic treatment and developed respiratory failure, with two patients requiring lung transplantation. These findings underscore the importance of early diagnosis using genetic testing for bronchiectasis caused by *WFDC2* variants, as well as for PCD and CF, and emphasize the need for appropriate management at tertiary care hospitals.

Together with the previously reported case series, the male-to-female ratio was approximately 50:50, and the median age at testing for *WFDC2* deficiency was 31 (interquartile range [IQR] 22–46) years (Table 1). All patients had a history of chronic sinusitis, and 64.3 % also experienced otitis media. The median nNO level was extremely low at 13.8 (IQR 9.0–17.1) nL/min. Although none of our three patients had a history of NRD, three patients in a previous report from the United States experienced unexplained NRD. In addition, *WFDC2* variants are potentially associated with female infertility. In contrast, no cases of male infertility have been reported. The mechanisms of female infertility in patients with *WFDC2* variants remain unclear, and the number of reported female infertility cases is limited to only three. To clarify the association between *WFDC2* variants and infertility, further studies with a larger number of patients, as well as detailed urological and gynecological evaluations, are needed.

The p.C97W mutation disrupts a critical disulfide bond with C109 and alters the structural configuration of WFDC2, leading to misfolding [11]. Although WFDC2 is a protein known to possess antimicrobial activity [14], the pathogenic role of *WFDC2* variants, independent of respiratory infections, in the development of bronchiectasis remains unclear. In a previous report, investigation of the ciliary integrity and mucociliary clearance capacity of *WFDC2*-deficient respiratory epithelium revealed that the ciliary beat frequency, ciliary ultrastructure, ciliary length, and mucociliary clearance were within the normal range [10]. In individuals with *WFDC2* variants, the secretion of WFDC2 in saliva, seminal fluid, and airway surface liquid is significantly reduced, accompanied by decreased serum concentrations of WFDC2 [10]. These findings suggest that assessing *WFDC2* expression through saliva and blood tests could serve as a valuable tool for screening and differential diagnosis. Thus, early diagnosis of *WFDC2*-related bronchiectasis may become feasible. Furthermore, timely intervention with protein replacement therapy could improve patient outcomes.

In 2016, we started a PCD clinic, and approximately 230 patients underwent diagnostic tests. Among the 31 patients with low nNO levels (<77 nL/min) but no PCD or CF gene mutations, three (9.7 %) were identified homozygous missense variant of *WFDC2*. According to the short-read whole-genome sequencing-based variant database of approximately 60,000 Japanese individuals (ToMMo 60KJPN), the allele frequency of the *WFDC2* variant (c.291C>G; p.Cys97Trp, chr20:45,480,009 C>G, rs780739822) is 0.000734 [15] (https://jmorp.megabank.tohoku.ac.jp/). This suggests that *WFDC2* variants should be included in the diagnostic workup for patients with chronic sinopulmonary disease, alongside PCD panels, particularly in Japanese and Korean populations. In April 2024, the Japanese government designated PCD as a refractory disease, and patients can now receive various forms of support, including medical fee assistance. Because *WFDC2* variants are associated with a more severe clinical course, patients with *WFDC2* variants require strong support from medical and social systems.

We identified the first three cases with *WFDC2* variants in Japan. The bronchiectasis caused by *WFDC2* variants (p.Cys97Trp) exhibited chronic rhinosinusitis since childhood, low nNO levels, upper lobe predominant bronchiectasis and severe respiratory dysfunction. Further research involving other Japanese cohorts is warranted to generalize and conduct more detailed findings and geographical analysis. Because *WFDC2* variants cause severe bronchiectasis in young individuals, the development of specific drugs

Table 1

Literature review on clinical findings in patients with *WFDC2* variants, including the present cases.

DBC-19804, DBC-21410, and DBC-24119 were cases from Fukujuji Hospital in Japan. UNC-376 II1, OP-2147 II1, OP-2032 II1, OP-1837 II1, OP-4281 II1, UNC-231 II1, OP-398 II1, UNC-186 II1, UNC-186 II2, CSU-150 II2, and OP-4474 II1 were reported from the United States[10]. P1946-21, P1969-21, P2678-21, P2783-21, P5-21, and P5-22 were reported from Korea[11].

hom = homozygous; het = heterozygous; F = female; M = male; N/A = data not available

*We calculated median age at testing for *WFDC2* variants under the assumption that P1946-21 was 31 years old, P1969-21 was 36 years old, P2678-21 was 46 years old, P2783-21 was 31 years old, P5-21 was 21 years old, and P5-22 was 21 years old.

	WFDC2 variants	Age at testing for *WFDC2* variants	Sex	Bronchiectasis	Neonatal respiratory distress	Sinusitis	Otitis media	Nasal nitric oxide (nL/min)	Percent predicted FEV_1 (%)	*P. aeruginosa*	Infertility	Lung transplant
Number of cases (%) or median [IQR]		31 [22, 46]*	Female 11/20 (55)	17/18 (94.4)	3/6 (50)	20/20 (100)	9/14 (64.3)	13.8 [9.0, 17.1]	52 [29, 67]	15/15 (100)	Total 3/5 (60), Male 0/2 (0), Female 3/3 (100)	5/20 (25)
DBC-19804 (Case 1)	c.291C>G; p. Cys97Trp; hom.	31	F	Yes	No	Yes	Yes	15.5	66.5	Yes	N/A	No
DBC-21410 (Case 2)	c.291C>G; p. Cys97Trp; hom.	42	F	Yes	No	Yes	Yes	10.2	52.0	Yes	N/A	Yes
DBC-24119 (Case 3)	c.291C>G; p. Cys97Trp; hom.	34	F	Yes	No	Yes	No	48.9	39.4	Yes	N/A	No
UNC-376 II1	c.2T>A; p.Met 1?; het. deletion, het.	22	F	Yes	N/A	Yes	Yes	16.8	73	Yes	N/A	No
OP-2147 II1	c.145T>C; p. Cys49Arg; hom.	30	M	Yes	Yes	Yes	Yes	5.5	79	Yes	No	No
OP-2032 II1	c.145T>C; p. Cys49Arg; het. deletion exon 1–2; het.	14	M	Yes	N/A	Yes	Yes	5.3	67	Yes	N/A	No
OP-1837 II1	c.145T>C; p. Cys49Arg; hom.	52	M	Yes	N/A	Yes	No	16.6	N/A	Yes	N/A	No
OP-4281 II1	c.145T>C; p. Cys49Arg; hom.	19	M	Yes	N/A	Yes	No	2.3	38	Yes	N/A	No
UNC-231 II1	c.145T>C; p. Cys49Arg; hom.	52	F	Yes	Yes	Yes	No	33.7	41.6	Yes	Yes	No
OP-398 II1	c.145T>C; p. Cys49Arg; het. c.271G>A; p. Gly91Ser; het.	26	F	N/A	N/A	Yes	Yes	N/A	N/A	N/A	N/A	No
UNC-186 II1	c.145T>C; p. Cys49Arg; het. c.307T>C; p. Cys103Arg; het.	46	M	Yes	Yes	Yes	Yes	10.8	64	Yes	No	No
UNC-186 II2	c.145T>C; p. Cys49Arg; het. c.307T>C; p. Cys103Arg; het.	51	F	Yes	N/A	Yes	Yes	17.8	25	Yes	Yes	Yes
CSU-150 II2	c.307T>C; p. Cys103Arg; hom.	48	F	Yes	N/A	Yes	No	12	22	Yes	Yes	No
OP-4474 II1	c.326G>A; p. Cys109Tyr; hom.	7	M	No	N/A	Yes	Yes	N/A	67	N/A	N/A	No

(*continued on next page*)

Table 1 (*continued*)

	WFDC2 variants	Age at testing for *WFDC2* variants	Sex	Bronchiectasis	Neonatal respiratory distress	Sinusitis	Otitis media	Nasal nitric oxide (nL/min)	Percent predicted FEV_1 (%)	*P. aeruginosa*	Infertility	Lung transplant
P1946-21	c.291C>G; p. Cys97Trp; hom.	31–35	M	N/A	N/A	Yes	N/A	N/A	N/A	N/A	N/A	No
P1969-21	c.291C>G; p. Cys97Trp; hom.	36–40	F	Yes	N/A	Yes	N/A	N/A	29	Yes	N/A	Yes
P2678-21	c.291C>G; p. Cys97Trp; hom.	46–50	F	Yes	N/A	Yes	N/A	N/A	21	Yes	N/A	Yes
P2783-21	c.291C>G; p. Cys97Trp; hom.	31–35	F	Yes	N/A	Yes	N/A	N/A	22	Yes	N/A	Yes
P5-21	c.291C>G; p. Cys97Trp; hom.	21–25	M	Yes	N/A	Yes	N/A	N/A	85	N/A	N/A	No
P5-22	c.291C>G; p. Cys97Trp; hom.	21–25	M	Yes	N/A	Yes	N/A	N/A	71	N/A	N/A	No

targeting this variant is encouraged, in addition to ongoing efforts to treat PCD.

CRediT authorship contribution statement

Masashi Ito: Writing – original draft, Visualization. **Kozo Morimoto:** Writing – original draft, Project administration, Conceptualization. **Minako Hijikata:** Writing – review & editing, Visualization, Investigation, Data curation. **Hirotsugu Hasegawa:** Resources. **Keiko Wakabayashi:** Investigation. **Akiko Miyabayashi:** Investigation. **Naoto Keicho:** Writing – review & editing, Conceptualization.

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Declaration of competing interest

The authors state that they have no conflicts of interest.

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