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CASE REPORT

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X -linked inheritance of primary ciliary dyskinesia and retinitis pigmentosa due to *RPGR* variant: A case report and literature review

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Abstract

Bronchiectasis is a chronic respiratory condition characterized by irreversible bronchial dilation, often caused by infection or inflammation. It can be associated with primary ciliary dyskinesia (PCD), a hereditary disorder affecting cilia function in various organs and flagella. PCD's genetic heterogeneity leads to varying disease severity. PCD may be more prevalent in Asia, but its diagnosis is often delayed in Japan. This study reviewed a case of PCD and retinitis pigmentosa (RP) with the relevant literature. The patient had a persistent cough, sputum, and diffuse bronchiectasis. He was diagnosed with a combination of PCD and RP, with the presence of an X-linked retinitis pigmentosa GTPase regulator (*RPGR*) variant confirmed through electron microscopy, retinal scan, and genetic testing. Although co-occurrence of bronchiectasis and RP is rare, PCD should be considered in cases of persistent wet cough in childhood or unidentified bronchiectasis aetiology. Ophthalmologists should consider concomitant PCD in RP patients.

KEYWORDS
bronchiectasis, inherited retinal dystrophy, primary ciliary dyskinesia, retinitis pigmentosa, retinitis pigmentosa GTPase regulator

INTRODUCTION

Bronchiectasis is characterized by excessive mucus production, causing bronchial dilation. It affects approximately 350,000–500,000 individuals in the United States,[1] with an annual incidence of 7 per 1000 individuals aged 65 and older.[2] The potential causes of bronchiectasis include nontuberculous mycobacteria, diffuse panbronchiolitis, sinus bronchial syndrome, childhood lung infections, and cystic fibrosis. Diagnostic algorithms utilizing nasal nitric oxide (NO) measurements, high-speed video microscopy (HSVM), transmission electron microscopy (TEM), and genetic testing, can aid in the diagnosis of primary ciliary dyskinesia (PCD),[3] although diagnostic criteria remain unclear in Japan. Non-specific bronchiectasis symptoms, including chronic cough and sputum contribute to delayed diagnosis, and the underlying cause may remain unknown. We present a case of PCD suspected based on the presence of juvenile bronchiectasis and retinitis pigmentosa (RP), revealing a retinitis pigmentosa GTPase regulator (*RPGR)* gene abnormality.

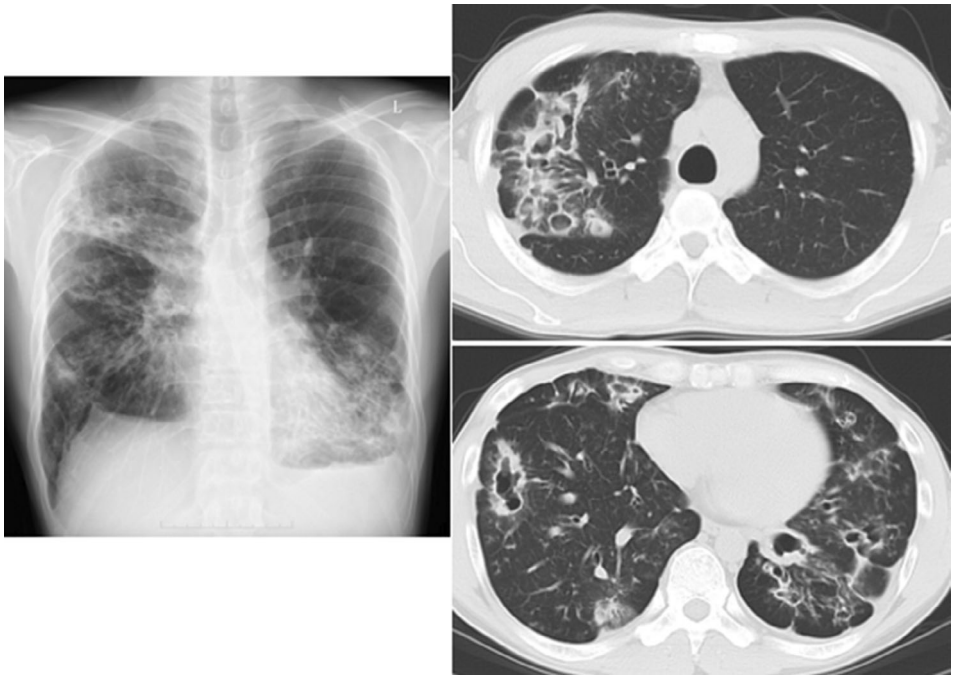

FIGURE 1 Chest radiograph and computed tomography. Prominent bronchiectasis was observed predominantly in the right upper lobe and both lower lobes of the lungs. Some cases of bronchiectasis exhibit cystic dilatation and contain mucous plugs.

There are few reports of PCD and RP co-occurrence and we include six further reported cases.

CASE REPORT

A 32-year-old male presented with a chronic, productive cough. He was diagnosed with RP due to night blindness before entering elementary school, similar to his maternal grandfather. Aged 8 years, he developed a persistent cough with sputum and was diagnosed with bronchiectasis. He also experienced recurrent bilateral otitis media. He resumed regular visits to our hospital after undergoing sinus surgery, aged 32 years.

Chest computed tomography (CT) revealed marked diffuse bronchiectasis in both lungs (Figure 1), and the patient experienced a persistent cough, green sputum, and intermittent low-grade fever. Bronchoscopy was performed; the bronchial lavage fluid was neutrophil-dominant with no predominant bacteria. A dose of 600 mg/day of erythromycin was initiated, and the sputum and fever mildly improved. Blood tests were performed every 3 months, and the C-reactive protein (CRP) levels remained between 2 and 3 mg/L. Over a period of 2 years, the cough became more severe, and CRP levels were consistently 5–6 mg/L. The patient's weight fell from 65 to 54 kg over 5 years. CT revealed worsening bronchiectasis and worsening of the wet cough disrupted daily life. PCD was suspected based on the RP and worsening juvenile bronchiectasis. Nasal NO measurement is available in limited facilities in Japan,[4,5] therefore, a morphological examination of the respiratory cilia was used as a PCD screening tool. The mucosa was surgically harvested from both inferior turbinates. TEM of the samples revealed sparse cilia with interspersed microvilli in the longitudinal section of the epithelial cell layer.

The absence of outer dynein arms (ODA) in most microtubule doublets and inner dynein arms (IDA) in all microtubule doublets was observed (Figure 2A). There were disruptions of the 9 + 2 symmetry of the microtubules and the absence of the whole part of the IDA structure from all the microtubular doublets (Figure 2B). According to the 'international consensus guideline for reporting transmission electron microscopy results in the diagnosis of primary ciliary dyskinesia', these abnormalities are categorized as Class 1 defects, strongly suggesting PCD.[6]

As the patient had young children and desired further testing for future planning, he was referred to the Center for Medical Genetics at Keio University School of Medicine to determine the causative gene and then to the Initiative on Rare and Undiagnosed Diseases (IRUD), led by the Japan Agency for Medical Research and Development (AMED), that diagnoses rare, intractable, and new diseases through genetic testing, where conventional medical methods are ineffective.[7] Blood samples were collected and genomic deoxyribonucleic acid (DNA) was extracted from the whole blood. Genomic DNA was enriched for target regions using the Twist Comprehensive Exome Panel (Twist Bioscience, San Francisco, United States), and exome sequencing was performed using NovaSeq 6000 (Illumina Inc., San Diego, United States). Exome analysis identified a heterozygous *RPGR* variant (NM_001034853.2), that is, c.1234C > T, p.(Arg412Ter). The presence of this nonsense variant was confirmed using Sanger sequencing.

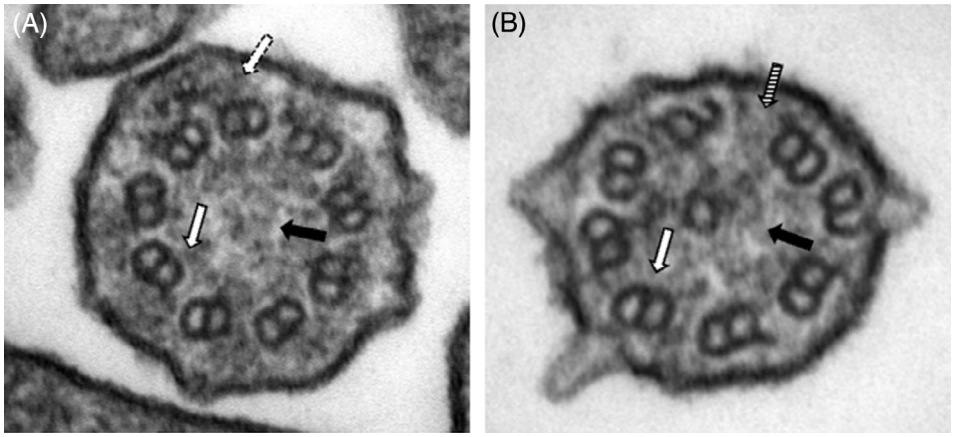

FIGURE 2 Electron micrographs of transverse sections of the axonemes of the patient's nasal cilia (×200,000). (A) Absence of outer dynein arms (ODA, dashed white arrow) in seven of the nine outer microtubule doublets and of inner dynein arms (IDA, white arrow) in all nine outer microtubule doublets. There is also a complete loss of central microtubules (black arrow). (B) Disruptions of the 9 + 2 symmetry of the microtubules (hatched arrow) and absence of the whole part of the IDA structure from all the microtubular doublets (white arrow). There is also a partial loss of central microtubules (black arrow).

This rare variant is registered as pathogenic in ClinVar[8] and has not been reported in gnomAD or any representative Japanese database.

Given the progression of respiratory symptoms, a PCD diagnosis is plausible. At present, the pulmonary function remains intact; however, the patient is amenable to various future medical interventions, such as vaccination, physical rehabilitation, nutritional guidance, psychological counselling, and lung transplantation, if necessary.

DISCUSSION

We diagnosed a 38-year-old male who had been diagnosed with bronchiectasis and inherited RP in childhood, with PCD. Further investigation revealed that both PCD and RP were caused by X chromosomal *RPGR* gene abnormalities.

PCD is a rare genetic disorder causing abnormalities in flagella and cilia. Typical PCD symptoms include neonatal dyspnoea, an early onset cough, sputum production, recurrent lower respiratory tract infection, bronchiectasis, otitis media, and sinusitis.

Although several algorithms can aid PCD diagnosis using nasal NO measurement, HSVM, TEM, and genetic testing, the diagnostic criteria remain unclear in Asia. Most diagnostic methods are multi-phase and not covered by insurance. Although nasal NO is used for PCD screening elsewhere, this measurement is only available in a few facilities throughout Japan.[4,5] Therefore, TEM is the primary diagnosis method for PCD in Japan.[9]

In patients with suspected PCD, diagnosis can be confirmed through genetic testing. The most common pattern of inheritance is autosomal recessive, although X-chromosome and autosomal dominant inheritances have also been observed. Over 40 PCD-associated genetic variants have been identified.[10] A study of 244 Chinese individuals from 52 studies reported that *DNAH5, DNAH11, CCDC39*, and *CCDC40* were the most frequently detected variants and that the spectrum was similar to that observed in Western countries, except for a higher frequency of HYDIN1 variants. The frequency of PCD in Japan is estimated to be one in 8000–10,000.[9] The PCD gene variant may have a higher prevalence in Asia compared with Europe and the United States.[11] A recent report suggests that PCD is genetically heterogeneous between different ethnicities, and Japanese PCD patients have a characteristic genetic spectrum.[12]

Most patients with PCD develop bronchiectasis, which is common and increasing in incidence in Asia.[13–15] The average age of PCD diagnosis in the Chinese population is 13.1 years, later than the age of diagnosis in Europe (5.3 years).[16] A meta-analysis also showed later PCD diagnosis in Japan, with 46.8% of cases diagnosed at 18 years or older.[9]

Inherited retinal dystrophy (IRD) is a comprehensive term for progressive disorders caused by genetic variants. To date, more than 300 distinct genetic variants have been identified. RP is the most prevalent form of IRD and causes extensive degeneration of photoreceptors and the retinal pigment epithelium. This degeneration results in progressive visual impairment and is the second leading cause of visual impairment in Japan. The frequency of RP is approximately 1 in 4000–5000. The mode of inheritance can be autosomal recessive, autosomal dominant, or X-linked. In 1996, the *RPGR* gene was identified as the causative gene for RP.[17] A genetic panel analysis of 677 Danish individuals with diagnosed or suspected inherited RP revealed that approximately half had some genetic abnormality, with approximately 17% being *RPGR* variants.[8] A study that analysed 1210 Japanese families with IRDs reported that 12% of RP cases were X-linked, with *RPGR* being the causative gene in approximately 67% of cases. Mammalian photoreceptors are equipped with specialized connecting cilia that link their inner and outer segments, where the *RPGR* protein localizes. The mechanism underlying the ocular phenotype in patients with the *RPGR* variant is thought to be due to dysfunction

TABLE 1 Case reports of the co-occurrence of RP and PCD.

No.	Publication	Region/race	Gene	Pedigree of family	References
1	1992	Netherland	RP3 locus (in Xp21.1-p11.4)	Four generations	15
2	2003	USA	NM_001034853.2:c.517G > C	Six generations	16
3	2003	UK	NM_001034853.2:c.789_790del	Four generations	17
4	2006	France	NM_001034853.2:c.572_619 + 9del	Two generations	18
5	2012	Poland	NM_001034853.2:c.154G > A	Seven generations	19,20
6		Australia	NM_001034853.2:c.824G > T	de novo	20
Present case	2023	Japan	NM_001034853.2:c.1234C > T	Three generations	

of the photoreceptors connecting the cilia, and is currently being studied.[18]

The *RPGR* gene was discovered approximately 30 years ago. Although the number of PCD studies has increased in recent years owing to the proliferation of genetic diagnostic techniques, few case reports exist on the co-occurrence of RP and PCD, with only six cases identified to date (Table 1).

In 1980, the nasal cilia in patients with RP who frequently had concurrent sinusitis and bronchiectasis demonstrated microstructural abnormalities under TEM. An X-linked gene was subsequently identified in a family with multiple members with RP, and seven of the 10 affected males had evidence of recurrent respiratory infections or biopsy evidence of PCD.[19] All three affected male members of a family with X-linked RP presented with hearing loss and recurrent infections of the upper respiratory tract.[20] In a family affected by X-linked RP in the UK, three of four impacted male members exhibited a persistent pattern of chest infections from an early age, continuing into adulthood.[21] In a family from France affected by X-linked RP, both impacted male members displayed recurring episodes of bronchitis, sinusitis, and otitis media persisting from an early age.[22] A study of a seven-generation family with X-linked inheritance of both RP and PCD reported that four of the 14 male members with RP were also diagnosed with PCD, suggesting a potential association.[23,24] A 17-year-old male with no family history of RP or PCD exhibited progressive symptoms of RP and diagnostic indications for PCD from age 2 years.[24]

This study presents the case of a 38-year-old male diagnosed with combined PCD and RP caused by an *RPGR* gene variant. Although reports of PCD have increased in recent years, this is the seventh reported case of concurrent PCD and RP. Patients with PCD often reach adulthood without a diagnosis unless they have a typical clinical course, such as requiring neonatal intensive care or experiencing situs inversus. PCD and RP are difficult to treat at present; however, early diagnosis allows the implementation of management strategies that can halt disease progression. The diagnosis rate of PCD may increase if physicians proactively consider PCD as a differential when patients present with a wet cough or bronchiectasis since childhood and if ophthalmologists are aware that PCD may occur in combination with RP.

AUTHOR CONTRIBUTIONS

All the authors have read and approved the final version of the manuscript. Aoi Kuroda wrote the manuscript. Ho Namkoong, Eri Iwami, Akihiro Tsutsumi, and Takahiro Nakajima collected patient information. Ho Namkoong, Hisato Suzuki, and Jiro Iimura made the clinical diagnoses. Hajime Shinoda and Kenjiro Kosaki performed the genetic analyses and genetic counselling of the patient. Ho Namkoong and Takeshi Terashima reviewed and supervised the manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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