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A Rare Presentation of X-Linked Primary Ciliary Dyskinesia Due to Xq22.3 Deletion

Li YAN[1], Yan SU[1], He LI[1]

1 Department of Pulmonary and Critical Care Medicine, Hebei General Hospital, Shijiazhuang, China.

Correspondence to: Li Yan, MD
Department of Pulmonary and Critical Care Medicine, Hebei General Hospital,
No. 348 of Heping West Road, Xinhua District, Shijiazhuang, 050051, China
TEL.: 18032006399; E-MAIL: yanli_hgh@126.com

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Abstract

BACKGROUND: Primary ciliary dyskinesia (PCD) is a rare genetic disorder caused by mutations affecting the structure or function of motile cilia, with more than 50 causative genes identified to date. PCD is predominantly inherited in an autosomal recessive manner; however, X-linked recessive inheritance is exceptionally rare.
CASE PRESENTATION: We report a male pediatric patient with recurrent pulmonary infections, chronic sinusitis, and situs inversus. Genetic analysis identified an approximately 720.3 kb hemizygous deletion in the Xq22.3 region, consistent with a rare X-linked recessive form of PCD.
CONCLUSION: This case highlights the importance of genetic testing for identifying rare PCD variants, facilitating early diagnosis and informing clinical management to improve long-term outcomes.

CASE REPORT

INTRODUCTION

Primary ciliary dyskinesia (PCD) is a genetically heterogeneous disorder of abnormal ciliary motility, predominantly inherited in an autosomal recessive pattern (Stevanovic *et al.* 2021). The estimated prevalence of PCD in the general population is approximately 1 in 20,000 individuals, rising to 5% among children with recurrent respiratory infections (Niziolek *et al.* 2022). PCD is frequently underdiagnosed or misdiagnosed, underscoring the need for accurate diagnostic methods given its multisystem involvement and variable clinical presentation (Horani & Ferkol, 2020). This report describes a rare X linked recessive case of PCD confirmed by genetic testing and aims to increase awareness of uncommon PCD associated genetic variants.

CASE PRESENTATION

First hospitalization: Approximately one month before admission, unexplained exertional dyspnea and chest tightness developed in the absence of fever, cough, sputum production, chest pain, dizziness, or headache. These symptoms were initially not medically evaluated. One week prior, following a cold, he developed cough with white viscous sputum, worsening dyspnea, and reduced exercise tolerance, prompting admission.

Since onset, mental status, appetite, sleep quality, bowel and bladder habits had remained normal, and no significant weight change was reported. The patient had a history of recurrent pulmonary infections and chronic sinusitis during childhood, a transient episode of hearing loss, trauma to the right eye eight years earlier without

permanent sequelae, and surgical treatment of a left humeral injury two years earlier. No known food or drug allergies were reported, and there was no history of tobacco or alcohol use. No relevant familial diseases, infectious conditions, or genetic disorders were documented, and the patient was born to nonconsanguineous parents.

Physical examination upon admission: Body temperature was 36.2 °C, pulse rate 88/minute, respiratory rate 20/minute, and blood pressure was 126/89 mmHg. The patient measured 166 cm in height and was conscious, alert, and cooperative. There were no petechiae on the skin or mucous membranes, no superficial lymphadenopathy, no conjunctival edema or scleral icterus, no lip cyanosis, and the pharynx and tonsils appeared normal.

Pulmonary auscultation revealed coarse breath sounds accompanied by coarse crackles. Dextrocardia was identified, with a regular heart rhythm and normal heart sounds; no murmurs were audible over any valvular auscultation area. The abdomen was soft, without tenderness, rebound tenderness, or guarding. No edema was present in the lower extremities.

Auxiliary examinations: Laboratory investigations showed a white blood cell count of 5.49×10^9/L, hemoglobin level of 178.00 g/L, and platelet count of 336.00×10^9/L. C-reactive protein was measured at 0.28 mg/L, and procalcitonin at 0.03 μg/L. The respiratory pathogen panel, sputum culture, purified protein derivative test, (1,3)-β-D-glucan assay, rheumatoid factor, antinuclear antibody panel, and vasculitis screening were all within normal limits or negative.

Chest computed tomography performed on 14 September 2019 demonstrated diffuse bronchiectasis involving multiple lung lobes with bronchial wall thickening, multiple tree-in-bud opacities along the bronchovascular bundles, and mild bronchiectasis in the right upper lobe and left middle lobe. Situs inversus of the cardiac, pulmonary, and abdominal viscera was also present (Figures 1 and 2).

Pulmonary function testing showed a forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio of 71% and a predicted FEV_1 of 69%, consistent with moderate obstructive ventilatory dysfunction. Total lung capacity and gas exchange functions were within normal limits.

Clinical course: The initial diagnoses were (1) pulmonary infection, (2) suspected bronchial asthma, and (3) suspected PCD. Treatment was initiated with cefoperazone sodium and sulbactam sodium for infection control. Expectorant therapy included Eucalyptol, Lemonene, and Pinene Enteric soft capsules, as well as Fudosteine tablets. Ipratropium bromide was administered via nebulization, along with other supportive measures. Improvement in the clinical condition was observed following treatment, and the patient was discharged.

During the four years following discharge, episodes of coughing and sputum production recurred intermittently, accompanied by easy fatigability and exertional dyspnea, particularly during physical education activities. Symptomatic relief was achieved intermittently with oral medications.

Second outpatient visit: On August 25, 2023, the patient presented to the outpatient clinic with worsening cough and increased sputum production. Pulmonary function tests yielded normal results. Fractional exhaled nitric oxide was 11 nmol/L, and nasal nitric oxide (nNO) was 29 nmol/L, measured using a standardized chemiluminescence analyzer with tidal breathing sampling, which is markedly below the established diagnostic threshold for PCD (<77 nmol/L).

With informed consent obtained from the patient's parents, peripheral blood samples were collected on

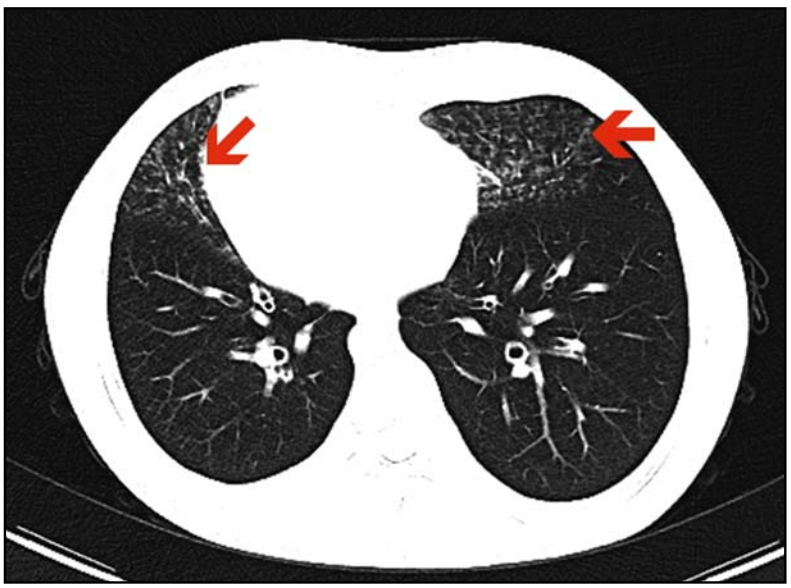

Fig. 1. Chest CT (Hebei General Hospital, September 14, 2019)
Note: The lung window image shows tree-in-bud opacities, as indicated by the arrow.
Axial chest computed tomography (lung window) obtained on 14 September 2019 shows diffuse bronchiectasis with bronchial wall thickening and multiple tree in bud opacities along the bronchovascular bundles; the arrow indicates representative tree in bud lesions.

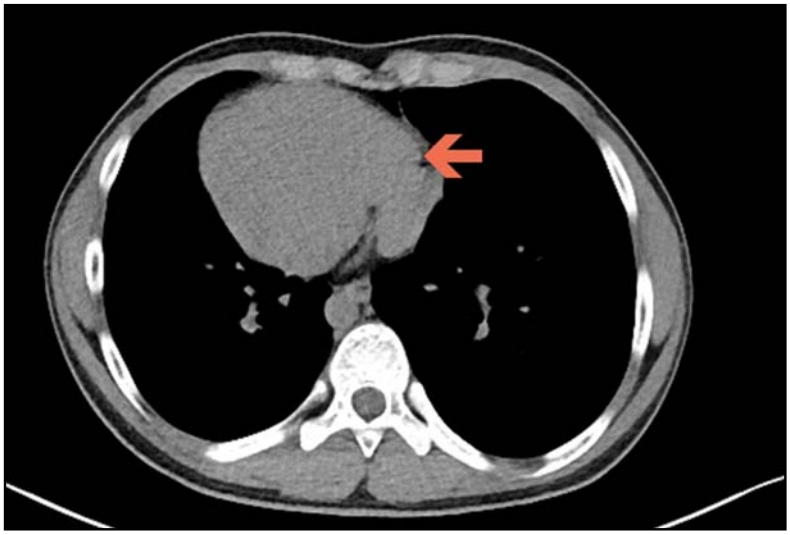

Fig. 2. Chest CT (Hebei General Hospital, September 14, 2019)
Note: The mediastinal window image shows dextrocardia, as indicated by the arrow
Axial chest computed tomography (mediastinal window) obtained on 14 September 2019 demonstrates dextrocardia and situs inversus of the thoracic structures; the arrow highlights the right sided cardiac position.

September 6, 2023, for whole-exome sequencing (WES), supported by a grant from the China Rare Disease Alliance. Whole-exome sequencing was performed on the Illumina NovaSeq 6000 platform with an average coverage depth exceeding 100×. Read-depth–based CNV analysis was conducted using CNVkit (v0.9.9) with GRCh37/hg19 as the reference, and the deletion size (~720.3 kb) was determined by comparing normalized read-depth ratios with control samples.

Peripheral blood genomic DNA was analyzed by whole-exome sequencing on the Illumina NovaSeq 6000 platform, achieving an average on-target coverage depth exceeding 100×. Copy number variation was assessed using a read-depth–based pipeline (CNVkit v0.9.9) with GRCh37/hg19 as the reference genome, and normalized read-depth ratios were compared with control samples to identify regions of copy loss. This analysis revealed an approximately 720.3 kb hemizygous deletion in the Xq22.3 region encompassing DNAAF6, CLDN2, and TBC1D8B. The sequencing report issued on October 10, 2023 documented this deletion (Table 1, Figure 3). Pathogenic variants in the DNAAF6 gene are recognized as causative of X-linked PCD type 36 (Ciliary Dyskinesia, Primary, 36, X-Linked; CILD36) [MIM:300991]. Large copy-number deletions involving the DNAAF6 gene have been reported in multiple individuals diagnosed with PCD (Blanchon *et al.* 2020; Li *et al.* 2022). Based on the gene content and current evidence, this Xq22.3 deletion was classified as a pathogenic variant.

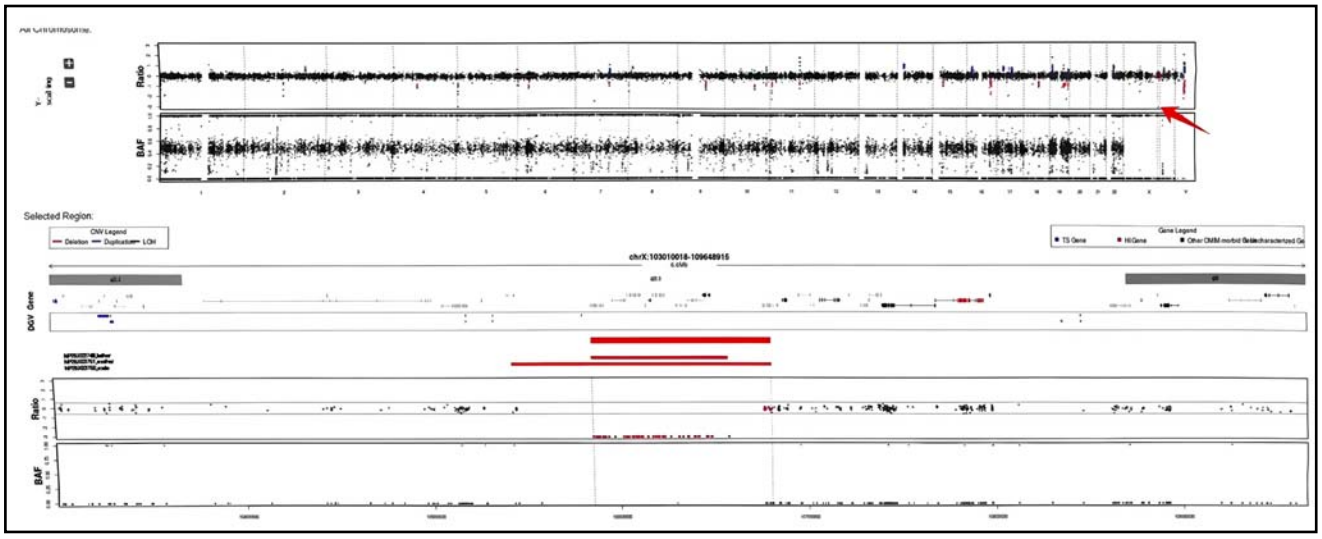

Fig. 3. Copy Number Variation (CNV) plot
Note: The arrow marks a hemizygous deletion in the Xq22.3 chromosomal region.
Read depth–based copy number variation analysis using whole exome sequencing demonstrates a hemizygous deletion in the Xq22.3 region; the arrow marks the segment with reduced normalized read depth corresponding to the ~720.3 kb deletion encompassing DNAAF6, CLDN2, and TBC1D8B.

Tab. 1. Summary of molecular genetic testing results

Chromosomal banding	Variant type	Relevant genes within the region	Related diseases	Source of variation	Variant classification
Xq22.3	hemizygous deletion	*DNAAF6*	X-linked primary ciliary dyskinesia 36 [MIM:300991]	Mother	Pathogenic mutations

Summary of the approximately 720.3 kb hemizygous deletion in the Xq22.3 region, including genomic coordinates, affected genes (DNAAF6, CLDN2, TBC1D8B), variant classification, and key clinical features observed in the patient with X linked primary ciliary dyskinesia.

DISCUSSION

The primary clinical features of PCD include recurrent respiratory tract infections, sinusitis, otitis media, bronchiectasis, situs inversus, infertility, and reduced fertility. The clinical manifestations and imaging findings of PCD are often nonspecific and may be misinterpreted as other respiratory conditions. In this case, initial symptoms included chest tightness, dyspnea, and cough. Pulmonary function testing showed obstructive ventilatory dysfunction, which contributed to an initial differential diagnosis of bronchial asthma in this patient. Therefore, early and definitive diagnosis is essential to minimize the likelihood of misdiagnosis or delayed recognition.

A defining characteristic of PCD is impaired ciliary motility. Motile cilia are located on the apical surface of respiratory epithelial cells, where outer dynein arms generate sliding forces between microtubule doublets. Structural abnormalities of ODA disrupt mucociliary clearance, leading to chronic respiratory infections—consistent with the patient's phenotype.

Motile cilia are also distributed in other organ systems; for example, the ependymal lining of the brain ventricles and the fallopian tubes contain motile ciliated cells. Additionally, the flagella of spermatozoa share a structural core with motile cilia and exhibit similar motility properties (Horani & Ferkol, 2020).

Mutations at distinct genetic loci may influence various anatomical sites, structural components, functional pathways, and the severity of disease manifestations. Currently, nearly 50 gene mutations have been identified as causative of PCD (Legendre *et al.* 2020). Several studies have reported that mutations in *RPGR*, *OFD1*, and *DNAAF6/PIH1D3* may result in X-linked forms of PCD (Thomas *et al.* 2024). The *DNAAF6* gene is critical for the assembly of ODA and a subset of IDA; specific point mutations in *DNAAF6* result in an X-linked form of early-onset PCD, characterized by defective axonemal dynein assembly. This variant is considered relatively rare and typically affects only male individuals carrying the X-linked pathogenic DNAAF6 mutation, resulting in absent ciliary dynein arms. In contrast, female carriers with heterozygous mutations are generally unaffected and usually asymptomatic (Olcese *et al.* 2017). Reports describing such genetic changes remain limited within the Chinese population.

Although large deletions involving DNAAF6 have been reported (Blanchon *et al.* 2020; Li *et al.* 2022), this case presents a previously unreported 720.3 kb deletion spanning DNAAF6, CLDN2, and TBC1D8B. To our knowledge, this exact CNV has not been documented in public databases (such as ClinVar) or in previously reported Chinese cohorts. Additionally, co deletion of CLDN2 (a tight junction protein) and TBC1D8B (a membrane trafficking regulator) may contribute to the patient's chronic sinusitis, an aspect that has been underexplored in prior DNAAF6 related PCD studies.

Beyond DNAAF6, the deletion includes CLDN2 (critical for epithelial barrier function) and TBC1D8B(regulating vesicular transport). While DNAAF6deficiency directly causes ciliary dynein arm defects, CLDN2loss may exacerbate mucosal barrier disruption, worsening sinusitis. TBC1D8Bdeletion could affect ciliary membrane homeostasis, though its role in PCD requires further functional validation.

In this case, an approximately 720.3 kb hemizygous deletion was identified in the Xq22.3 chromosomal region. This deletion affects several functional genes within the locus, including *DNAAF6*, *CLDN2*, and *TBC1D8B*. The pathogenic variant in *DNAAF6* is associated with CILD36 (Ciliary Dyskinesia, Primary, 36, X-linked), indicating that a copy number deletion at this site disrupts gene structure and function, ultimately resulting in disease. Core clinical features of CILD36 include chronic airway disease, recurrent sinusitis, and pulmonary infections beginning in childhood due to defective ciliary motility. Infertility from sperm flagellar abnormalities is also commonly observed, and approximately half of affected patients present with situs inversus or heterotaxy.

Additional cilia-related genes located in the Xq22.3 region include *OFD1*. Mutations in *OFD1* are typically associated with oral-facial-digital syndrome type I, an X-linked dominant disorder that is frequently lethal in male embryos; thus, most surviving patients with this condition are female. Growth retardation during childhood has been noted in certain patients with PCD, particularly among those harboring mutations in *DNAH5* or *DNAI1* (Svobodová *et al.* 2013). The 19 year old patient described in this report, with a height of 166 cm, demonstrates relatively short stature that may be related to underlying PCD.

Early and accurate diagnosis remains challenging due to the rarity of PCD and its nonspecific clinical presentation. Available diagnostic methods include transmission electron microscopy (TEM), assessment of ciliary beat frequency and pattern, nNO measurement, and genetic testing. Limited access to TEM and ciliary motion analysis in many facilities often hinders confirmation, whereas genetic testing provides a valuable tool for earlier identification of PCD. This case illustrates how combining a characteristic PCD phenotype with markedly reduced nasal nitric oxide and confirmatory genetic testing for a DNAAF6 containing Xq22.3 deletion aligns with current stepwise PCD diagnostic algorithms that integrate clinical features, nNO measurement, and molecular analysis. Currently, pathogenic variants in more than 50 genes have been identified, accounting for approximately 60% of PCD cases (Horani *et al.* 2013). As genetic testing technologies become more accessible and widely adopted, increased use may facilitate earlier recognition of PCD, thereby reducing the frequency of missed or delayed diagnoses.

In clinical practice, patients with recurrent, long standing respiratory infections accompanied by situs inversus should be carefully assessed, and PCD should be considered in the differential diagnosis. Early diagnostic confirmation through genetic testing or ultrastructural examination of respiratory mucosa is essential for timely intervention and may help prevent or delay disease related complications. As genetic testing technologies advance, further progress in genomics is expected to support development of targeted therapies for specific PCD associated gene variants.

FUNDING

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