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CASE SERIES

Two Distinct Clinical Presentations of Primary Ciliary Dyskinesia (PCD): Diagnostic Utility of Whole-Exome Sequencing in a Genetically Heterogeneous Disorder

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Abstract: Primary ciliary dyskinesia (PCD) is a rare, genetically heterogeneous disorder with variable clinical presentation. In cases where traditional diagnostic tools such as transmission electron microscopy (TEM) or nasal nitric oxide (nNO) measurement are inconclusive/unavailable, molecular diagnostics via whole-exome sequencing (WES) may provide essential insights. In this case report, we present two male infants with diverse phenotypes and genotypes. 1st patient was ultimately diagnosed with PCD thanks to WES, while 2nd patient was strongly suggestive of PCD. The 1st patient portrayed in his clinical history symptoms such as perinatal respiratory distress, situs inversus, and recurrent otitis media. He was found to carry a known pathogenic homozygous variant c.461A>C (p.His154Pro), in the *CCDC103* gene. The second patient exhibited more complex phenotype, including diaphragmatic hernia, absence of the pericardium, significant delay in the motor development. WES identified two variants in both *DNAH5* and *DNAH9*. Parental testing identified the maternal origin for the c.10243-6C>T (p.?) and c.308del (p.Phe103Serfs*31) variants in the *DNAH9* gene and a paternal origin for the c.1206T>A (p.Asn402Lys) variant in the *DNAH5* gene. The second variant c.5124G>T (p.Glu1708Asp) in the *DNAH5* gene in the proband arose de novo. At the time of analysis, these variants were classified as variants of uncertain significance (VUS) or likely benign, with limited segregation data and no definitive functional validation. Although the genetic findings were not diagnostic on their own, the clinical picture (situs inversus, neonatal respiratory distress, recurrent infections) was strongly suggestive of PCD. Both cases illustrate the crucial role of WES in establishing a molecular diagnosis of PCD, particularly when the use of traditional diagnostic methods is inconclusive. Moreover, they demonstrate the value of genomic testing in guiding the clinical management and informing about prognosis in diseases like PCD.

Keywords: DNAH5, DNAH9, CCD103, WES, pediatric

Introduction

Primary ciliary dyskinesia (PCD) is a rare, genetically heterogeneous disorder characterized by defective motility of the respiratory cilia.[1] This impairment leads to symptoms such as chronic respiratory tract infections, chronic sinusitis, otitis media, conductive hearing impairment, and bronchiectasis. It is often associated with situs inversus (about 50% patients with PCD) or heterotaxy (up to 12% of patients with PCD).[1,2] In the majority of individuals diagnosed with PCD, respiratory distress is evident shortly after birth, even in the cases of full-term delivery. This triggers the need for a prolonged oxygen supply due to hypoxaemia.[1]

The prevalence of PCD is estimated between 1 in 2000 and 1 in 40,000 live births, but according to some sources it is underdiagnosed.[3] Its frequency is notably higher in Europe and it is estimated to affect between 1 in 10,000 and 1 in 15,000 patients.[1]

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Currently, mutations in more than 40 genes have been implicated in the pathogenesis of PCD, involving genes encoding different proteins (axonemal, cytoplasmic or regulatory proteins. These proteins are essential for ciliary structure and function.[4] Among the most frequently mutated genes in PCD is the *DNAH5* gene, which accounts for approximately 15–28% of genetically confirmed cases in two original cohort studies.[1,5,6] Mutations in this gene typically disrupt the outer dynein arms, which are crucial for effective ciliary beating.[6] While *DNAH5* mutations represent the most frequent cause of PCD (15–28%), mutations in *DNAI1* are also recurrently observed, and contribute to approximately from 4% up to 13% of cases - depending on the cohort that was studied.[5,6] In addition to dynein-related genes, mutations in genes such as *CCDC39* and *CCDC40* (encoding components of the nexin–dynein regulatory complex) also form the genetic background of PCD. They are associated with inner dynein arm defects and phenotypes that present with more severe lung diseases.[4]

Mutations in another gene - *CCDC103*, such as the p.His154Pro variant, have also been linked to PCD. This mutation disrupts the oligomerization process of the *CCDC103* protein, which is essential for the proper assembly and function of the dynein arm complexes. Above mentioned disruption results in defects, particularly affecting the inner (or both) dynein arm structures.[7]

The diagnosis of PCD is challenging due to its clinical and genetic heterogeneity, symptoms that overlap with other respiratory conditions and limitations of traditional diagnostic methods. Nasal nitric oxide (nNO) measurement, high-speed video microscopy, and transmission electron microscopy (TEM) are commonly used diagnostic tools. However, some patients may not be accurately diagnosed with these traditional methods alone.[8,9] This applies especially to the patients without evident ultrastructural defects. For instance, approximately 30% of individuals with PCD may exhibit normal ciliary ultrastructure, as assessed by electron microscopy.[9]

Advances in molecular genetics, especially the use of Whole Exome Sequencing (WES), have significantly improved the accuracy of diagnostic procedures. WES enables the identification of rare or novel pathogenic variants in known and novel genes associated with PCD. This provides crucial insights for accurate diagnosis and tailored patient management.[10] In the study by Loges et al, WES enabled the identification of biallelic loss-of-function variants in the *DNAH9* gene in individuals with laterality defects and subtle ciliary dysfunction.[10]

This report presents two clinically distinct cases of PCD, diagnosed thanks to WES, highlighting the genetic and clinical complexity of this condition. The study emphasizes also the value of comprehensive genetic testing, which is a necessary way to precise diagnosis of rare conditions, like PCD.

Case Presentation

Case 1

A male infant, born from the fourth pregnancy and third delivery at 39th week of gestation via cesarean section, presented with perinatal respiratory distress. Birth measurements were: weight - 3350g, body length - 53 cm, head circumference - 35 cm, chest circumference - 34 cm; and Apgar score - 10. The course of the pregnancy was complicated by gestational diabetes in the mother, treated with insulin.

The patient was referred to the Clinical Genetics Department at 10 months of age due to situs inversus, dextrocardia (previously evaluated in the pediatric cardiology department), recurrent respiratory tract infections, and chronic otitis media with effusion.

Genomic DNA was extracted from peripheral blood and subjected to whole-exome sequencing (WES) in a certified clinical laboratory, using the Twist Human Core Exome Plus Kit and Illumina technology, achieving an average depth of 100× across target regions.

WES identified a known pathogenic homozygous variant c.461A>C (p.His154Pro) in the *CCDC103* gene. Parental testing confirmed biallelic inheritance. Genetic testing of the siblings revealed carrier status in the sister, 7 years older, and a normal result in the brother, 2 years older. Based on the clinical picture and molecular findings, the patient was diagnosed with PCD, type 17.

At his most recent follow-up visit at the age of 3 years and 8 months, the patient remained under the care of the National Institute of Tuberculosis and Lung Diseases (Rabka-Zdrój, Poland). He exhibited recurrent lower respiratory

tract infections and chronic otitis media (currently with a third tympanostomy). Physical examination showed: height 96 cm (75–90 percentiles according to WHO standards for the physical development of children aged 0–5 years), weight 15.3 kg (75–90 percentiles), an umbilical hernia, and a left retractile testis. The child follows a full diet and does not suffer from constipation. The boy receives daily saline inhalations and bronchodilator treatment with salbutamol. The appearance of the patient (Case 1) at current age is presented in the Figure 1.

Case 2

The second patient is a male infant born from the second pregnancy and first delivery at 38 weeks of gestation by cesarean section. He had a birth weight of 2620g, body length 50 cm, head circumference 34 cm and chest circumference 28 cm. His Apgar score was 7. The course of the pregnancy was complicated by bleeding in the first trimester and recurrent reproductive tract and urinary tract infections in the mother. Prenatal ultrasound examination of the fetus at 16 weeks' gestation showed hernia of the umbilical cord. Amniocentesis was performed at 20 weeks' gestation. Comparative genomic hybridisation to microarray (aCGH) study revealed a normal balanced male karyotype: arr(X, Y)×1, (1–22)×2. Echocardiography of the fetus showed mesocardia with the apex of the heart directed to the right.

He was referred to the Clinical Genetics Department at 12 months of age due to multiple congenital anomalies, including situs inversus, dextrocardia, absence of the pericardium, pulmonary hypoplasia, suspected pentalogy of Cantrell and recurrent respiratory infections. After birth, he underwent a three-stage surgical procedure to close the diaphragmatic hernia and close the abdominal wall at the site of the umbilical hernia with a 12 cm wide hernia sac containing loops of intestine, a fragment of the liver and a fragment of the spleen.

On physical examination at 12 months of age, the child's height was 71 cm (<3rd percentile), weight was 7300 g (<3rd percentile) and head circumference was 42.5 cm (<3rd percentile). Dysmorphic features included mild occipital

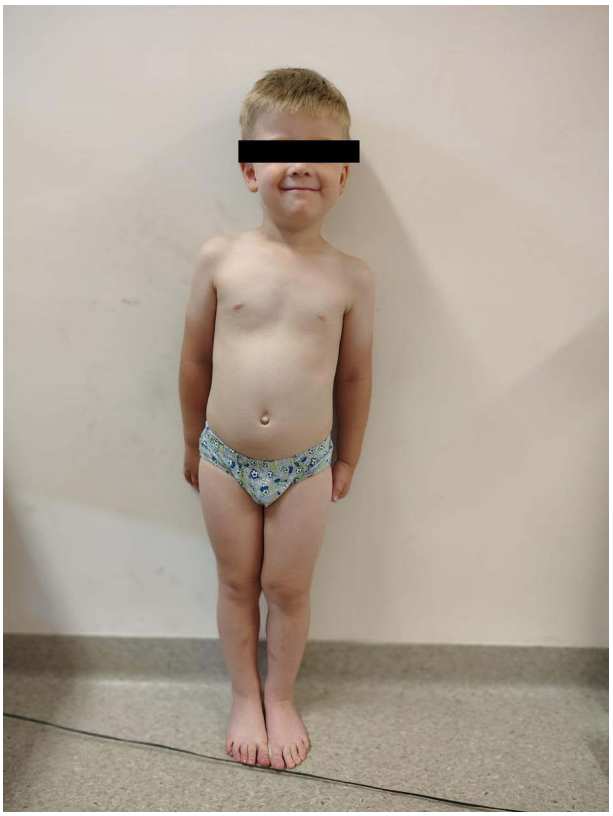

Figure 1 Appearance of the patient (Case 1) at current age (3 years and 8 months) - normal growth and psychomotor development.

asymmetry, closed anterior fontanelle, hypotelorism, tented upper lip and retrognathia. Postoperative scars were visible on the chest and abdomen. The testes were retracted. A delay in motor development was also noted - he only sat with assistance. A delay in speech development was also present - the patient was only just babbling.

Multispecialty evaluations were conducted and the patient has visited following departments: cardiology, surgery, hematology, neurology, nutrition, gastroenterology, and rehabilitation. He was fed by nasogastric tube for 17 months.

Whole-exome sequencing (WES) was performed in a certified clinical laboratory, using the Twist Human Core Exome Plus Kit for target enrichment and sequenced on the Illumina NovaSeq6000 platform (2×100 bp).

Whole exome sequencing (WES) identified two variants in each of the dynein-related genes, *DNAH5* and *DNAH9*. Parental testing identified the maternal origin for the c.10243-6C>T (p.?) and c.308del (p.Phe103Serfs*31) variants in the *DNAH9* gene and a paternal origin for the c.1206T>A (p.Asn402Lys) variant in the *DNAH5* gene. The second variant c.5124G>T (p.Glu1708Asp) in the *DNAH5* gene in the proband arose de novo. All four variants were classified as variants of uncertain significance (VUS) or likely benign, based on current ClinVar data. No definitive pathogenic or likely pathogenic variants were detected.

Additionally, due to two episodes of thrombosis, a thrombophilia panel was performed. Heterozygous variants were detected in the *MTHFR* gene: c.665C>T and c.1286A>C. Further hematological evaluation and periodic serum homocysteine monitoring were recommended.

At the age of 2 years and 4 months, the patient's weight was 10 kg (<3rd percentile). The patient walked independently, speech development was progressing intensively. Figures 2 and 3 portray the patient's (Case 2) phenotype.

Additional Diagnostic Methods Regarding Case 1 and Case 2

Due to limited access, diagnostic tests such as nasal nitric oxide (nNO) measurement, high-speed video microscopy (HSVM), and transmission electron microscopy (TEM) were not performed. The diagnosis was established through clinical evaluation and was confirmed by Whole-Exome Sequencing. In both cases, trio WES was performed, including the patient and both biological parents. In Case 1, additional testing of siblings was carried out: the patient's sister was found to be a heterozygous carrier of the pathogenic variant in the *CCDC103* gene, whereas the brother did not carry the variant. In Case 2, the patient is an only child, and no additional family members beyond the parents were tested. The summary of all relevant variants identified by whole-exome sequencing (WES) in both Case 1 and Case 2 is presented in Table 1.

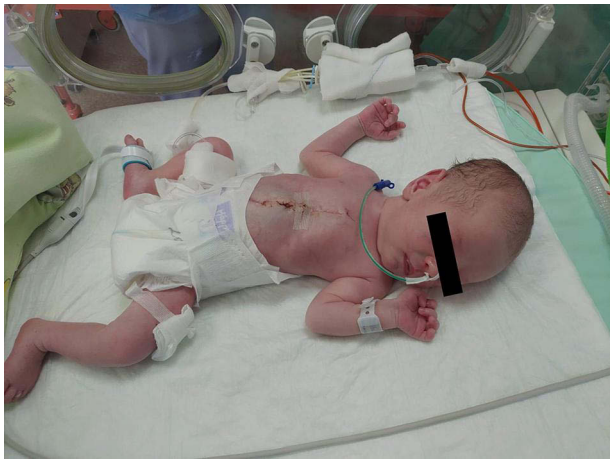

Figure 2 Case 2 - the patient after the three-stage surgical procedure - muscle hypotonia can be seen.

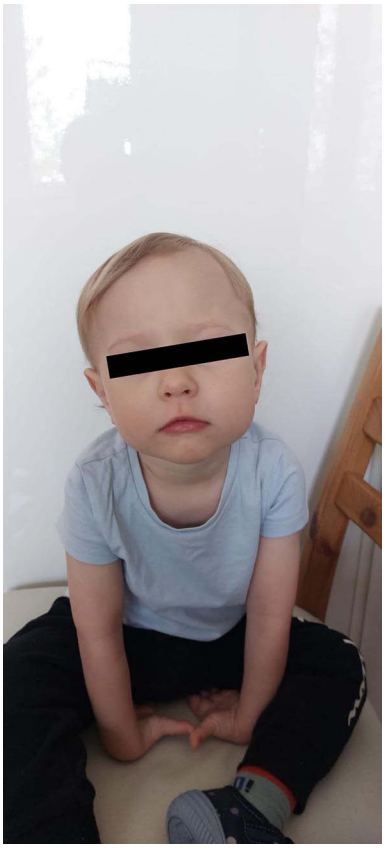

Figure 3 Appearance of the patient (Case 2) showing few dysmorphic features: thickened frontal suture, hypotelorism, tented upper lip.

Discussion

The genetic diversity of PCD is increasingly recognized as a cause of the broad clinical spectrum of this disorder. The two cases described in this report illustrate how patients may present with some common features of PCD, as well as some different clinical symptoms at the same time. Moreover, the patients carried distinctly different underlying genotypes.

Clinical and Genetic Analysis of Case 1 and Case 2

In the first case, a homozygous *CCDC103* p.His154Pro mutation was identified. This missense variant has been described as a mutation which is prevalent in UK individuals of South Asian origin (mostly Pakistani) and was also found in an Irish Traveller family.[7]

Table 1 Summary of All Relevant Variants Identified by Whole-Exome Sequencing (WES) in Both Case 1 and Case 2

Case	Gene	Variant (cDNA)	Protein Change	Zygosity	Inheritance/ Phase	ACMG/ClinVar Classification	Rationale
1	*CCDC103*	c.461A>C	p.His154Pro	Homozygous	Biallelic confirmed	Pathogenic (ClinVar)	Known founder variant in PCD; functional studies; phenotype match
2	*DNAH9*	c.308del	p.Phe103SerfsTer31	Heterozygous	Maternal	VUS	No functional validation
2	*DNAH9*	c.10243-6C>T	–	Heterozygous	Maternal	VUS	Unknown effect
2	*DNAH5*	c.5124G>T	p.Glu1708Asp	Heterozygous	De novo	Likely benign	Common variant
2	*DNAH5*	c.1206T>A	p.Asn402Lys	Heterozygous	Paternal	VUS	Conflicting literature, insufficient data

The p.His154Pro variant impairs oligomerization of the *CCDC103* protein, resulting in a reduced protein-folding ability.[7] Importantly, individuals with this variant often display a non-diagnostic or even normal ciliary ultrastructure on transmission electron microscopy (TEM), which may delay or conceal diagnosis using traditional methods.[7] In the Irish Traveller family described by Casey et al, affected individuals with p.His154Pro homozygosity showed inconsistent ciliary ultrastructure - from normal to completely absent dynein arms. This depicts the limitations of relying on TEM method alone in the process of diagnosis.[11] These findings clearly support and justify the use of genetic testing in suspected PCD even when the standard diagnostics are inconclusive.

The second patient carried variants in *DNAH5* gene, the most commonly mutated gene in genetically confirmed PCD cases, and *DNAH9* - a gene associated with milder or atypical phenotypes.[1,10] Loges et al reported that biallelic pathogenic variants in the *DNAH9* gene may result in laterality defects with no or only mild respiratory symptoms, often remaining undiagnosed without the aid of genetic sequencing.[10] In recent work by Al-Mutairi et al, the authors systematically investigated five individuals with confirmed primary ciliary dyskinesia (PCD) from three unrelated Arabic families, identifying several novel pathogenic variants in the *DNAH5* gene.[12] Using a combination of whole-exome sequencing, segregation analysis, transmission electron microscopy (TEM) and immunofluorescence (IF), they confirmed the pathogenicity of these variants. In all five cases, TEM revealed complete absence of outer dynein arms, and IF analysis confirmed the lack of *DNAH5* protein in the ciliary axoneme. Particularly relevant to our case, the authors emphasized that compound heterozygous missense variants in *DNAH5*, even when not previously classified as pathogenic, may cause classical PCD phenotypes when supported by functional and clinical evidence. Furthermore, in silico prediction tools, including REVEL, DANN, MutPred, and PolyPhen-2, showed high pathogenicity scores for such variants, reinforcing their role in disease causation. These findings support our interpretation that the de novo missense variant in *DNAH5* identified in Case 2 (c.5124G>T, p.Trp1708Cys), despite limited data in current databases, may still be disease-causing when occurring with another variant in trans. In our case, this is further supported by the phenotypic consistency, including situs inversus, congenital heart defects, and chronic respiratory infections.

Concerning the *DNAH9* variants in Case 2, both variants were maternally inherited. *DNAH9* has been recognized as a causative gene in milder or atypical PCD phenotypes, particularly those involving laterality defects.[10]

Although the variant c.10243-6C>T is currently classified as likely benign in ClinVar, its impact has not been fully functionally evaluated. Similar variants have been associated with PCD in the literature. Isa et al presented a case with a novel *DNAH9* gene mutation in a compound heterozygous state (the *DNAH9* variant c.11086C>T p.(His3696Tyr) causing an amino acid change from His to Tyr at position 3696 and the *DNAH9* variant c.7150G>A p.(Gly2384Arg) causing an amino acid change from Gly to Arg at position 2384).[13] These variants according to SIFT MutationTaster were disease-causing (c.11086C>T) or deleterious and disease-causing (c.7150G>A). It is worth to underline that above mentioned variants were classified as of uncertain significance according to ACMG guidelines.

The diagnosis of PCD in Case 2 was based both on WES, as well as on the clinical image. The findings were suggestive of PCD but we acknowledge that additional functional assessments such as nNO and HSVM were not performed, which limits the diagnostic certainty. This is a limitation that clearly affects the proper diagnosis.

Shamseldin et al identified biallelic pathogenic or likely pathogenic variants in known PCD genes in 38 of 56 families, resulting in a diagnostic yield of 68% based on WES.[14] This finding underscores the utility of genomic testing not only for diagnosis confirmation but also for the information about genotype-phenotype relationships, management strategies, and the ability to conduct accurate genetic counseling for families.

Clinical Features and Prevalence

PCD is most commonly characterized by neonatal respiratory distress, persistent wet cough, nasal congestion, otitis media, and situs anomalies.[1,8] In a large multicenter study, Leigh et al identified four highly predictive features of PCD: neonatal respiratory distress, chronic wet cough, persistent nasal congestion, and laterality defects. The presence of at least three of these markers yielded a diagnostic specificity above 96%.[8] Our first patient presented with three of these four key features. This finding supports the clinical suspicion of PCD even before the genetic testing.

The second patient showed a more complex phenotype, but also had situs inversus, chronic respiratory symptoms, and neonatal distress, meeting the same predictive threshold.

A meta-analysis by Goutaki et al estimated the prevalence of chronic cough and sputum production at over 85%, with otitis media affecting roughly 74% of PCD patients.[3] Bronchiectasis and neonatal respiratory distress were each present in more than half of the cases, while situs abnormalities occurred in approximately 50%.[3]

The clinical profiles of both of our patients align well with this symptom spectrum. They illustrate the importance of early recognition and diagnosis, especially in atypical or syndromic presentations.

The comparison between phenotypic features (mutations in *CCD103, DNAH5, DNAH9*) according to OMIM and our cases is clearly portrayed in Table 2.

Differential Diagnosis of PCD

PCD often presents with chronic respiratory symptoms that overlap with several more common pediatric and adult conditions, making differential diagnosis essential. Disorders that should be considered include: cystic fibrosis, primary immunodeficiencies, bronchial asthma, bronchiectasis of other etiologies.[18] Neonatal respiratory distress - particularly when persistent and unexplained is a characteristic feature of PCD but may also occur in congenital heart diseases and other structural abnormalities.[19]

Importantly, low levels of nasal nitric oxide (nNO), a non-invasive biomarker, are useful in distinguishing PCD from other conditions. Shapiro et al demonstrated that patients with PCD (including those with situs ambiguus or heterotaxy), consistently exhibit significantly reduced nNO levels, even compared to patients with complex cardiac anomalies without ciliary dysfunction.[19] Additionally, high-speed video microscopy and TEM can help differentiate PCD from secondary ciliary dyskinesias (eg. caused by infection or inflammation). These methods enable to reveal cilia immobility, partial loss or invalid structure of cilia, although normal ultrastructural findings on TEM do not exclude the disease.[18]

Given the clinical overlap with other chronic respiratory diseases, awareness of the characteristic constellation of symptoms combined with laterality defects or a family history should prompt targeted diagnostic testing to avoid misdiagnosis and treatment delays.

The Role of Next Generation Sequencing in PCD Diagnosis

WES has emerged as a highly valuable tool in the diagnostic workflow for PCD, especially in cases where traditional diagnostic methods do not yield conclusive results or are unavailable. Oh et al demonstrated a diagnostic yield of 17% using WES alone in a cohort of 47 Korean patients clinically suspected of PCD. The yield was even higher when WES was combined with TEM findings.[20] Importantly, nearly half (47.1%) of the identified pathogenic or likely pathogenic variants were novel. This fact underlines the utility of WES in uncovering previously unreported mutations.[20] Similarly, Black et al emphasized the advantages of WGS and WES in detecting not only single-nucleotide variants but also structural variants that may be missed by targeted gene panels. These methods increase the molecular diagnostic yield in genetically heterogeneous conditions like PCD.[21] Their study showed that in seven of eight patients, WGS successfully identified pathogenic variants in known PCD genes such as *DNAH5, DNAAF4*, and *DNAH11*.[21] Together, these findings support the incorporation of WES into early stages of the PCD diagnostic algorithm, especially in the situations, when advanced ultrastructural or functional testing is limited.

Prognosis and Quality of Life in PCD

Despite earlier assumptions that PCD is a mild respiratory disorder, recent studies have shown that affected children may experience significant respiratory morbidity, including reduced lung function. Rubbo et al demonstrated that children with PCD in England had lower mean forced expiratory volume in one second (FEV_1) values (76.8% predicted) compared to children with cystic fibrosis, especially in younger age groups. Nearly one-third of the patients affected with PCD required intravenous antibiotic therapy within the previous 12 months.[22] Moreover, about 24% of children required hearing aids due to moderate or profound hearing loss. What is more, patients with impaired nutritional status (low BMI) demonstrated poorer lung function.[22]

Beyond physiological parameters, PCD substantially impacts patient's quality of life (QOL).[23] As highlighted by Yılmaz and Akgün, the chronic burden of symptoms, intensive daily treatments, and complications such as infertility contribute to diminished health-related QOL (HRQOL). This concerns particularly the physical and emotional

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Table 2 Phenotypic Features According to OMIM Versus Case 1 and Case 2

Clinical or Molecular Features	*CCDC103*, Phenotype MIM Number: 614679[15]	Case 1 (Mutation in the *CCDC103* Gene)	*DNAH5*, Phenotype MIM Number: 608644[16]	*DNAH9*, Phenotype MIM Number: 618300[17]	Case 2 (Mutations in the *DNAH5* and *DNAH9* Genes)
Head	• Chronic sinusitis	–	–	–	–
Ears	• Chronic otitis	• Chronic otitis media with effusion	• Chronic otitis media	–	–
Nose	• Chronic rhinitis	–	• Chronic rhinosinusitis	• Rhinitis	–
Heart	• Dextrocardia (in some)	• Dextrocardia • Situs inversus	–	• Situs inversus • Congenital heart defects (in some patients)	• Dextrocardia • Absence of the pericardium
Respiratory & Lung	Respiratory: • Recurrent cough • Recurrent respiratory infections • Bronchiectasis	Lung: • Respiratory distress Respiratory: • Recurrent respiratory tract infections	Respiratory: • Bronchiectasis • Immotile cilia • Absent outer dynein arms of respiratory cilia seen on transmission electron microscopy Lung: • Respiratory distress (neonate) • Chronic cough • Recurrent pneumonia	Respiratory: • Chronic cough • Upper respiratory tract symptoms	Lung: • Pulmonary hypoplasia Respiratory: • Recurrent respiratory infections
Abdomen	Abdomen: • Situs inversus	Abdomen: • Situs inversus • An umbilical hernia	Abdomen: • Heterotaxy (in some patients) • Situs inversus (in some patients)	Abdomen: • Situs inversus	Abdomen: • Situs inversus
Genitourinary	–	Internal genitalia (Male): • Left retractile testis	Internal genitalia (Male): • Immotile sperm • Infertility	Internal genitalia (Male): • Infertility • Azoospermia	Internal genitalia (Male): • Retracted testes
Laboratory abnormalities	• Immotile or weakly motile cilia • Loss of ciliary beat coordination • Inner and outer dyneim arm defects, variable	• nNO/TEM/HSVM: not performed; diagnosis established based on clinical criteria and WES findings.	• Decreased nasal nitric oxide (nNO)	• Decreased bending of distal ciliary axoneme • Abnormal ciliary beat pattern, subtle	• nNO/TEM/HSVM: not performed; diagnosis established based on clinical criteria and WES findings.
Miscellaneous	• Onset at birth	–	• Genetic heterogeneity • Laterality defects including situs inversus totalis and heterotaxy • Absence or presence of laterality defects can occur in same family	• Onset in childhood • Relatively mild phenotype	–
Molecular basis	• Caused by mutation in the dynein, axonemal, assembly factor 19 gene	• Caused by mutation in the dynein, axonemal, assembly factor 19 gene	• Caused by mutation in the dynein, axonemal, heavy chain 5 gene	• Caused by mutation in the dynein, axonemal, heavy chain 9 gene	• Caused by mutation in the dynein, axonemal, heavy chain 5 gene • - Caused by mutation in the dynein, axonemal, heavy chain 9 gene
Other	–	–	–	–	• Suspected Pentalogy of Cantrell • Diaphragmatic hernia • Dysmorphic features: mild occipital asymmetry, closed anterior fontanelle, hypotelorism, tented upper lip and retrognathia • Delay in motor development

domains.[23] Standardized assessment tools such as the PCD-QOL questionnaire can reveal how PCD may affect above mentioned aspects of the patient's daily life and well-being.[23] Therefore, timely diagnosis, personalized care plans and psychological support are crucial to gain long-term outcomes and maintain high QOL in affected individuals.

Conclusion

This study highlights the diagnostic and genetic complexity of primary ciliary dyskinesia (PCD) in early childhood, based on two distinct clinical cases. In Case 1, a homozygous pathogenic variant in *CCDC103* confirmed the diagnosis. In Case 2, rare heterozygous variants in *DNAH5* and *DNAH9* were detected, but their pathogenicity and clinical relevance remains uncertain due to limited evidence and the absence of confirmed biallelic inheritance. These findings support the use of whole-exome sequencing (WES) as a key component of the diagnostic process in suspected PCD, particularly when standard tests such as nasal nitric oxide measurement or ultrastructural analysis are unavailable. As shown in recent studies, some variants initially classified as VUS may prove clinically significant when integrated with phenotype and segregation data. Therefore, careful genotype–phenotype correlation and follow-up analyses are essential in rare, heterogeneous disorders such as PCD.

AI Statement

The authors acknowledge the use of Generative AI tools (Grammarly Grammar Checker, ChatGPT4o) only for the purpose of English language correction and improvement.

Ethical Approval Statement

This study was approved by the Ethics Committee of the Medical University of Lublin, Poland (committee reference number: KE-0254/69/04/2024).

Consent for Publication

The consent for the publication has been obtained from the parents of the patients (their official guardians), according to the applicable regulations in Poland (the patients are under 16 years of age). The parental consent included publication of the images.

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Disclosure

The authors report no conflicts of interest in this work.

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