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The expanding phenotype of *OFD1*-related disorders: Hemizygous loss-of-function variants in three patients with primary ciliary dyskinesia

William B. Hannah[1,2,3] 🅘 | Suzanne DeBrosse[1,3] | BreAnna Kinghorn[4] |
Steven Strausbaugh[2,5] | Moira L. Aitken[6] 🅘 | Margaret Rosenfeld[4] | Whitney E. Wolf[7] |
Michael R. Knowles[8] | Maimoona A. Zariwala[9] 🅘

[1]Center for Human Genetics, University Hospitals Cleveland Medical Center, Cleveland, Ohio

[2]Department of Internal Medicine, University Hospitals Cleveland Medical Center, Cleveland, Ohio

[3]Department of Genetics and Genome Sciences, Case Western Reserve University, Cleveland, Ohio

[4]Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington

[5]Department of Pediatrics, University Hospitals Cleveland Medical Center, Cleveland, Ohio

[6]Department of Medicine, University of Washington, Seattle, Washington

[7]Department of Pharmacoengineering and Molecular Pharmaceutics, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina

[8]Department of Medicine, Marsico Lung Institute, University of North Carolina, Chapel Hill, North Carolina

[9]Department of Pathology and Laboratory Medicine, Marsico Lung Institute, University of North Carolina, Chapel Hill, North Carolina

Correspondence
Maimoona A. Zariwala, Department of Pathology and Laboratory Medicine, Marsico Lung Institute, University of North Carolina, 7219 A Marsico Hall, Chapel Hill, NC 27599-7248, USA.
Email: maimoona_zariwala@med.unc.edu

William B. Hannah, 905 S Lasalle Street, GSRB 1, Durham, NC 27710, USA.
Email: william.hannah@duke.edu

Abstract

Background: *OFD1* has long been recognized as the gene implicated in the classic dysmorphology syndrome, oral-facial-digital syndrome type I (OFDSI). Over time, pathogenic variants in *OFD1* were found to be associated with X-linked intellectual disability, Joubert syndrome type 10 (JBTS10), Simpson-Golabi-Behmel syndrome type 2 (SGBS2), and retinitis pigmentosa. Recently, *OFD1* pathogenic variants have been implicated in primary ciliary dyskinesia (PCD), a disorder of the motile cilia with a phenotype that includes recurrent oto-sino-pulmonary infections, situs abnormalities, and decreased fertility.

Methods: We describe three male patients with PCD who were found to have hemizygous pathogenic variants in *OFD1*, further supporting that PCD is part of a clinical spectrum of *OFD1*-related disorders. In addition, we provide a review of the available clinical literature describing patients with *OFD1* variants and highlight the phenotypic variability of *OFD1*-related disease.

Results: Some individuals with hemizygous *OFD1* variants have PCD, either apparently isolated or in combination with other features of *OFD1*-related disorders.

Conclusion: As clinicians consider the presence or absence of conditions allelic at *OFD1*, PCD should be considered part of the spectrum of *OFD1*-related disorders.

Understanding the *OFD1*-related disease spectrum may allow for more focused genetic testing and more timely management of treatable sequelae.

1 | INTRODUCTION

OFD1, residing on chromosome Xp22.2, has long been known to be the gene implicated in the classic dysmorphology syndrome, oral-facial-digital syndrome type I (OFDSI, MIM 311200) (Ferrante et al., 2001). Over recent years, multiple phenotypes have been identified as allelic to OFDSI including primary ciliary dyskinesia (PCD, MIM 244400). PCD is a disorder of the motile cilia with a phenotype that includes recurrent oto-sino-pulmonary infections, neonatal respiratory distress, bronchiectasis, situs abnormalities, and decreased fertility (Knowles, Daniels, Davis, Zariwala, & Leigh, 2013). Herein, we describe three individuals with PCD due to hemizygous loss-of-function in *OFD1*, supporting that PCD is part of a clinical spectrum of *OFD1*-related disorders. To this end, we open with a brief description of clinical features known to be caused by *OFD1* variants.

In 1954, OFDSI was described in girls who had dysmorphic features involving the mouth, face, and digits (Papillon-Léage & Psaume, 1954). Classically, it was thought that OFDSI was inherited in an X-linked dominant pattern and that it could be lethal in males (Gorlin, Anderson, & Scott, 1961); however, males with OFDSI have been described (Goodship, Platt, Smith, & Burn, 1991).

In 2006, a family was reported to have a distinct phenotype that segregated with an *OFD1* frameshift variant (Budny et al., 2006). The male index patient had macrocephaly, intellectual disability, obesity, recurrent upper and lower airway infections, high-arched palate, low-set ears, and short fingers. Other affected males were noted to have chronic respiratory tract infections, and some had macrocephaly; heterozygous females were unaffected. The authors acknowledged that this was a different phenotype than OFDSI and had X-linked recessive inheritance. Given the phenotypic overlap with Simpson-Golabi-Behmel syndrome (MIM 312870), this condition was recognized as Simpson-Golabi-Behmel Syndrome type 2 (SGBS2, MIM 300209). Due to chronic respiratory tract infections in affected individuals and abnormal high-speed video microscopy (HSVM) of the nasal epithelium in the index case, PCD was recognized as part of this spectrum of disease. These data suggested that SGBS2 and PCD could exist concurrently in individuals with hemizygous loss-of-function in *OFD1*. This X-linked inheritance of PCD differs from the vast majority of PCD, which is usually autosomal recessive.

Other conditions associated with *OFD1* variants include Joubert syndrome type 10 (JBTS10, MIM 300804) (Coene et al., 2009) and non-syndromic retinitis pigmentosa (RP23, MIM 300424) (Webb et al., 2012). Some individuals with *OFD1* variants have overlapping features of OFDSI, JBTS10, and/or other associated symptoms (Field et al., 2012; Tsurusaki et al., 2013; Wentzensen et al., 2016).

Further characterizing a spectrum of disease associated with *OFD1* variants, an affected patient and unrelated fetus with hemizygous loss-of-function were described as having features of SGBS2 and JBTS10 (Thauvin-Robinet et al., 2013). A 13-year-old boy had intellectual disability, polydactyly, oculomotor apraxia, molar tooth sign (MTS), obesity, and chronic sinusitis and bronchitis. His nasal nitric oxide (nNO), a diagnostic tool for PCD, was 78 nl/min (a value <77 nl/min has a very good detection rate for PCD given a compatible clinical phenotype (Shapiro et al., 2016)). The fetus described in this case (Thauvin-Robinet et al., 2013) was reported to be the first subject identified with an *OFD1* variant who had situs inversus.

Clearly, there is variable expressivity observed in individuals with hemizygous loss of *OFD1* function. In fact, some individuals appear to have features of multiple conditions that are associated with *OFD1* variants. PCD is an important part of *OFD1*-related disease, and the three patients described in this report contribute to our understanding of syndromic PCD and the *OFD1* phenotype.

2 | CASE REPORTS

2.1 | Case 1

A 33-year-old man has a history of recurrent sinus infections and recurrent pneumonia. Sputum cultures have grown *Nocardia farcinica*, methicillin-sensitive *Staphylococcus aureus*, and *Mycobacterium chelonae*. Computerized tomography (CT) imaging of the chest demonstrated bronchiectasis of the left lower lobe, inferior lingula, and medial segment of the right middle lobe. Spirometry results included forced vital capacity (FVC) 3.99 liters (L) (82% predicted), forced expiratory volume in the first second (FEV1) 2.62 L (65% predicted), and forced expiratory flow between 25 to 75% of FVC (FEF25-75) of 1.59 L/s (38% predicted). There are no known situs abnormalities, and fertility status is unknown. There was no neonatal

respiratory distress, and there were no significant episodes of early otitis media. There is no history of congenital heart disease or polycystic kidney disease. Electroretinograms did not demonstrate retinitis pigmentosa but were suspicious for retinal dystrophy. A nNO had been measured at 43 and 52 nl/min. Electron microscopy demonstrated normal ciliary ultrastructure (Figure 1).

Dysmorphic features include macrocephaly, nasal shortening, mid-face hypoplasia, alopecia, high-arched palate, and postaxial polydactyly. BMI is 35 kg/m^2. He has developmental delay and mild intellectual disability. He has a history of neonatal hypotonia, poor feeding as an infant with gastrostomy tube placement at age 3 months, gastroesophageal reflux, and episodes of apnea that began at age 3 weeks. CT imaging of the head as an infant demonstrated enlarged ventricles and an abnormal appearance of the white matter of the brain. Although he had nuclear magnetic resonance imaging (MRI) performed as an infant as part of a research study, neither the original images nor a radiologist report is available. He had transient hypoglycemia and transient hyperammonemia as an infant. As an adult, he had a relative decrease in non-switched memory and switched memory B cells with normal immunoglobulin concentrations except for a slight increase in IgG subclass 4.

Multiple molecular tests were nondiagnostic. Ultimately, clinical exome sequencing identified a de novo hemizygous pathogenic *OFD1* (NM_003611.2) variant: c.2789_2793delTAAAA (p.Ile930Lysfs*8). No other reported variants appeared to be disease-causing in this individual. Specifically, a single variant was identified in *DYNC1H1* (a gene associated with neurologic features and excluded as disease-causing given the phenotype and inheritance from an asymptomatic father), only a single variant was identified in *BBS7* (a gene associated with autosomal recessive disease), and two variants were identified in cis in *CEP290* (a gene that is associated with disease only in the presence of biallelic variants). There were no other variants reported in genes known to be implicated in PCD, cystic fibrosis, or surfactant disorders.

2.2 | Case 2

A 16-year-old male patient has a history of the following constellation of symptoms: neonatal respiratory distress
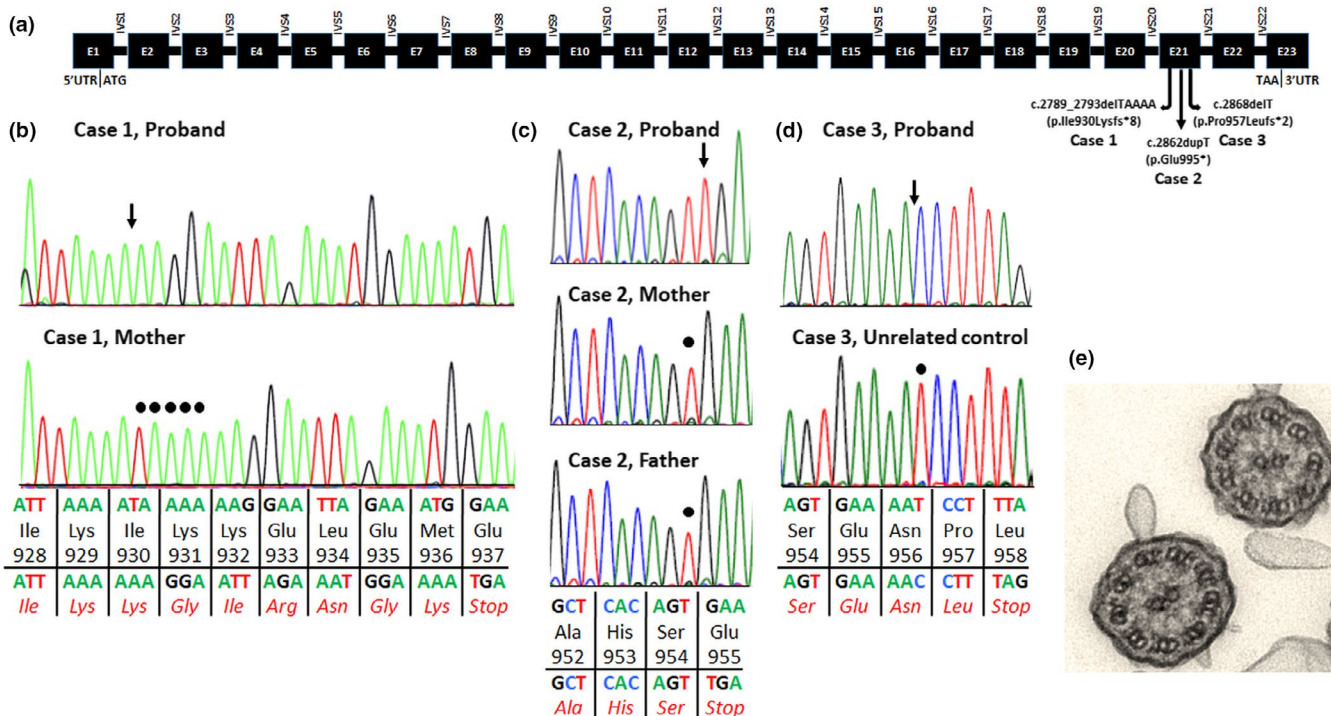

FIGURE 1 (a) The *OFD1* transcript (NM_003611.2) is 3,651 base pairs and consists of 23 exons (represented by black rectangles), encoding a 1,012 amino acid protein. Exon 1 contains the entire 5′ untranslated region (5′UTR) and the start codon (ATG). Exon 23 contains the stop codon (TAA) and the entire 3′ untranslated region (3′UTR). The pathogenic hemizygous variants in the three cases described are all located in exon 21 and shown above. Introns (IVS) are represented by horizontal lines. (b-d) Electropherograms for hemizygous variant in Case 1 affected (top) and wild-type mother (bottom) (b), Case 2 affected (top) and wild-type mother and father (bottom) (c), and Case 3 affected (top) and wild-type unrelated control (bottom) (d). An arrow points to the pathogenic variant in the affected individual's electropherogram, and a circle marks the wild-type sequence at that nucleotide in the controls (parents in b and c; unrelated control in d). Wild-type sequence, amino acid residue, and codon number are shown above the horizontal line. The sequence with the hemizygous variant and amino acid residues (in red) are shown below the horizontal line. (e) Transmission electron microscopy of the Case 1 proband demonstrating normal ciliary ultrastructure with the characteristic 9 + 2 microtubule pair organization and normal dynein arms

following a full-term gestation, recurrent ear infections (with tympanostomy tube placements, mastoidectomies, and mastoid debridement), recurrent sinusitis (with bilateral endoscopic maxillary antrostomies and bilateral endoscopic total and anterior–posterior ethmoidectomies), and recurrent pneumonia with a daily wet cough. At 9 months of age, he had acute respiratory failure, was intubated, and had tracheostomy placement with decannulation at 5 years of age. At age 15 years, chest CT showed no evidence of bronchiectasis. He is unable to cooperate with spirometry or measurement of nNO. Previous cultures demonstrated *Pseudomonas aeruginosa*, methicillin-sensitive *Staphylococcus aureus*, and *Candida*. There are no situs abnormalities, and fertility status is unknown. He has not had electron microscopy assessment of ciliary ultrastructure or HSVM.

Dysmorphic features include macrocephaly, large forehead, deep-set eyes, low nasal bridge, short and upturned nose, thick lips with a wide mouth, and postaxial polydactyly of the hands. BMI is 31 kg/m^2. Neurologic features include intellectual disability. He is minimally verbal and minimally able to ambulate. He has a history of chronic cerebral atrophy, seizures, hypotonia, and apnea. He has gastroesophageal reflux and had a Nissen fundoplication and gastrostomy tube placement, and had dysphagia requiring a diet of pureed and soft foods. MRI of the brain demonstrated a large arachnoid cyst and mild to moderately enlarged ventricles, but no MTS. Other past medical history includes nephrocalcinosis requiring diuretics, atrial septal defect status post Amplatzer placement, iatrogenic adrenal insufficiency, and immunodeficiency with hypogammaglobulinemia and a deficiency of class switching memory B cells that has at times required intravenous immunoglobulins.

Genetic testing of 20 genes implicated in PCD and *CFTR* (Table 1) identified only a de novo pathogenic variant, c.2862dupT (p.Glu995*), in *OFD1*.

2.3 | Case 3

A 32-year-old man of Hispanic ethnicity was referred to pulmonology with the following history: recurrent sinus infections with three surgical interventions, recurrent pneumonia, and situs inversus totalis. CT imaging of the chest demonstrated bronchiectasis. Spirometry results were FVC 2.31 L (47.7% predicted), FEV1 0.98 L (25.0% predicted), and FEF25-75 0.31 L/s (6.3% predicted). Sputum cultures grew *H. influenza* and oral flora. This patient is reported to have had two daughters, but it is not known if assisted reproductive technologies were used. DNA was not available for paternity testing, thus if donor sperm were not used, his daughters would be obligate carriers, information that would be useful to the family for reproductive counseling. However, we are unable to contact his family. There is no known history of congenital heart disease, polycystic kidney disease, or

retinitis pigmentosa. The nNO level was 54.5 nl/min. Electron microcopy demonstrated normal ciliary ultrastructure.

This individual has no history of intellectual disability. Otherwise, details regarding his neurologic and ophthalmologic review of systems are not known.

As part of his PCD evaluation, exome sequencing was performed through the Yale Center for Mendelian Genomics (NIH/NHLBI Mendelian Exome Project) followed by analysis of genes associated with PCD and other respiratory conditions (Table 1). A hemizygous pathogenic *OFD1* variant, c.2868delT (p.Pro957Leufs*2), was identified and parental specimens are not available for variant segregation analysis.

3 | DISCUSSION

Few publications have suggested an *OFD1* variant as a cause of PCD. As above, a family was characterized in which affected males have features of SGBS2 and PCD segregating with a hemizygous *OFD1* variant (Budny et al., 2006). Previously, a family in which affected males had features of Simpson-Golabi-Behmel syndrome and macrocephaly and died of pneumonia was described with the phenotype segregating with a Xp22 locus (Brzustowicz, Farrell, Khan, & Weksberg, 1999), but no *OFD1* genetic testing was reported in this family. As mentioned, a 13-year-old boy with features of intellectual disability, SGBS2, JBTS10, and PCD was described with the same hemizygous *OFD1* variant as the individual described in Case 1 (c.2789_2793delTAAAA) (Thauvin-Robinet et al., 2013). Notably, the individual described by Thauvin-Robinet et al. had inherited maternally the c.2789_2793delTAAAA variant, whereas this was a de novo variant in Case 1. Clearly, these reports suggest an association of PCD with *OFD1* variants, but very few individuals with PCD due to an *OFD1* variant have been described.

As others have acknowledged, the PCD phenotype is clearly present in some individuals with *OFD1* variants. As we characterize the spectrum of *OFD1*-related disease, there are diagnostic implications. If syndromic features of *OFD1*-related disease are found, then focused genetic testing can be considered rather than large panel testing for PCD or JS. Conversely, when a pathogenic *OFD1* variant is identified, the patient should be evaluated for PCD. Indeed, the individual in Case 1 was diagnosed with PCD after his genetic testing returned and a referral for nNO testing was made.

Furthermore, the individuals described in this manuscript have some notable features that highlight the variable expressivity of *OFD1*-related disorders (Table 2). All three individuals have symptoms that support a PCD phenotype, and the individuals in Cases 1 and 3 had nNO levels in the diagnostic range. As detailed, the dysmorphic features, cognitive function, neurologic symptoms, and other organ dysfunction observed in these three patients are varied. The individuals in

TABLE 1   Genes analyzed for the presence of pathogenic/likely pathogenic variant

	Genes (alternative name)	Transcript Identifier	Disease association	Case 2: Ambry Panel	Case 3: Whole-Exome Sequencing
1	ARMC4	NM_018076.2	PCD	Yes	Yes
2	CCDC103	NM_213607.1	PCD	Yes	Yes
3	CCDC114	NM_144577.3	PCD	Yes	Yes
4	CCDC151	NM_145045.4	PCD	No	Yes
5	CCDC39	NM_181426.1	PCD	Yes	Yes
6	CCDC40	NM_017950.3	PCD	Yes	Yes
7	CCDC65 (DRC2)	NM_033124.4	PCD	No	Yes
8	CCNO	NM_021147.4	PCD	No	Yes
9	CFAP298 (C21orf59)	NM_021254.2	PCD	No	Yes
10	CFAP300 (C11orf70)	NM_032930.2	PCD	No	Yes
11	DNAAF1 (LRRC50)	NM_178452.4	PCD	Yes	Yes
12	DNAAF2 (KTU)	NM_018139.2	PCD	Yes	Yes
13	DNAAF3	NM_001256714.1	PCD	Yes	Yes
14	DNAAF4 (DYX1C1)	NM_130810.3	PCD	No	Yes
15	DNAAF5 (HEATR2)	NM_017802.3	PCD	Yes	Yes
16	DNAH1	NM_015512.4	PCD	No	Yes
17	DNAH11	NM_001277115.1	PCD	Yes	Yes
18	DNAH5	NM_001369.2	PCD	Yes	Yes
19	DNAH8	NM_001206927.1	PCD	No	Yes
20	DNAH9	NM_001372.3	PCD	No	Yes
21	DNAI1	NM_012144.3	PCD	Yes	Yes
22	DNAI2	NM_023036.4	PCD	Yes	Yes
23	DNAJB13	NM_153614.2	PCD	No	Yes
24	DNAL1	NM_031427.3	PCD	No	Yes
25	DRC1 (CCDC164)	NM_145038.3	PCD	No	Yes
26	GAS8	NM_001481.2	PCD	No	Yes
27	GAS2L2	NM_139285.3	PCD	No	Yes
28	HYDIN	NM_032821.2	PCD	No	Yes
29	LRRC56	NM_198075	PCD	No	Yes
30	LRRC6	NM_012472.4	PCD	Yes	Yes
31	MCIDAS	NM_001190787.1	PCD	No	Yes
32	NME8 (TXNDC3)	NM_016616.4	PCD	Yes	Yes
33	OFD1	NM_003611.2	PCD; OFD1	Yes	Yes
34	PIH1D3	NM_001169154.1	PCD	No	Yes
35	RPGR	NM_000328.2	PCD	Yes	Yes
36	RSPH1	NM_080860.3	PCD	No	Yes
37	RSPH3	NM_031924.4	PCD	No	Yes
38	RSPH4A	NM_001010892.2	PCD	Yes	Yes
39	RSPH9	NM_152732.4	PCD	Yes	Yes
40	SPAG1	NM_172218.2	PCD	Yes	Yes
41	STK36	NM_001243313	PCD	No	Yes
42	TTC25	NM_031421.2	PCD	No	Yes
43	ZMYND10	NM_015896.2	PCD	No	Yes

(Continues)

TABLE 1 (Continued)

	Genes (alternative name)	Transcript Identifier	Disease association	Case 2: Ambry Panel	Case 3: Whole-Exome Sequencing
44	*CFTR*	NM_000492.3	Cystic Fibrosis	Yes	Yes
45	*SFTPB*	NM_000542.3	SMDP1	No	Yes
46	*SFTPC*	NM_001172410.1	SMDP2	No	Yes
47	*ABCA3*	NM_001089.2	SMDP3	No	Yes
48	*CSF2RA*	NM_001161529.1	SMDP4	No	Yes
49	*CSF2RB*	NM_000395.2	SMDP5	No	Yes
50	*SERPINA1*	NM_000295.4	A1AT deficiency	No	Yes

Note: PCD, Primary ciliary dyskinesia (MIM# 244400); OFD1, Oral-facial-digital syndrome I (MIM# 311200); Cystic fibrosis (MIM# 219700); A1AT, Alpha-1-Antitrypsin deficiency (MIM# 613490); SMDP, Surfactant metabolism dysfunction protein [MIM#s for *SFTPB* (265120); *SFTPC* (610913); *ABCA3* (610921; *CSF2RA* (300770); and *CSF2RB* (614370)].

Cases 1 and 2 have overlapping features of both SGB2 and JBTS10 although there is no MRI of brain available for Case 1, and imaging was negative for MTS in Case 2. They both have a history of polydactyly, obesity, macrocephaly, intellectual disability, hydrocephalus, hypotonia, and breathing abnormalities. Both Cases 1 and 2 demonstrate a deficiency of memory B cells, and Case 2 had hypogammaglobulinemia. It is not clear if this contributed to recurrent infections. To our knowledge, deficiency of memory B cells is not a characteristic finding in individuals with *OFD1* variants, but this observation is noteworthy as we learn more about *OFD1*-related disorders.

Additionally, the patient described in Case 3 is reported to have had children. Because most men with PCD are infertile, this is an important finding. The range of male fertility in PCD is variable including immotile spermatozoa, oligozoospermia, azoospermia, and normal number of spermatozoa with normal or partially impaired motility (Munro et al., 1994). We are limited in interpreting the implications of his reported fertility because we do not know if assisted reproductive technologies were used; there is no molecular confirmation of paternity, and the fertility of men with *OFD1* loss-of-function is not well understood. Seminal analysis of individuals with hemizygous loss-of-function variants in *OFD1* may be useful in further describing *OFD1*-related disorders.

We are still learning about the function of OFD1 and its role in ciliopathies. Tissue culture and animal studies provide insight into the function of OFD1. It is clear that OFD1 is located at the nucleus and the centrosome/basal body (Thauvin-Robinet et al., 2013), that it regulates centriole length (Thauvin-Robinet et al., 2014), and that OFD1 autophagy at centriolar satellites affects ciliogenesis (Tang et al., 2013). Antisense morpholinos in zebrafish lead to laterality defects and other anomalies (Ferrante et al., 2009). *OFD1* knockout animals have laterality defects and paucity of embryonic node cilia as well as abnormal HOX gene expression in limb buds (Ferrante et al., 2006). Tissue culture and animal studies support the importance of *OFD1* in ciliary function and development among other functions.

Although genotype–phenotype correlation of *OFD1* variants is not completely understood, there have been studies that have characterized symptoms implicated by various pathogenic variants (Prattichizzo et al., 2008; Thauvin-Robinet et al., 2006). Little is known regarding *OFD1* variants that cause PCD. Note that the individual and the fetus with PCD-like features described by Thauvin-Robinet et al. both had a variant leading to a stop codon in exon 21 (Thauvin-Robinet et al., 2013). A family and an unrelated individual have been described with JBTS10 due to exon 21 *OFD1* variants leading to a stop codon; although it is unclear if affected people had PCD, individuals in the family had fatal recurrent infections, and the unrelated individual had recurrent middle-ear infections (Coene et al., 2009). In light of these observations, it is pertinent that all three individuals described herein had pathogenic variants in exon 21 of *OFD1* that led to a premature stop codon (Figure 1). We do recognize that other individuals with PCD-like features did have pathogenic variants upstream of exon 21 (Budny et al., 2006; Tsurusaki et al., 2013; Wentzensen et al., 2016). Future characterization of PCD-causing *OFD1* variants will be useful.

Recognizing the clinical features of *OFD1*-related disorders and making a genetic diagnosis could have significant therapeutic implications. Diagnosing PCD is of critical importance to allow for appropriate management. Expert consensus guidelines outline clinical recommendations for both otolaryngology care as well as routine and individualized care for pulmonary manifestations (Shapiro et al., 2016). Furthermore, evidence-based therapeutic options for individuals with PCD are an active area of investigation. This research includes a phase 2, double-blinded, placebo-controlled randomized controlled trial evaluating multiple interventions (CLEAN-PCD, ClinicalTrials.gov identifier NCT02871778). Clearly, recognizing the phenotype of individuals with *OFD1*-related disorders can facilitate a diagnosis, and an accurate diagnosis of PCD has therapeutic implications.

TABLE 2 Clinical features of current cases and of *OFD1*-associated syndromes

Features	Case 1	Case 2	Case 3	PCD	OFDSI	JBTS	SGBS
MIM # when condition is associated with *OFD1*	N/A	N/A	N/A	Not assigned	311200	300804	300209
Gender	Male	Male	Male	Both	Classically female, but males have been described	Both (but JBTS10 is XLR)	Classically male
Ethnicity	English, Czechoslovakian	White	Hispanic	Multiple ethnicities	Multiple ethnicities	Multiple ethnicities	Multiple ethnicities
Inheritance pattern	XLR, de novo variant	XLR, de novo variant	XLR	AR (occasionally XLR)	Classically XLD	AR (occasionally XLR)	XLR
Variant	c.2789_2793delTAAAA (p.Ile930Lysfs*8)	c.2862dupT (p.Glu995*)	c.2868delT (p.Pro957Leufs*2)	N/A	N/A	N/A	N/A
Laterality defects	No	No	Situs inversus totalis	Yes	No	No	No
Oto-sino-pulmonary disease	Yes	Yes	Yes	Yes	No	No	No
Nasal nitric oxide (nL/min)	43 and 52	Not performed	54.5	Low	Presumed Normal	Presumed Normal	Presumed Normal
Neurologic symptoms	Hypotonia, poor feeding, apneic episodes	Hypotonia, apnea, dysphagia/feeding difficulties, seizures	None known	No	MRI findings as below	Hypotonia, poor feeding, irregular breathing. JSRD can include occipital encephalocele	Hypotonia, occasionally seizures
MRI of brain	Unknown	No MTS. Large arachnoid cyst, enlarged ventricles.	Unknown	Normal	Agenesis corpus callosum, porencephaly, hydrocephalus, polymicrogyria, Dandy-Walker malformation	MTS, agenesis of corpus callosum	Occasionally CNS abnormalities (agenesis of corpus callosum, Chiari malformations, etc.
Macrocephaly	Yes	Yes	Not known	No	No	No	Yes
Dysmorphic features	Nasal shortening, midface hypoplasia, high-arched palate, postaxial polydactyly	Large forehead, deep-set eyes, low nasal bridge, short and up-turned nose, thick lips with wide mouth, postaxial polydactyly	None known	No	Oral frenuli, lobulated or bifid tongue, cleft lip/palate, dental anomalies, alar hypoplasia, lateral placement of inner canthi, digit anomalies	Broad forehead, arched eyebrows, ptosis, wide-spaced eyes, open mouth, polydactyly	Coarse facies, hypertelorism, downslanting palpebral fissures, macroglossia, cleft lip/palate, digit anomalies, short webbed neck.
Intellectual disability	Yes	Yes	No	No	Yes	Yes	Yes

(Continues)

TABLE 2 (Continued)

Features	Case 1	Case 2	Case 3	PCD	OFDSI	JBTS	SGBS
Renal anomalies	No	No	No	No	Polycystic kidney disease	JSRD can include cystic dysplasia or nephronophthisis	Occasionally such as cystic or large kidneys or duplication of renal pelvis
Congenital heart disease	No	ASD	No	Yes	No	No	Occasionally
Retinitis pigmentosa	No but abnormal electroretinogram	No	Not known	Not classically (occasionally with *RPGR* variants)	No	JSRD can include retinal dystrophy	No
Other features	Immunodeficiency as described in case	Immunodeficiency as described in case	Reported to have fathered children as described in case	Neonatal respiratory distress, infertility	Fibrocystic liver and pancreas	JRSD can include ocular coloboma among other ophthalmologic anomalies and hepatic fibrosis.	SGBS is associated with increased risk of specific tumors (but SGBS2 is not known to be)
References	Current study	Current study	Current study	Shapiro et al., 2016	Jones, Jones, & Del Campo, 2013; Papillon-Léage Mme & Psaume J. 1954	Parisi, 2009	Jones et al., 2013

Note: Comparison of the phenotypes of Case 1, Case 2, Case 3, PCD, JBTS, and SGBS.
This table highlights some of the important characteristics of these conditions but is not meant to be a thorough summary of all phenotypic features. Individuals with features of these syndromes due to *OFD1* variants may not fit well into the classic descriptions provided in the table (i.e., individuals with JBTS10 may have laterality defects, individuals with SGBS2 are not known to have the same cancer predisposition as individuals with SGBS, etc.).
Abbreviations not used previously: AR, autosomal recessive; JSRD, Joubert syndrome and related disorders; XLD, X-linked dominant; XLR, X-linked recessive.

Our summary points follow:

1. PCD is an important part of the phenotype in some patients with *OFD1*-related disorders.
2. As has been suggested by other clinicians, we agree that individuals with *OFD1* variants can have a spectrum of disease. The phenotype may include features of PCD, JBTS10, SGBS2, OFDSI, and RP23. It may be useful to consider the *OFD1* phenotype as a spectrum of disease that can include some features of multiple classic conditions.
3. Understanding the phenotype of *OFD1*-related disorders may allow for more focused genetic testing.
4. Any patient with a hemizygous, pathogenic *OFD1* variant should be evaluated for possible PCD.

The phenotype of *OFD1*-related disorders is expanding, and there are important implications for diagnosis and treatment.

INFORMED CONSENT

All three individuals provided informed consent. Cases 1 and 2 were enrolled through the UNC IRB. Case 3 was enrolled through the University of Washington IRB.

ORCID

William B. Hannah https://orcid.org/0000-0003-1643-0737

Moira L. Aitken https://orcid.org/0000-0001-8053-5088

Maimoona A. Zariwala https://orcid.org/0000-0003-1619-1393

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