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Respiratory Manifestations in 38 Patients With Alström Syndrome

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Summary.

Objectives: Alström syndrome (AS) is a rare, multi-system condition characterized by retinal degeneration, sensorineural hearing loss, obesity, insulin-resistant diabetes, hypertriglyceridemia, cardiomyopathy, hepatorenal disease, and recurrent respiratory infections. It belongs to a group of genetic disorders known as primary ciliopathies, which includes autosomal dominant and recessive polycystic kidney diseases, as well as Joubert and Bardet–Biedl syndromes. Prior studies have suggested phenotypic overlap between primary ciliopathies affecting the non-motile, sensory cilia, and primary ciliary dyskinesia (PCD), a motile ciliopathy characterized by respiratory tract disease.

Methods: We describe the burden of oto-sinopulmonary disease in 38 individuals with AS and examines the degree of clinical overlap between PCD and AS. Evaluation at the NIH Clinical Center included clinical examination, chest imaging, and clinical history surveys, as well as measurement of nasal nitric oxide (nNO) in nine patients.

Results: Recurrent otitis media was ubiquitous in the AS cohort (92%) with 50% requiring pressure equalization tube placement. A history of bronchitis/pneumonia and sinusitis was reported in 61% and 50% of individuals, respectively. PCD-characterizing symptoms (laterality defects, unexplained neonatal respiratory distress, year-round nasal congestion, and wet cough) were far less prevalent in the AS cohort compared to PCD, and the average nNO production in the AS cohort was 232 ± 57.1 nl/min compared to a cut-off of <77 nl/min for PCD.

Conclusions: These data suggest that the oto-sino-respiratory complications in AS are prominent enough to warrant increased clinical attention, but significantly impaired respiratory cilia function as seen in PCD is unlikely in AS. (www.clinicaltrials.gov, trial NCT00068224)

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Keywords

Alström syndrome; ciliopathy; bronchiectasis and primary ciliary dyskinesia; developmental biology; nitric oxide

INTRODUCTION

Alström syndrome (AS; OMIM 203800) is a rare monogenic disorder characterized by progressive multi-organ pathology including retinal degeneration, sensorineural hearing loss, cardiomyopathy, obesity, insulin-resistant diabetes, hypertriglyceridemia, and hepatic and renal disease. Cognitive function of individuals with AS is normal. The estimated prevalence of AS is less than one per 1 million in the general population.¹

Mutations in *ALMS1* cause AS; to date over 200 pathogenic variants have been identified.² The function of the protein encoded by *ALMS1* is not well understood but it has been implicated in ciliary function, cell cycle regulation, microtubule organization, and intracellular transport, supporting the inclusion of AS in a group of genetic disorders known as ciliopathies.^{3–7}

Cilia are highly conserved structures that are nearly ubiquitous in the human body. The three major types—embryonic nodal, motile, and primary (non-motile) cilia—are classically considered to have distinct structures and functions. Embryonic nodal cilia have a “9+0” axonemal microtubule arrangement with dynein arms. They beat in a rotary fashion and direct leftward flow across the embryonic node, thus establishing left-right asymmetry during development. Motile cilia have a “9+2” microtubule arrangement associated with a synchronous beating motion. They are found along the central nervous system ependyma, the airway epithelium, and the Fallopian tubes where this synchronous motion is responsible for creating a current to propel mucus.^{8–10} These are the cilia implicated in the pathogenesis of primary ciliary dyskinesia (PCD), a disease in which upper and lower respiratory tract disease results from impaired mucociliary clearance.^{11,12} Primary (non-motile) cilia, the last category, serve as the “sensory antennae” of the cell, transmitting mechanical and chemical signals from the environment to intracellular pathways. In contrast to embryonic nodal and motile cilia, their “9+0” axonemal microtubule arrangement without dynein arms is immotile.^{8–10} Although the existence of primary, non-motile cilia on most eukaryotic cells was known for a century, their clinical significance has only recently been appreciated following the localization of the polycystic kidney disease proteins to these cilia. Since then, primary, non-motile cilia have been shown to be defective in syndromic and non-syndromic forms of hepatorenal fibrocystic diseases including autosomal dominant and recessive forms of polycystic kidney disease, Joubert and Bardet–Biedl syndromes as well as AS. Except for AS, pulmonary disease is not a typical feature of disorders of non-motile primary cilia.

Despite the classical distinction between motile and primary cilia, it has been suggested that there is a degree of clinical overlap between PCD and the non-motile ciliopathies.^{9,10} In 2008, Driscoll et al. reported a threefold-increased prevalence of bronchiectasis compared to controls in patients with autosomal dominant polycystic kidney disease (ADPKD), a primary ciliopathy with no known pulmonary features.¹³ This suggests that patients with disorders of

the primary cilia may also be at risk of chronic respiratory disease. AS is a highly variable disorder with the type, age of onset, and severity of manifestations differing within and among families.^{14,15} Furthermore, genotype-phenotype correlations remain elusive, and the rarity of AS precludes studies on a large number of patients. Therefore, most of what is clinically known about AS has been learned through observation of patients. Approximately half of individuals with AS experience pulmonary symptoms, which is considered supporting evidence for the diagnosis of AS.^{14,15} However, there is relatively little specific data on respiratory tract disease in AS. Here, we describe the burden of upper and lower respiratory tract disease in AS in comparison with PCD based on our prospective evaluation of 38 patients with AS with specific attention to the distinct clinical features of PCD.^{16–18}

RESEARCH DESIGN AND METHODS

Participants

Patients with a clinical diagnosis of AS confirmed by mutations in *ALMS1* gene were qualified for enrollment. Between February 2013 and June 2014, 38 patients with AS were prospectively evaluated at the National Institutes of Health (NIH) Clinical Center under the NIH protocol “Clinical and Molecular Investigations into Ciliopathies” (www.clinicaltrials.gov, trial [NCT00068224](https://clinicaltrials.gov/ct2/show/study?term=NCT00068224)), approved by the Institutional Review Board of the National Human Genome Research Institute (NHGRI). Selected patients (based on availability and willingness to consent) were also evaluated with nasal NO and nasal mucosal biopsies under the NIH protocol “Research Respiratory Tract Procedures” (www.clinicaltrials.gov, trial [NCT00471250](https://clinicaltrials.gov/ct2/show/study?term=NCT00471250)), approved by the Institutional Review Board of the National Institute of Allergy and Infectious Diseases (NIAID). Patients or their parents gave written informed consent. In addition to pulmonary consultations, the evaluations at the NIH Clinical Center included otologic examinations, comprehensive blood and urine chemistries, abdominal ultrasonography, abdominal magnetic resonance imaging (MRI) on those who could tolerate the study without anesthesiology (N = 25), audiological evaluations, ophthalmologic examinations, bone density scans, and echocardiography.

Study Design

We assessed the burden of oto-sino-pulmonary disease in AS patients guided by disease manifestations that are frequently used in the diagnostic evaluation of PCD.^{18,19} First, in addition to the prospective evaluation of the patients at the NIH Clinical Center, a retrospective review of relevant medical records including neonatal, primary care, pulmonary care, and ear-nose-throat care records was performed by a single examiner (CB) for every patient. Second, a standardized clinical history survey (modified from Leigh et al.¹⁸ Supplementary Material), designed to evaluate the features of PCD was administered by a single examiner (CB) to patients or their guardians either via phone (N = 22), in-person (N = 11), or via e-mail (N = 1). Using these two methods in combination, we first determined the presence or absence of each general clinical feature, then gathered more specific data focusing on PCD-defining clinical criteria from past medical records. We were unable to perform the clinical history survey in four patients but did include data from their NIH visit and the review of their medical records in this study.

For otitis media, patients' and parents' ability to remember the exact number of otitis media episodes per year was limited; "recurrent otitis media" reported by patients and parents was classified as recurrent. In the medical record review, otitis media, cough, and wheezing were counted as recurrent or chronic if these diagnoses were used in a physician's clinical visit note.

Additionally, a chest X-ray (N = 35) or chest CT (N = 1) was obtained at the time of evaluation at the NIH. In vivo measurements of nasal nitric oxide (NO), was performed for nine patients at the time of their evaluation at the NIH. Nasal NO was measured by direct sampling with an NO analyzer (Seivers 280i NOA, Sievers Instrument, Boulder, CO) with a sampling flow rate of 0.3L/min while exhaling through a resistor using standardized methods of the Genetic Disorders of Mucociliary Clearance Consortium.²⁰ Nasal mucosal scrape biopsies were performed using a curettage technique as previously described and sent to the University of North Carolina for electron microscopy processing and interpretation.²¹

RESULTS

Patient Characteristics

The patients included 18 males and 20 females, ages 1.7–37.9 years (16.0 ± 10.5). There were eight younger children (< 5yr), 17 older children and adolescents (6–17 yr), and 13 adults (≥ 18 yr). There were 32 independent families; one family contributed three siblings, and four families contributed two siblings each, including two sets of fraternal twins. Races included 35 Caucasians and three African-Americans.

Lifetime Respiratory Involvement by Age at Evaluation

The lifetime-prevalence of respiratory disease is presented in Table 1. Recurrent otitis media was the most frequently reported (92%, 35/38) respiratory tract complication in this cohort. Nineteen (50%) patients had ear tubes placed; ten of these patients received multiple tubes. The prevalence of recurrent otitis media was relatively constant among the age groups with reports of recurrent otitis media in 100% (8/8) of patients under 5 years, 94% (16/17) of patients between 6 and 17 years, and 85% (11/13) of patients over 18 years (Table 1).

Twenty-three (61%) patients had at least one episode of bronchitis/pneumonia (Table 1). Of these 23 patients, in the past 5 years, seven had more than two episodes, four had at least one hospitalization due to bronchitis/pneumonia, and five required IV antibiotic treatment. Sinusitis occurred in 19 (50%) patients.

Chronic or recurrent wheezing occurred in 14 (37%) patients, chronic cough occurred in 16 (42%) patients, and persistent nasal congestion or rhinorrhea occurred in 18 (47%) patients (Table 1). For each of these measures, the prevalence was highest among patients under 5 years (63%, 5/8 for each) and lowest among patients over 18 years (23%, 3/13 for nasal congestion or rhinorrhea; 15%, 2/13 for chronic or recurrent wheezing; 31%, 4/13 for chronic cough.).

Imaging

At the time of NIH evaluation none of the patients had clinical signs or symptoms of active pulmonary infection. Among the 36 patients who had chest imaging performed (35 chest X-rays and one chest CT scan) at the NIH only one chest X-ray revealed a nodular density in the right upper lobe. No other imaging showed post-infectious lung pathology or evidence of bronchiectasis.

Based on abdominal ultrasonography and MRI, none of the patients had any evidence for thoracic or abdominal laterality defect (Table 2). Specifically there was no situs inversus totalis, situs ambiguus, dextrocardia, or other evidence of heterotaxia. There was no asplenia or polysplenia. Liver was normally positioned in all; there was no midline or left sided liver.

Characteristics of PCD in Alström Syndrome

We further specified the respiratory symptoms to compare the respiratory findings of AS patients with common clinical indicators of PCD (Table 2). Recurrent otitis media, onset less than 2 years of age was documented in 39% (15/38) of the Alström cohort. Four (11%) patients reported stable, persistent wet cough, and three (8%) patients reported stable, persistent nasal congestion (Table 2). Three (8%) patients had nasal polyps documented in the medical record, with two requiring sinus surgery (Table 2). No other patients reported prior sinus surgeries. Neonatal respiratory distress in a term infant was reported in 8% (3/37) of this cohort, with one patient excluded for known premature birth (Table 2).

The mean nNO production of the nine patients in the Alström cohort was 232 ± 57.1 nl/min (range 126–296 nl/min) (Table 2). Electron microscopy analysis of nasal ciliary biopsies from the initial four AS patients with nNO revealed no ultrastructural abnormalities. Initially, we attempted to perform nasal NO studies on all patients of an appropriate age. However, the visual and/or auditory impairment of many patients as well as their inability to exhale evenly for an adequate length of time made it impossible to perform this evaluation. Similarly, we had originally intended to collect nasal mucosa biopsies on each patient for EM analysis. However, given the difficulty we had with biopsy collection in the first two patients and the fact that both their nNO and nasal biopsies were normal, we decided to collect EM samples on subsequent patients only if they had a compelling clinical history and abnormal nNO. None of the subsequent patients fit these criteria.

ILLUSTRATIVE CASES

Case 1

This 5-year-old Caucasian male was diagnosed with AS at 14 months of age. He was born at 35 weeks gestation and subsequently was hospitalized for 7 days, during which time he required 2 days of CPAP support. The family reported recurrent otitis media beginning at 18 months of age that required the placement of bilateral ear tubes and an adenoidectomy at age 5. He had an estimated 10 episodes of bronchitis/pneumonia since birth with no reported IV antibiotic treatment. He uses a cough assist device in the setting of a year-round, seasonally fluctuating, wet, productive cough that began at age 4. The family reports chronic wheezing

starting at age 4 that is treated with daily nebulizers. Recurrent sinusitis and chronic nasal congestion are also present. His nNO production was 125.6 nl/min (normal >77 nl/min), and a chest X-ray at the time of evaluation was normal. Electron microscopic analysis of a nasal ciliary biopsy performed at the NIH demonstrated no ultrastructural abnormalities indicative of primary ciliary dyskinesia.

Case 2

This 4-year-old Caucasian female was diagnosed with AS at age 3. She began having recurrent otitis media at age 5 months with approximately 15 ear infections between the ages of 5 and 24 months. These resolved after placement of ear tubes at age 3. She had *Pseudomonas* pneumonia based on sputum culture at 5 months of age and had approximately eight episodes of bronchitis or pneumonia since that time. She uses a percussive vest for airway clearance in the setting of a stable, chronic, productive wet cough. Recurrent sinusitis and chronic nasal congestion are also present. Electron microscopic analysis of a bronchial ciliary biopsy performed by an outside physician prior to being assessed at the NIH demonstrated no ultrastructural abnormalities indicative of primary ciliary dyskinesia, and a normal sweat chloride level ruled out cystic fibrosis. Immune deficiency was ruled out by unremarkable immunological evaluations. Her chest X-ray at the time of evaluation was normal and chest CT showed no bronchiectasis. Due to lack of patient cooperation as a result of her young age and impaired vision, nNO measurement could not be performed at the time of NIH evaluation.

DISCUSSION

Oto-Sino-Pulmonary Disease in AS

These data demonstrate the high prevalence of upper and lower respiratory tract involvement in AS, consistent with prior reports of a high burden of respiratory illness in AS, and confirm the chronic character of respiratory disease in some AS patients.^{1,15}

Few studies have quantified the respiratory burden of disease in AS. A 2010 review by Marshall et al. of 182 patients with AS reported chronic asthma, sinusitis, a dry barking cough, and reduced forced expiratory volume in 1 sec in 53% of patients. Recurrent bronchopneumonia was a frequent finding although no data were available to quantify this observation.¹⁴ While these pulmonary symptoms do not match exactly those observed in our study, the overall increased prevalence of respiratory disease in AS patients does correlate with our findings.

Tympanostomy tubes are often placed in children with chronic otitis media to prevent recurrence and complications. In the United States, nearly 40% of otherwise healthy children will have experienced three or more otitis media infections by age 6 years, and 7% of children will have tympanostomy tubes by age 3 years.²² In this AS cohort, we found that 92% reported recurrent otitis media, and half of patients had tympanostomy tubes placed with one-quarter requiring multiple sets. The greater incidence of tube placement in this cohort suggests an increased disease burden in AS relative to the general population.

Imaging

Chest imaging studies performed at the time of evaluation at the NIH revealed one patient with a nodular density and no other post-infectious structural lung pathology. Prior studies have reported pathologic changes in the lungs of AS patients. Marshall et al. found structural fibrotic changes suggested by diminished diffusing capacity for carbon monoxide, ground glass opacification on imaging, or lung biopsy in six of 161 patients (ages 10–40 yr) with significant respiratory symptoms. Additionally, one of these patients had bronchiectasis and another lung showed changes consistent with bronchiolitis obliterans.¹⁴ The ages of these specific patients were not reported. Furthermore, a case report of a 13.5 year-old female described cystic bronchiectasis and interstitial fibrous bands in the right middle and lower lobes.²³ Given the rarity of AS, our study represents one of the largest cohorts of AS patients who underwent comprehensive prospective evaluations in a single center. Despite this, our number of patients may be relatively small or our patients' average age may be relatively young to detect structural lung pathology. Additionally, we relied primarily on chest X-rays, which have limited sensitivity for detecting subtle fibrotic and bronchiectatic changes. The study by Marshall et al. used carbon monoxide diffusing capacity and lung biopsies as well as imaging to detect lung pathology. Furthermore, the case report of the child with bronchiectasis was detected with chest CT, and only one patient in our cohort received a chest CT at the time of evaluation.

Higher Rates of Disease Among Younger Patients

Our study found higher lifetime rates of chronic or recurrent wheezing, chronic cough, and persistent nasal congestion or rhinorrhea among patients younger than 5 years as compared to patients older than 18 years. This may reflect a recall or reporting bias among adult patients rather than suggesting that the incidence rates of these conditions has increased over the previous decade. In a study of 182 AS patients, Marshall et al. found that the mean age of patients reporting pulmonary symptoms was 2 years (<12 mo–42 yr) and the mean age of patients reporting chronic asthma was 5 years (12 mo–32 yr).¹⁴ Although the ranges show these conditions affecting adult patients into the fourth and fifth decade of life, the means suggest that they are primarily pediatric illnesses in AS. The same study reported that the mean age for many of the life-threatening complications of AS is adolescence and adulthood.¹⁴ Since the burden of disease affecting other organ systems in AS increases with age, a reporting bias among adult patients may account for a portion of our findings.

Comparison to PCD

We evaluated the burden for AS patients of respiratory manifestations commonly observed in PCD. This hypothesis was built on the finding by Driscoll et al. of bronchiectasis in patients with ADPKD, which suggested a pathophysiologic overlap between disorders of motile cilia, such as PCD, and non-motile ciliopathies, including ADPKD and AS.¹³

For all measures, the prevalence of respiratory manifestations among patients with AS was lower than the rates reported for PCD in the literature. Specifically, the PCD-characterizing symptoms including laterality defects, unexplained neonatal respiratory distress, year-round nasal congestion, and wet cough were far less prevalent in the AS cohort compared to the

PCD population. While laterality defects are observed in 53% of patients with PCD,¹⁸ none of the patients in our AS cohort had any evidence of a laterality defect on imaging.

Two of our measures were less stringently defined than in the PCD literature. Neonatal respiratory distress is often qualified in the PCD literature as being “unexplained” and occurring only in full-term infants.^{16,17} Our study excluded one patient with known preterm birth, but did not stringently screen for other known causes of neonatal respiratory distress such as meconium aspiration. Additionally, the PCD literature specifies otitis media with effusion. Our study did not specify effusion although the placement of ear tubes in half of patients with recurrent otitis media suggests the presence of effusion. These broader definitions may have resulted in an inflated prevalence among the AS cohort; however, despite this the frequencies of unexplained neonatal distress and recurrent otitis media in our AS cohort were much lower than reported in the PCD population.

The average nNO production for the nine AS patients in our cohort was 232 nl/min, while the range used to screen for PCD is <77 nl/min.^{18,20} Furthermore, PCD is associated with a range of ultrastructural abnormalities in motile cilia.^{10,11} In contrast, the four AS patients in our cohort with electron microscopic evaluation of respiratory cilia had normal respiratory ciliary ultrastructure. However, given the small number of Alström patients sampled and the reported finding that in approximately one third of PCD patients the ultrastructural anatomy of the motile cilia may be completely normal,¹⁸ it is still possible that AS may impair the function of motile cilia.

Study Limitations

Three factors may complicate generalizing this study to the overall AS patient population. First, it relied on a small cohort and we were not able to perform nasal no measurements or nasal mucosal biopsies for EM in all patients. However given the rarity of AS, our cohort represents the largest AS cohort comprehensively evaluated in a single center.¹⁵ Second, because AS is a phenotypically heterogeneous condition, it is difficult for any cohort to reliably represent the disease burden of the overall patient population. Third, although we evaluated all patients prospectively at the NIH Clinical Center, for the historical data such as frequency of respiratory symptoms we had to rely on patients’ and parents’ reports and past medical records.

CONCLUSION

AS is a severe ciliopathy characterized by progressive multi-system organ dysfunction. To date, few studies have focused on the respiratory tract complications of AS. However, the high prevalence of oto-sino-pulmonary complications in this cohort, as well as the characteristics of two representative cases, illustrate the potential severity and complexity of upper and lower respiratory tract involvement in AS. This may better guide the management of patients to include earlier referrals and screenings for respiratory complications, as well as help inform future studies on the molecular pathophysiology of AS.

These data suggest a phenotypic overlap between AS and PCD. However, severely abnormal motile cilia function is unlikely in AS given nasal nitric oxide levels significantly higher

than in the range observed in PCD, absence of laterality defects, and the relatively lower presence of stable, year-round wet cough; stable, year-round nasal congestion; and neonatal respiratory distress in this AS cohort as compared to PCD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AS	Alstrom syndrome
nNO	Nasal nitric oxide
PCD	Primary ciliary dyskinesia

REFERENCES

1. Marshall JD, Maffei P, Collin GB, Naggert JK. Alström syndrome: genetics and clinical overview. *Curr Genomics* 2011;12:225–235. [PubMed: 22043170]
2. Marshall JD, Muller J, Collin GB, Milan G, Kingsmore SF, Dinwiddie D, Farrow EG, Miller NA, Favaretto F, Maffei P, et al. Alström syndrome: mutation spectrum of ALMS1. *Hum Mutat* 2015;36:660–668. [PubMed: 25846608]
3. Hearn T, Spalluto C, Phillips VJ, Renforth GL, Copin N, Hanley NA, Wilson DI. Subcellular localization of ALMS1 supports involvement of centrosome and basal body dysfunction in the pathogenesis of obesity, insulin resistance, and type 2 diabetes. *Diabetes* 2005;54:1581–1587. [PubMed: 15855349]
4. Li G, Vega R, Nelms K, Gekakis N, Goodnow C, McNamara P, Wu H, Hong NA, Glynne R. A role for Alström syndrome protein, Alms1, in kidney ciliogenesis and cellular quiescence. *PLoS Genet* 2007;3:0009–0020.
5. Knorz VJ, Spalluto C, Lessard M, Purvis TL, Adigun FF, Collin GB, Hanley NA, Wilson DI, Hearn T. Centriolar association of ALMS1 and likely centrosomal functions of the ALMS motif-containing proteins C10orf90 and KIAA1731. *Mol Biol Cell* 2010;21:3617–3629. [PubMed: 20844083]
6. Collin GB, Marshall JD, King BL, Milan G, Maffei P, Jagger DJ, Naggert JK. The Alström syndrome protein, ALMS1, interacts with α -actinin and components of the endosome recycling pathway. *PLoS ONE* 2012;7:e37925.
7. Andersen J, Wilkinson C, Mayor T. Proteomic characterization of the human centrosome by protein correlation profiling. *Nature* 2003;426:570–574. [PubMed: 14654843]
8. Satir P, Christensen ST. Overview of structure and function of mammalian cilia. *Annu Rev Physiol* 2007;69:377–400. [PubMed: 17009929]

9. Badano JL, Mitsuma N, Beales PL, Katsanis N. The ciliopathies: an emerging class of human genetic disorders. *Annu Rev Genomics Hum Genet* 2006;7:125–148. [PubMed: 16722803]
10. Leigh MW, Pittman JE, Carson JL, Ferkol TW, Dell SD, Davis SD, Knowles MR, Zariwala MA. Clinical and genetic aspects of primary ciliary dyskinesia/kartagener syndrome. *Genet Med* 2009;11:473–487. [PubMed: 19606528]
11. Stillwell PC, Wartchow EP, Sagel SD. Primary ciliary dyskinesia in children: a review for pediatricians, allergists, and pediatric pulmonologists. *Pediatric Allergy Immunol Pulmonol* 2011;24:191–196.
12. Sagel SD, Davis SD, Campisi P, Dell SD. Update of respiratory tract disease in children with primary ciliary dyskinesia. *Proc Am Thorac Soc* 2011;8:438–443. [PubMed: 21926396]
13. Driscoll JA, Bhalla S, Liapis H, Ibricevic A, Brody SL. Autosomal dominant polycystic kidney disease is associated with an increased prevalence of radiographic bronchiectasis. *Chest* 2008;133:1181–1188. [PubMed: 18263686]
14. Marshall JD, Bronson RT, Collin GB, Nordstrom AD, Maffei P, Paisey RB, Carey C, Macdermott S, Russell-Eggitt I, Shea SE, et al. New Alström syndrome phenotypes based on the evaluation of 182 cases. *Arch Intern Med* 2005;165:675–683. [PubMed: 15795345]
15. Marshall JD, Beck S, Maffei P, Naggert JK. Alström syndrome. *Eur J Hum Genet* 2007;15:1193–1202. [PubMed: 17940554]
16. Knowles MR, Daniels LA, Davis SD, Zariwala MA, Leigh MW. Primary ciliary dyskinesia: recent advances in diagnostics, genetics, and characterization of clinical disease. *Am J Respir Crit Care Med* 2013;188:913–922. [PubMed: 23796196]
17. Leigh MW, Shapiro AJ, Pittman JE, Davis SD, Lee H, Krischer J, Ferkol TW, Atkinson JJ, Sagel SD, Rosenfeld M, et al. Definition of clinical criteria for diagnosis of primary ciliary dyskinesia. *Am J Respir Crit Care Med* 2012;185:A2483.
18. Leigh MW, Ferkol TW, Davis SD, Lee H-S, Rosenfeld M, Dell SD, Sagel SD, Milla C, Olivier KN, Sullivan KM, et al. Clinical features and associated likelihood of primary ciliary dyskinesia in children and adolescents. *Ann Am Thorac Soc* 2016;13:1305–1313. [PubMed: 27070726]
19. Shapiro AJ, Zariwala MA, Ferkol T, Davis SD, Sagel SD, Dell SD, Rosenfeld M, Olivier KN, Milla C, Daniel SJ, et al. Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD foundation consensus recommendations based on state of the art review. *Pediatr Pulmonol* 2015;51:115–132. [PubMed: 26418604]
20. Leigh MW, Hazucha MJ, Chawla KK, Baker BR, Shapiro AJ, Brown DE, Lavange LM, Horton BJ, Qaqish B, Carson JL, et al. Standardizing nasal nitric oxide measurement as a test for primary ciliary dyskinesia. *Ann Am Thorac Soc* 2013;10:574–581. [PubMed: 24024753]
21. Olin JT, Burns K, Carson JL, Metjian H, Atkinson JJ, Davis SD, Dell SD, Ferkol TW, Milla CE, Olivier KN, et al. Diagnostic yield of nasal scrape biopsies in primary ciliary dyskinesia: a multicenter experience. *Pediatr Pulmonol* 2011;46:483–488. [PubMed: 21284095]
22. Rosenfeld RM, Schwartz SR, Pynnonen a M, Tunkel DE, Hussey HM, Fichera JS, Grimes AM, Hackell JM, Harrison MF, Haskell H, et al. Clinical practice guideline: tympanostomy tubes in children-executive summary. *Otolaryngol Head Neck Surg* 2013;149:8–16. [PubMed: 23818537]
23. Kaya A, Orbak Z, C yir A, Doeray H, Ta demir , Ozantürk A, Bingo F. Combined occurrence of Alström syndrome and bronchiectasis. *Pediatrics* 2014;133:e780–e783. [PubMed: 24534407]
24. Noone PG, Leigh MW, Sannuti A, Minnix SL, Carson JL, Hazucha M, Zariwala MA, Knowles MR. Primary ciliary dyskinesia: diagnostic and phenotypic features. *Am J Respir Crit Care Med* 2004;169:459–467. [PubMed: 14656747]
25. Bush A, Chodhari R, Collins N, Copeland F, Hall P, Harcourt J, Hariri M, Hogg C, Lucas J, Mitchison HM, et al. Primary ciliary dyskinesia: current state of the art. *Arch of Dis Child* 2007;92: 1136–1140. [PubMed: 17634184]
26. Min YG, Shin JS, Choi SH, Chi JG, Yoon CJ. Primary ciliary dyskinesia: ultrastructural defects and clinical features. *Rhinology* 1995;33:189–193. [PubMed: 8919209]

TABLE 1—

Lifetime Respiratory Involvement by Age at Evaluation

	5 years (N = 8)	6–17 years (N = 17)	18 years (N = 13)	All patients (N = 38)
Recurrent otitis media	8 (100%)	16 (94%)	11 (85%)	35 (92%)
Sinusitis	5 (63%)	7 (41%)	7 (54%)	19 (50%)
Nasal congestion or rhinorrhea	5 (63%)	10 (59%)	3 (23%)	18 (47%)
Bronchitis or pneumonia	6 (75%)	8 (47%)	9 (69%)	23 (61%)
Chronic cough	5 (63%)	7 (41%)	4 (31%)	16 (42%)
Chronic or recurrent wheezing	5 (63%)	7 (41%)	2 (15%)	14 (37%)

TABLE 2—
Comparison of Clinical Features in Alström Syndrome Cohort Patients and PCD Patients From the Literature

	Alström syndrome	Primary ciliary dyskinesia	References
Unexplained neonatal respiratory distress	8%	57–80%	10,16,18,24,25
Recurrent otitis media, onset < 2 years	39%	>80%	16
Stable, persistent wet cough	11%	84–100%	10
Stable, persistent nasal congestion	8%	76–100%	24,25
Nasal polyps	8%	15%	26
Average nNO production	232 ± 57.1 nl/min	<77 nl/min	20
Laterality defect	0%	53%	18