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Phenotype-genotype associations in Primary Ciliary Dyskinesia: where do we stand?

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Take home message:

Defining distinct PCD clinical phenotypes and their associations to genotypes in large collaborative clinical and research networks could have important implications to clinical management and subsequently patients' quality of life.

The study by Shoemark et al. [1], published in this issue of the European Respiratory Journal, is the first large-scale multinational study investigating genotype-phenotype correlations in Primary Ciliary Dyskinesia (PCD), a genetically heterogeneous rare disease. The study confirmed genotype-phenotype relationships reported by previous smaller studies and identified new relationships, bringing the importance of defining distinct PCD phenotypes into the spotlight.

PCD: a heterogeneous disease

PCD is a rare genetic multiorgan disease with an estimated prevalence of 1 in 10,000 [2, 3]. It is characterised by genetic heterogeneity and so far, mutations in 50 genes have been described [4, 5]. These disease-causing mutations lead to defects in the structure or function of cilia [6, 7], impairing mucociliary clearance and resulting in recurrent progressive upper and lower respiratory disease [8-10]. Situs inversus occurs in about 50% of people while an additional 10-12% presents with other heterotaxic syndromes sometimes combined with congenital heart defects [11, 12]. Subfertility is reported commonly in male and female patients though still not well described, and in rarer cases other organ systems are affected resulting in hydrocephalus, retinitis pigmentosa or renal abnormalities [13, 14]. Until recently, PCD was perceived as one disease with the largest group of patients fitting what was considered a typical clinical presentation: runny nose, many ear infections in childhood, and progressive lung disease leading to bronchiectasis in adulthood [15]. This presentation remains common; however, as the diagnostic procedures for PCD improved and our understanding of the disease deepened, we became aware of important phenotypical variations [16]. We now consider PCD more as an umbrella term for a spectrum of ciliopathies with overlapping clinical features [17].

Older studies describing the clinical features of PCD such as symptoms or lung function showed important heterogeneity, underlining the possibility of distinct PCD phenotypes as in other chronic respiratory diseases [9, 18-25]. During the past 5-6 years, several studies assessed possible associations of PCD disease severity with genotype or corresponding ultrastructural groups; a selected summary presented in Table 1. A multicentre study in North American children described that lung disease was worse in those with isolated inner dynein arm (IDA), central apparatus (CA) and microtubular disorganization (MTD) ultrastructural defects, most of whom had biallelic mutations in CCDC39 or CCDC40 genes, compared to those with outer dynein arm (ODA) defects [26]. A large multinational cohort of 991 children and adults with PCD highlighted differences in FEV1 z-scores between ultrastructural defect groups, and patients with a microtubular defect had worse lung function than patients with a non-diagnostic transmission electron microscopy (TEM) and patients with ODA or IDA defects [21]. Studies examining disease progression reported similar results. In a large British adult cohort, patients with microtubular defects had the greatest annual FEV1 decline compared with patients with outer (ODA) or combined ODA/IDA defects and patients with normal or inconclusive TEM [25]. A longitudinal study including 137 North American children showed that those with CCDC39 or CCDC40 mutations had significantly diminished lung function and growth parameters compared to those with DNAH5 mutations [18]. Similarly, patients with PCD and CCDC39 or CCDC40 mutations had the worst evolution of lung function in an Italian cohort, while patients with DHAH11 mutations the most favourable [24].

What the study found

The study of Shoemark et al. [1] is a large multinational collaborative study including paediatric and adult patients. The authors investigated phenotype-genotype relationships using clinical, diagnostic, and genetic data from 396 people with genetically confirmed PCD. Cluster analyses confirmed established associations from previous studies between defects in ciliary structure and function and genetics. Patients with defects in the central complex and nexin-dynein regulatory complex gene functional groups, corresponding primarily to mutations in the CCDC39 and CCDC40 genes, were more likely to have lower lung function at diagnosis compared to those with dynein structural gene mutations. This cluster of patients included a defined group with no history of rhinitis. On the other hand, patients with preserved lung function at diagnosis had predominantly a DNAH11 gene mutation and were less likely to have had a history of neonatal respiratory distress (NRDS). Interestingly, patients with a DNAH5 mutation, which is the most common genetic cause of PCD, were the largest and most phenotypical diverse group regarding lung function and symptom history.

The authors applied the novel non-hypothesis driven method, topological data analysis, to identify clusters of clinical data including among others anthropometric data, lung function results and symptom history, and diagnostic data including ciliary beat pattern and results from TEM. Exploratory cluster analyses were first applied in 199 patients and thereafter validated in the second half of the population including 197 patients. Validation analyses confirmed the association between a mutation in CCDC39 and lower lung function at diagnosis and higher proportion of reported NRDS and contrasting higher lung function at diagnosis and less reported NRDS in patients with a DNAH11 mutation.

What difficulties did the study face?

The study by Shoemark et al. is a well-conducted important study that brings us one step closer to understanding phenotypes in PCD and their relationship with different genotypes [1]. However, the study also faced certain methodological difficulties – difficulties that are very hard to overcome due to the rarity and heterogeneity of PCD. Despite this study being the largest yet to explore phenotype-genotype associations, it was limited by small sample sizes in certain genotype groups. The study included in total 396 patients with PCD who had mutations in 31 different genes. Only six of these 31 gene mutations had a sample size larger than 20 patients. The authors tried to overcome this by grouping gene mutations into five categories depending on the structural or functional consequence of the mutations, however the smallest group still had only 13 patients. Another limitation was the restrictions related to the clinical data used to explore phenotype-genotype associations such as incompleteness, a major issue with all studies including retrospective chart data, and the cross-sectional design where only data at time of diagnosis were included. As previously shown, disease progression in PCD is highly variable and could also depend on genotype. It would therefore be essential for future studies to include longitudinal data to understand time-varying associations between phenotypes and genotypes.

How to bring research on PCD phenotypes further

The challenges the authors encountered in this study are typical for research on phenotypes particularly in rare diseases and they underline where to focus the efforts in PCD research to further define distinct clinical phenotypes and improve patient care.

Genetic testing has recently become more widespread, not only in research but also as part of the diagnostic process for PCD patients, however still many patients have not undergone testing. In addition to its role in confirming PCD diagnosis, the identification of disease-causing mutations in PCD patients will allow for even larger collaborative studies on phenotype-genotype associations. To achieve this, clinicians should ideally refer all their PCD patients, even the ones with resolved diagnosis, for genetic testing. Targeted testing on a subset of genes, guided by other tests such as TEM, could be a preferable solution for these patients. Identification of well genotyped patients through the international PCD registry will allow larger studies in the future [27], also for the less common gene mutation groups. A new online open database registering PCD gene mutations and specific combinations of variants is being set up in the framework of the BEAT-PCD clinical research collaboration supported by the ERS and could potentially have an important role in this process [28].

Another issue that hinders most phenotype-genotype studies is the limited available clinical data. So far, clinical data are mostly derived from chart reviews, leading to missing and often unreliable information, particularly on symptoms. To address this and improve the quality of clinical data used in research, a large multidisciplinary team developed the FOLLOW-PCD, a PCD-specific form for standardised prospective data collection, including also patient-reported information on symptoms during routine clinical follow-up [29]. Furthermore, it is important to identify which clinical measures would help us to best characterize PCD disease severity and its progression. Lung function measured via spirometry might be widely available and included in most studies but does not provide the most sensitive information on lung disease in PCD [22]. Thus, we might need to select and incorporate longitudinal information from multiple

modalities accounting both for structural and functional lung impairment over the patients' lifetime to phenotypically characterize PCD [30]. Standardised prospective collection of appropriate clinical data will allow us to get better evidence on PCD clinical phenotypes, severity and disease prognosis.

Implications for patient care

Defining distinct PCD clinical phenotypes and their associations with genotypes could have important implications for clinical management and subsequently patients' quality of life. It could contribute to personalised clinical care decisions and potential early measures to prevent or delay disease progression. On the other hand, this process could help us identify patients with less typical phenotypic profiles who might remain still undiagnosed so they could be referred for PCD diagnostic testing.

The study by Shoemark et al. shows what could be done so far and paves the way for future studies to build on its findings and improve further the definition of phenotype-genotype associations in PCD. We expect this to be a long process and one thing is certain: large collaborative clinical and research networks are the only way to achieve this.

Table 1: Selected studies reporting phenotype-genotype associations among patients with PCD

First author, journal, year	Study design, country, data collection period. Time followed up	Inclusion criteria, age	N	Main findings
Shoemark, Eur Respir J, 2021	Retrospective, cross-sectional United Kingdom, Netherlands, France Collected until 2019	People with genetically confirmed PCD Median age 11 y (IQ range 4-18 y)	396	• Genotype groups: 171 (43%) dynein structure defect (most frequent: DNAH5), 94 (24%) dynein assembly defect (most frequent: CCDC103), 50 (13%) radial spoke/central complex defect (most frequent: RSPH4A), 68 (17%) N-DRC/molecular ruler (most frequent: CCDC39), 13 other defects. • N-DRC or molecular ruler defects associated with poor FEV1 (-2.7 z-scores, SD 1.6) and absence of history of rhinitis. • Dynein structure defects associated with preserved lung function (-1.4 FEV1 z-scores, SD 1.4) and absence of NRDS
Pifferi, Chest, 2020	Prospective, longitudinal Italy Collected 2008-2018 Mean follow-up 5 y (range 1-10 y)	People aged >5 years with confirmed PCD 66 children enrolled, mean age 10 y (SD 4 y) 69 adults enrolled, mean age 34 (SD 11 y)	135	• 131 with EM results: 33 (25%) had ODA/IDA, 33 (25%) had IDA/CA/MTD, 14 (11%) had CA, 25 (19%) had ODA only, 26 (20%) had normal EM. • Children: BMI lowest in those with CA defect (-0.76 z-score, SD 2.09). Lung function worst in those with IDA/CA/MTD (FEV1 z-scores -1.29, SD 0.82) or CA alone (FEV1 z-scores -1.62, SD 1.02). • Adults: Worst lung function in those with IDA/CA/MTD defects (FEV1 z-scores -3.72, SD 1.28). • Genotype comparisons: worst lung function among those with CCDC39 and CCDC40 (FEV1 z-scores -1.38, SD 0.78)
Davis, Am J Respir Crit Care Med, 2019	Prospective, longitudinal USA, Canada Collected 2006-2011 Median follow-up 6 y (range 1-6 y)	People aged <19 years with confirmed PCD Age at enrollment 8 y (SD 5 y)	137	• 55 (40%) had ODA defects, 20 (15%) had ODA+IDA defects, 41 (30%) had IDA/CA/MTD defects, 12 (9%) had normal ultrastructure, 9 (6%) had other defects. • CCDC39 and CCDC40 mutations (IDA/CA/MTD defects) associated with lower FEV1 (-15 %predicted) and weight (-0.8 z-scores) and height (-0.60 z-scores) than DNAH5 (ODA defects) • Lung function decline (FEV1) was highest among those with IDA/CA/MTD defects
Halbeisen, Eur Respir J, 2018	Retrospective, cross-sectional 14 different countries Collected until 2016	People aged >5 years with a definite, probable, or clinical PCD diagnosis	991	• 689 with TEM results: 425 (43%) had ODA or IDA, 134 (14%) had MT defects, 123 were non-diagnostic • Patients with MT defects had worse lung function (-1.91 FEV1 z-scores, -1.08 FVC z-scores than patients with non-diagnostic TEM (-1.19 FEV z-scores, -0.74 FVC z-scores and patient with ODA or IDA defects (-1.50 FEV1 z-scores, -0.73 FVC z-scores)
Shah, Eur Respir J, 2016	Retrospective, longitudinal United Kingdom Data period: 1980-2014 median follow-up 7 y (range 1-34 y)	People aged >17 y with confirmed PCD Median age 35 y (range 19-75 y)	151	• 138 with TEM results: 92 (67%) had IDA and/or ODA defects, 27 (20%) had MTD defects, 19 (13%) had normal/inconclusive result. • Greatest annual FEV1 decline in patients MTD defects (-0.75% predicted, 95% CI -2.08-0.58) compared with ODA/IDA (-51% predicted, 95% CI -1.41-0.39) and normal/inconclusive TEM (-0.13% predicted, 95%CI -1.53-1.28).
Davis, Am J Respir Crit Care Med, 2015	Prospective, longitudinal USA, Canada Collected 2006-2012	People aged <19 years with confirmed PCD Median age 8 y (range 5-11 y)	118	• 54 (46%) had ODA defects, 18 (15%) had ODA+IDA defects, 40 (34%) had IDA/CA/MTD defects, 6 (5%) had CA or IDA only. • Patients with IDA/CA/MTD defects had worse lung function (72 % predicted FEV1, IQ range 58-88), more radiographic disease (3.5 lobes with bronchiectasis), and poorer growth (BMI 46th percentile) than those with ODA or ODA+IDA.

Abbreviations: CA: central apparatus; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; IDA: inner dynein arm; MT: microtubular; MTD: microtubular disorganization; ODA; outer dynein arm; N-DRC: nexin-dynein regulatory complex; PCD: primary ciliary dyskinesia; TEM: transmission electron microscopy; y: years

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