Concept sheet for publication

(Version 01)

Title of project/abstract:

An international study on genotype/phenotype correlation with focus on lung function in patients with Primary Ciliary Dyskinesia (PCD)

Writing team

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Possible data providers

- All ERN (European reference network) - Lung members and supporting partners
- All members of BEAT-PCD and BESTCILIA
- All members of the AG PCD of the GPP ("Gesellschaft für Pädiatrische Pneumologie")

Authorship suggestion

Data providers and departments involved in the study will be offered a co-authorship according to the **criteria of the International Committee of Medical Journal Editors**, which include all the following: i) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; ii) drafting the work or revising it critically for important intellectual content; iii) final approval of the version to be published; and iv) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authors are suggested as Johanna Raidt as first and Henrike Krenz as second author, as well as Heymut Omran as last and Kim Nielsen as second last author. Other authors in alphabetic order. Trial sites are offered a maximum of three co-authorships (1: > 5 PCD patients; 2: > 30 PCD patients; 3: > 60 PCD patients) among investigators.

All other partners and collaborators contributing to this trial shall be duly acknowledged in the publication.

This effort is supposed to result in a joint international publication with all participating centers, but importantly each center or national register retains the possibility and rights to publish the results separately and independently of the overall publication.

Background

Primary Ciliary Dyskinesia (PCD) is a rare genetic disorder characterized by dysfunction of motile cilia associated with recurrent infections of the airways, laterality defects (*Situs inversus*

totalis in about 50% of cases) and fertility problems. At present, mutations in > 40 genes associated with PCD and mucociliary clearance disorders have been identified, representing most likely two thirds of all human cases. While being involved in the majority of identified PCD-genes, our working group has a great expertise in genetic analysis and diagnostic work-up of patients with PCD.

Hallmark symptom of PCD is the chronic purulent lung disease due to the reduced mucociliary clearance. Chronic inflammation and recurrent infections of the airways promote continuous lung damage, bronchiectasis and could finally lead to total lung failure. For other congenital diseases with chronic lung conditions, e.g. Cystic fibrosis (CF), an affected lung function with a steady decline is well described and spirometry is widely used to monitor disease progression (1). For PCD there are only limited data available and studies often comprise small cohorts. In general, available data assume a decline of lung function in PCD patients compared to healthy individuals (2-4), but less pronounced than in CF (4, 5). Altogether, results of the studies remain heterogeneous, in particular concerning the influence of an early diagnosis and a proper treatment on lung function (2, 4, 6, 7).

Furthermore, despite a significant progression in genetically solved cases there are almost no data on genotype specific lung function in patients with PCD. Recently, there are few studies indicating an association between specific ultrastructural or genetic defects, e.g. patients carrying mutations in the genes *MCIDAS, CCNO, CCDC39* and *CCDC40* and a severe clinical course in particular a worse respiratory phenotype (8-11). There might be a less severe phenotype in PCD sub-types due to mutations in genes encoding radial spoke components (12). Currently a systematic review shows the high variation of spirometric indices in a great PCD cohort (13). These findings underline the great necessity of detailed characterization of genotype specific phenotypes with focus on important parameters such as lung function to better understand the natural history of distinct PCD-variants with a view to improve individual patient care by tailored treatment activity according to likely disease severity.

Aims:

The aims of this paper are:

- Correlation between genotype and lung function of patients with genetically confirmed PCD in an international cohort on a longitudinal basis
- Determine further parameters, such as body mass index (BMI), possibly associated with lung function in genetically confirmed PCD patients

Methods

Inclusion criteria:

- Patients with a genetically confirmed diagnosis of PCD (bi-allelic mutations in a gene, known to cause PCD) with typical clinical symptoms of PCD and at least one other method confirming PCD-diagnosis
- Children and adults diagnosed with PCD of all age groups and able to perform spirometry
- Longitudinal datasets with measurements of lung function (FEV1, FVC, FEV1/FVC, FEF25-75) (with date and height at the performed measurement, respectively)
  → at least 3-4 different measurements in at least 2 years of follow up are expected - in cases where this is not possible, sporadic data could also be provided
- Delivery of datasets to the international PCD registry (14) with all necessary values within the anticipated time schedules

Data preparation:

1. Genotype of patients including information of the exact mutations by indicating the disease specific gene including both DNA- and protein-level
   (e.g. *DNAH5* (Exon 20: c.3036_3041delAGCG, p.V1014Lfs*20 het. + Exon 25: c.C3949T, p.Q1317* het.)).

   → Results of segregation of autosomal recessive mutations should be provided

   → In genetically unclear or implausible cases, access to genetic analysis and further analyses e.g. immunofluorescence analysis (IF) and transmission electron microscopy (TEM) within the framework of this research project is offered

2. Obligatory values for calculating %-predicted and z-scores values of lung function:
   - Height (at date of measurement)
   - Ethnicity (as defined in lung function reference material)
   - Age at measurement (as defined by date of birth and date of lung function measurement)
   - Sex

   All lung function variables will be converted into sex-, height-, age-, and ethnicity-adjusted %-predicted values and z-scores using relevant reference materials, e.g. values of the Global lung function initiative (GLI) 2012 (15). Furthermore, data quality checks and identification of outliers and implausible values will be performed. If required, we will

contact the referring centre. Contribution of longitudinal data of patients provides important additional information on natural history of patients with different genotypes.

3. Analysis of further parameters possibly correlated with lung function in PCD patients:
    - Nationality / country of origin
    - Weight (at date of measurement, for calculation of body mass index (BMI))
    - Age, when clinical PCD diagnosis has been established (based on clinical and diagnostical findings (such as nasal NO, high-speed videomicroscopy analysis (HVMA), TEM, IF and/or genetics)
    - Laterality status
    - Supplemental oxygen therapy dependency
    - thoracic surgery (e.g. lobectomy)
    - scoliosis
    - thoracic malformations (e.g. funnel chest)
    - Status of *Pseudomonas aeruginosa*

Possible figures (might be changed depending on available datasets)

- Descriptive statistics for demographic and clinical characteristics of international patient cohort including genotype
- Results of lung function including z-score values (FEV1, FVC, FEV1/FVC, FEF25-75)
- Correlation between total lung function z-scores and genotype in relation to age/time
- Correlation between total lung function z-scores and other possibly associated parameters (in relation to age/time)

Funding:

- Registry Warehouse (Horizon 2020, GA n° 777295)
- Eva Luise Köhler Research Award
- Care-for-Rare Science Award
- DFG funding
- Local funding

Target journal(s):

- American Journal of Respiratory and Critical Care Medicine and Lancet RM
- Other possibilities: Thorax, European Respiratory Journal, Chest

Anticipated Milestones:

- All interested partners consent this concept sheet until 31.10.2019
- All partners deliver datasets to the international PCD registry with all the necessary values until 31.12.2019
- Writing team finished analysis and circulates a draft of the manuscript by 28.2.2020
- All involved authors comment on the manuscript within 2 weeks/by 15.3.2020
- Circulation to involved authors for final approval/submission to target journal by 31.3.2020

Literature

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