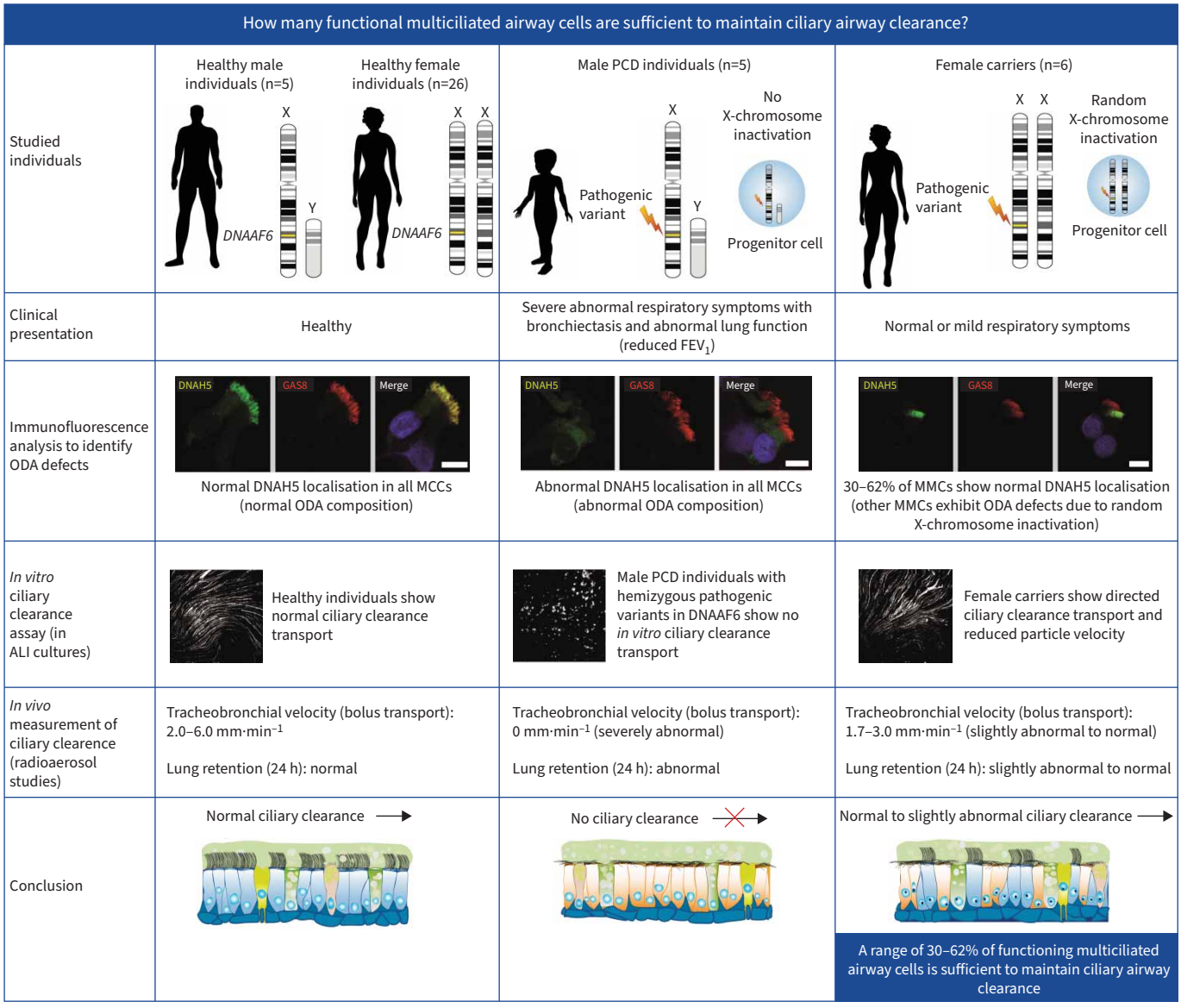
EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
N.T. LOGES ET AL.

A range of 30–62% of functioning multiciliated airway cells is sufficient to maintain ciliary airway clearance

Niki T. Loges, June Kehlet Marthin, Johanna Raidt, Heike Olbrich, Inga M. Höben, Sandra Cindric, Diana Bracht, Julia König, Cynthia Rieck, Sebastian George, Tim Luis Kloth, Kai Wohlgemuth, Petra Pennekamp, Bernd Dworniczak, Mathias G. Holgersen, Jobst Römel, Christian Schmalstieg, Isabella Aprea, Jann Mortensen, Kim G. Nielsen and Heymut Omran



GRAPHICAL ABSTRACT Overview of the study. PCD: primary ciliary dyskinesia; FEV_1: forced expiratory volume in 1 s; ODA: outer dynein arm; MCC: multiciliated cell.

Link to published version: https://doi.org/10.1183/13993003.01441-2023

Eur Respir J 2024; 64: 2301441

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
N.T. LOGES ET AL.

A range of 30–62% of functioning multiciliated airway cells is sufficient to maintain ciliary airway clearance

Niki T. Loges[1], June Kehlet Marthin[2,3], Johanna Raidt[1], Heike Olbrich[1], Inga M. Höben[1], Sandra Cindric[1], Diana Bracht[1], Julia König[1], Cynthia Rieck[1], Sebastian George[1], Tim Luis Kloth[1], Kai Wohlgemuth[1], Petra Pennekamp[1], Bernd Dworniczak[1], Mathias G. Holgersen[2], Jobst Römel[4], Christian Schmalstieg[1], Isabella Aprea[1], Jann Mortensen[2,5], Kim G. Nielsen[2,3] and Heymut Omran[1]

[1]Department of General Pediatrics, University Children's Hospital Muenster, Muenster, Germany. [2]Danish PCD Centre, Danish Paediatric Pulmonary Service, Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [3]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. [4]Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. [5]Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

Corresponding author: Heymut Omran (Heymut.Omran@ukmuenster.de)

Shareable abstract (@ERSpublications)
Restoring cilia function in 30–62% of defective respiratory cells is sufficient to improve ciliary clearance in PCD individuals https://bit.ly/45PQQg9

Cite this article as: Loges NT, Marthin JK, Raidt J, *et al*. A range of 30–62% of functioning multiciliated airway cells is sufficient to maintain ciliary airway clearance. *Eur Respir J* 2024; 64: 2301441 [DOI: 10.1183/13993003.01441-2023].

This article has an editorial commentary: https://doi.org/10.1183/13993003.01573-2024

Received: 25 Aug 2023
Accepted: 16 June 2024

Abstract

Background Primary ciliary dyskinesia is a genetic disorder caused by aberrant motile cilia function that results in defective ciliary airway clearance and subsequently leads to recurrent airway infections and bronchiectasis. We aimed to determine: how many functional multiciliated airway cells are sufficient to maintain ciliary airway clearance?

Methods To answer this question we exploited the molecular defects of the X-linked recessive primary ciliary dyskinesia variant caused by pathogenic variants in *DNAAF6* (*PIH1D3*), characterised by immotile cilia in affected males. We carefully analysed the clinical phenotype and molecular defect (using immunofluorescence and transmission electron microscopy) and performed *in vitro* studies (particle tracking in air–liquid interface cultures) and *in vivo* studies (radiolabelled tracer studies) to assess ciliary clearance of respiratory cells from female individuals with heterozygous and male individuals with hemizygous pathogenic *DNAAF6* variants.

Results Primary ciliary dyskinesia male individuals with hemizygous pathogenic *DNAAF6* variants displayed exclusively immotile cilia, absence of ciliary clearance and severe primary ciliary dyskinesia symptoms. Owing to random or skewed X-chromosome inactivation in six female carriers with heterozygous pathogenic *DNAAF6* variants, 54.3±10% (range 38–70%) of multiciliated cells were defective. Nevertheless, *in vitro* and *in vivo* assessment of the ciliary airway clearance was normal or slightly abnormal. Consistently, heterozygous female individuals showed no or only mild respiratory symptoms.

Conclusions Our findings indicate that having 30–62% of multiciliated respiratory cells functioning can generate either normal or slightly reduced ciliary clearance. Because heterozygous female carriers displayed either no or subtle respiratory symptoms, complete correction of 30% of cells by precision medicine could improve ciliary airway clearance in individuals with primary ciliary dyskinesia, as well as clinical symptoms.