

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

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How many functional multiciliated airway cells are sufficient to maintain ciliary airway clearance?			
Studied individuals	<p>Healthy male individuals (n=5)</p> <p>Healthy female individuals (n=26)</p>	<p>Male PCD individuals (n=5)</p>	<p>Female carriers (n=6)</p>
Clinical presentation	Healthy	Severe abnormal respiratory symptoms with bronchiectasis and abnormal lung function (reduced FEV ₁)	Normal or mild respiratory symptoms
Immunofluorescence analysis to identify ODA defects	<p>Normal DNAH5 localisation in all MCCs (normal ODA composition)</p>	<p>Abnormal DNAH5 localisation in all MCCs (abnormal ODA composition)</p>	<p>30–62% of MMCs show normal DNAH5 localisation (other MMCs exhibit ODA defects due to random X-chromosome inactivation)</p>
<i>In vitro</i> ciliary clearance assay (in ALI cultures)	<p>Healthy individuals show normal ciliary clearance transport</p>	<p>Male PCD individuals with hemizygous pathogenic variants in DNAAF6 show no <i>in vitro</i> ciliary clearance transport</p>	<p>Female carriers show directed ciliary clearance transport and reduced particle velocity</p>
<i>In vivo</i> measurement of ciliary clearance (radioaerosol studies)	<p>Tracheobronchial velocity (bolus transport): 2.0–6.0 mm·min⁻¹</p> <p>Lung retention (24 h): normal</p>	<p>Tracheobronchial velocity (bolus transport): 0 mm·min⁻¹ (severely abnormal)</p> <p>Lung retention (24 h): abnormal</p>	<p>Tracheobronchial velocity (bolus transport): 1.7–3.0 mm·min⁻¹ (slightly abnormal to normal)</p> <p>Lung retention (24 h): slightly abnormal to normal</p>
Conclusion	<p>Normal ciliary clearance →</p>	<p>No ciliary clearance → →</p>	<p>Normal to slightly abnormal ciliary clearance →</p> <p>A range of 30–62% of functioning multiciliated airway cells is sufficient to maintain ciliary airway clearance</p>

GRAPHICAL ABSTRACT Overview of the study. PCD: primary ciliary dyskinesia; FEV₁: forced expiratory volume in 1 s; ODA: outer dynein arm; MCC: multiciliated cell.



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Restoring cilia function in 30–62% of defective respiratory cells is sufficient to improve ciliary clearance in PCD individuals <https://bit.ly/45PQQg9>

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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.

