

Title: Primary Ciliary Dyskinesia *GeneReview* – Other Tests Under Evaluation

Authors: Zariwala MA, Knowles MR, Leigh MW

Date: September 2015

Note: The following information is provided by the authors and has not been reviewed by *GeneReviews* staff.

**Other tests under evaluation** as screening or supportive tests for PCD, particularly when ciliary ultrastructure is normal:

- **High-speed videomicroscopy of ciliary motility.** Evaluation of ciliary beat frequency and ciliary beat pattern requires high-speed videomicroscopy of freshly obtained ciliary biopsies that are maintained in culture media under controlled conditions. Specific immotility/dysmotility patterns associated with PCD can be identified [Chilvers et al 2003, Toskala et al 2005, Raidt et al 2014]. Note: It is now recognized that ciliary videos must be repeated multiple times (including studies on cultured ciliary cells) in order to base the diagnosis of PCD on ciliary waveform analyses.
- **Measurement of nasal nitric oxide production.** Nitric oxide (NO), produced by the respiratory cells, is present in much higher concentrations in the upper airway than in the lower airway. For unknown reasons, individuals with PCD have very low nasal NO production that is approximately one-tenth of control values.
  - In individuals over age 5 years who can cooperate with palate closure maneuvers, this test is 98% sensitive and 99% specific for identifying individuals with an ultrastructural defect or biallelic pathogenic variants in *DNAH11* [Leigh et al 2013].
  - Rare individuals with PCD and approximately 50% of those with biallelic pathogenic variants in *RSPH1* have values above the cut-off (77nl/min) [Leigh et al 2013, Knowles et al 2014].
  - Other diseases in which nasal NO values may be low include acute viral infections and cystic fibrosis; therefore, nasal NO testing should be performed: (1) after [cystic fibrosis](#) has been ruled out by appropriate (sweat test or *CFTR* genetic testing); and (2) when the individual is at baseline health status. Testing should be repeated if there is concern about recent/current viral infection [Leigh et al 2013].
- **Mucociliary clearance analysis of radiolabeled particles.** Mucociliary clearance has been measured by assessing clearance of radiolabeled particles from the nasal passages or from the lower airways [De Boeck et al 2005, Marthin et al 2007]. For these studies, an aerosol containing radiolabeled particles is inhaled and then a gamma camera is used to track deposition and clearance of these insoluble particles.
- **Immunofluorescent staining of ciliary biopsy.** Immunofluorescent assays using antibodies specific to the ciliary components can be used to decipher the specific ciliary ultrastructural defect. For example, patients with outer dynein arm

(ODA) defects (as per electron microscopic analysis and/or presence of biallelic pathogenic variants in ODA-related genes such as *DNAH5* or *DNAI2*) show absence of ciliary staining using anti-DNAH5 or anti-DNAI2 antibodies [Fliegauf et al 2005, Loges et al 2008]. Inner dynein arm (IDA) defects, nexin-dynein regulatory complex defects, and radial spokes/central pair defects can be ascertained using inner dynein arm specific anti-DNALI1, nexin-related anti-GAS8/GAS11 antibodies, and radial spokes-related anti-RSPH1, anti-RSPH4A, and anti-RSPH9, respectively [Becker-Heck et al 2011, Merveille et al 2011, Frommer et al 2015].

- **Semen analysis.** Sperm count is typically normal, but sperm are immotile or motility is severely limited [Afzelius 2004].

## References

- Afzelius BA (2004) Cilia-related diseases. *J Pathol* 204:470-7
- Becker-Heck A, Zohn IE, Okabe N, Pollock A, Lenhart KB, Sullivan-Brown J, McSheene J, Loges NT, Olbrich H, Haeffner K, Fliegauf M, Horvath J, Reinhardt R, Nielsen KG, Marthin JK, Baktai G, Anderson KV, Geisler R, Niswander L, Omran H, Burdine RD. The coiled-coil domain containing protein CCDC40 is essential for motile cilia function and left-right axis formation. *Nat Genet* 2011;43:79-84.
- Chilvers MA, Rutman A, O'Callaghan C. Ciliary beat pattern is associated with specific ultrastructural defects in primary ciliary dyskinesia. *J Allergy Clin Immunol* 2003;112:518-24
- De Boeck K, Proesmans M, Mortelmans L, Van Billoen B, Willems T, Jorissen M. Mucociliary transport using 99mTc-albumin colloid: a reliable screening test for primary ciliary dyskinesia. *Thorax* 2005;60:414-7
- Fliegauf M, Olbrich H, Horvath J, Wildhaber JH, Zariwala MA, Kennedy M, Knowles MR, Omran H. Mislocalization of DNAH5 and DNAH9 in respiratory cells from patients with primary ciliary dyskinesia. *Am J Respir Crit Care Med*. 2005;171:1343-9.
- Frommer A, Hjej R, Loges NT, Edelbusch C, Jahnke C, Raidt J, Werner C, Wallmeier J, Große-Onnebrink J, Olbrich H, Cindrić S, Jaspers M, Boon M, Memari Y, Durbin R, Kolb-Kokocinski A, Sauer S, Marthin JK, Nielsen KG, Amirav I, Elias N, Eitan K, Shoseyov D, Haeffner K, Omran H. Immunofluorescence analysis and diagnosis of primary ciliary dyskinesia with radial spoke defects. *Am J Respir Cell Mol Biol*. 2015. Mar 19. Epub ahead of print.
- Knowles MR, Ostrowski LE, Leigh MW, Sears PR, Davis SD, Wolf WE, Hazucha MJ, Carson JL, Olivier KN, Sagel SD, Rosenfeld M, Ferkol TW, Dell SD, Milla CE, Randell SH, Yin W, Sannuti A, Metjian HM, Noone PG, Noone PJ, Olson CA, Patrone MV, Dang H, Lee HS, Hurd TW, Gee HY, Otto EA, Halbritter J, Kohl S, Kircher M, Krischer J, Bamshad MJ, Nickerson DA, Hildebrandt F, Shendure J, Zariwala MA. Mutations in RSPH1 cause primary ciliary dyskinesia with a unique clinical and ciliary phenotype. *Am J Respir Crit Care Med* 2014;189:707-17
- Leigh MW, Hazucha MJ, Chawla KK, Baker BR, Brown DE, LaVange LM, Horton BJ, Qaqish B, Carson JL, Davis SD, Dell SD, Ferkol TW, Atkinson JJ, Olivier KN, Sagel SD, Rosenfeld M, Milla C, Lee H-S, Krischer J, Zariwala MA, Knowles MR. Standardizing nasal nitric oxide measurement as a test for primary ciliary dyskinesia. *Ann Am Thorac Soc* 2013;10:574-81
- Loges NT, Olbrich H, Fenske L, Mussaffi H, Horvath J, Fliegauf M, Kuhl H, Baktai G, Peterffy E, Chodhari R, Chung EM, Rutman A, O'Callaghan C, Blau H, Tiszlavicz L, Voelkel K, Witt M, Zietkiewicz E, Neesen J, Reinhardt R, Mitchison HM, Omran H. DNAI2 mutations cause primary ciliary dyskinesia with defects in the outer dynein arm. *Am J Hum Genet* 2008;83:547-58

Marthin JK, Mortensen J, Pressler T, Nielsen KG. Pulmonary radioaerosol mucociliary clearance in diagnosis of primary ciliary dyskinesia. *Chest* 2007;132:966-76

Merveille AC, Davis EE, Becker-Heck A, Legendre M, Amirav I, Bataille G, Belmont J, Beydon N, Billen F, Clément A, Clercx C, Coste A, Crosbie R, de Blic J, Deleuze S, Duquesnoy P, Escalier D, Escudier E, Fliegauf M, Horvath J, Hill K, Jorissen M, Just J, Kispert A, Lathrop M, Loges NT, Marthin JK, Momozawa Y, Montantin G, Nielsen KG, Olbrich H, Papon JF, Rayet I, Roger G, Schmidts M, Tenreiro H, Towbin JA, Zelenika D, Zentgraf H, Georges M, Lequarré AS, Katsanis N, Omran H, Amselem S. CCDC39 is required for assembly of inner dynein arms and the dynein regulatory complex and for normal ciliary motility in humans and dogs. *Nat Genet.* 2011;43:72-8.

Raidt J, Wallmeier J, Hjej R, Onnebrink JG, Pennekamp P, Loges NT, Olbrich H, Häffner K, Dougherty GW, Omran H, Werner C. Ciliary beat pattern and frequency in genetic variants of primary ciliary dyskinesia. *Eur Respir J* 2014;44:1579-88.

Toskala E, Haataja J, Shirasaki H, Rautiainen M. Culture of cells harvested with nasal brushing: a method for evaluating ciliary function. *Rhinology* 2005;43:121-4