

Primary Ciliary Dyskinesia (PCD) via *DNAH11* Gene Sequencing – Test #743

Brief Description of Clinical Features: Primary Ciliary Dyskinesia (PCD; OMIM 244400) is a genetically heterogeneous disorder affecting the function of motile cilia (reviewed by Leigh et al. *Genetics in Medicine* 11:473-487, 2009). Motile cilia line the upper and lower respiratory airways, the ventricular system of the brain and spinal cord, and the female fallopian tubes. They are also components of the male sperm flagellum and required for sperm motility. Ciliary movement sweeps mucus, dirt and bacteria out of the lungs, nasal passageways, and ear canals, thus protecting them from recurrent infections. In the developing embryo, nodal cilia generate a rotational motion that determines the position of the internal organs. Without functional nodal cilia, thoracoabdominal orientation is random. The hallmark features of PCD are neonatal respiratory distress, chronic coughing, and recurrent sinus and/or ear infections; 80-100% of all PCD patients have one or more of these symptoms. In about 50% of individuals with PCD, the major visceral organs are reversed from their normal positions (also called *situs inversus* or Kartagener's syndrome). Fetal cerebral ventriculomegaly and hydrocephalus can also occur due to impaired circulation of the cerebrospinal fluid. In adults with PCD, male infertility and female sub-fertility are also common features. Prompt diagnosis of PCD is critical for the prevention of secondary respiratory complications, such as bronchiectasis, pneumonia and/or progressive loss of lung function.

Genetics: Cilia in the respiratory tract, brain and sperm flagella consist of nine peripheral microtubule doublets surrounding two central microtubules; nodal cilia in the embryo lack the central microtubules (reviewed in Ferkol & Leigh *Sem Perinatol* 30,335-340, 2006). All motile cilia have both inner and outer dynein arms attached at regular intervals to the peripheral microtubule doublets. The dynein arms consist of heavy, intermediate, and light dynein chains, and serve as molecular motors that drive microtubule sliding. Most frequently, patients with PCD have structural defects in the outer dynein arms (ODA), rendering the cilia immotile and non-functional. *DNAH11* encodes a dynein heavy chain of the ODA, and recessive mutations in *DNAH11* are known to cause PCD (Schwabe et al. *Hum Mut* 29:289-298, 2008). *DNAH11* is a large gene comprising 82 exons. To date, nine unique mutations have been described throughout the gene (Human Gene Mutation Database; www.hgmd.cf.ac.uk), and none of these have been found in more than a single patient. Most mutations result in premature protein termination (i.e. nonsense, frameshift, splicing), but a handful of missense mutations located in conserved domains also apparently cause PCD and possibly Asthenozoospermia (Zuccarello et al. *Hum Reprod* 23:1957-1962, 2008; Pifferi et al. *Eur Respir J* 35: 1413-1416, 2010). Interestingly, unlike with mutations in other dynein chains (i.e. *DNAH5*, *DNAI1*, and *DNAI2*), mutations in *DNAH11* only affect the beating frequency of the cilia, not the visible structure of the inner or outer dynein arms.

Description of This Particular Test This test involves bidirectional DNA sequencing of all 82 coding exons of the *DNAH11* gene, plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence one (Test #100; \$190) or two exons (Test #200; \$340) in family members of patients with a known mutation, or to confirm research results.

Reference Sequences: Genomic: NC_000007.13 mRNA: NM_003777.3 Protein: NP_003768.2

Indications for Test: Candidates for this test are patients with Primary Ciliary Dyskinesia, particularly those without ODA structural defects.

Sensitivity of Test: This test is predicted to detect at least one causative mutation in ~1-2% of all patients diagnosed with PCD (Bartoloni et al. *PNAS* 99:10282-10286, 2002).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2 - 3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

| | | |
|-------------------------|--|---------------------------------------|
| Price: | Sequencing of the <i>DNAH11</i> Gene: | \$3320 |
| CPT Codes: | | |
| Sample Ascertainment x1 | 83890 \$ 30 | DNA Isolation x1 83891 \$ 40 |
| Amplification x85 | 83898 \$1160 | Sequencing x85 83904 \$1730 |
| Separation x1 | 83894 \$ 190 | Interpretation/Report x1 83912 \$ 170 |

Accreditation: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

Contact: Dr. Keith Nykamp, keith.nykamp@preventiongenetics.com, www.preventiongenetics.com