

Primary Ciliary Dyskinesia (PCD) via *CCDC40* Gene Sequencing (Test #755)

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 inner and outer dynein arms attached at regular intervals to the nine peripheral microtubule doublets, which serve as molecular motors that drive microtubule sliding. Most frequently, patients with PCD have structural defects in the cilia, rendering them immotile. Recently, recessive, loss-of-function mutations in the *CCDC40* were found to cause defects in the inner dynein arm (IDA) assembly, as well as generalized axonemal disorganization (Becker-Heck et al. *Nat Genet* 43:79-85, 2011). These authors identified unambiguous mutations (i.e. nonsense, frameshift and splice-site) in 17 previously unresolved PCD cases.

Description of This Particular Test This test involves bidirectional DNA sequencing of all 20 coding exons of the *CCDC40* 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 (Test #200; \$340) exons in family members of patients with a known mutation, or to confirm research results.

Reference Sequences: Genomic: NC_000017.10 mRNA: NM_017950.2 Protein: NP_060420.2 CCDS_42395.1

Indications for Test: Candidates for this test are patients with Primary Ciliary Dyskinesia, particularly those with chronic upper and lower airway infections, situs ambiguous (Ivemark Syndrome; OMIM 208530) and ultrastructural studies that point to IDA defects and axonemal disorganization (Becker-Heck et al. 2011).

Sensitivity of Test: This test is predicted to detect at least one causative mutation in ~2-5% of all patients diagnosed with PCD, or ~65% of PCD patients with IDA defects **and** abnormal axonemal organization (Becker-Heck et al. 2011).

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

Specimen Requirements: See page 4 of Requisition Form.

Price:	Sequencing of the <i>CCDC40</i> Gene:	\$ 1060
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x20	83898 \$ 320	Sequencing x20 83904 \$ 480
Separation x1	83894 \$ 60	Interpretation/Report x1 83912 \$ 130

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

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