

Primary Ciliary Dyskinesia (PCD) via *LRRC50* Gene Sequencing – Test #752

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. The dynein arms consist of heavy, intermediate, and light dynein chains, and serve as molecular motors that drive microtubule sliding. Often, patients with PCD have structural defects in the inner (IDA) and/or outer dynein arms (ODA), rendering the cilia immotile and non-functional. *LRRC50* encodes a protein believed to be required for the pre-assembly of both IDA and ODA in the cytoplasm prior to their transport to the plasma membrane for incorporation into motile cilia. Recently, Loges et al. (*Am J Hum Genet* 85:883-889, 2009) identified a consanguineous family with a homozygous frameshift mutation (c.1349_1350insC; p.Pro451AlafsX5) in the *LRRC50* gene. When they subsequently analyzed the *LRRC50* locus in 58 PCD patients, they identified two different large deletions encompassing the *LRRC50* gene in a 4-year old child. Interestingly, this is the only report to date that large genomic rearrangements can cause PCD.

Description of This Particular Test This test involves bidirectional DNA sequencing of all 12 exons of the *LRRC50* 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_000016.9 mRNA: NM_178452.4 Protein: NP_848547.4 CCDS 10943.2

Indications for Test: Candidates for this test are patients with Primary Ciliary Dyskinesia, particularly those with IDA and ODA structural defects (Loges et al. 2009; Duquesnoy et al. *Am J Hum Genet* 85:890-896, 2009).

Sensitivity of Test: This test is predicted to detect at least one causative mutation in ~4-5% of all patients diagnosed with PCD and ~15% of PCD patients with both IDA and ODA structural defects (Duquesnoy et al. 2009).

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>LRRC50</i> Gene:	\$ 780
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x13	83898 \$ 220	Sequencing x13 83904 \$ 330
Separation x1	83894 \$ 50	Interpretation/Report x1 83912 \$ 110

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