

## Primary Ciliary Dyskinesia (PCD) via *RPGR* Gene Sequencing – Test #753

**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 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. 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. 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:** PCD is most often inherited in an autosomal recessive pattern. Occasionally, however, symptoms of PCD and Retinitis Pigmentosa (RP; OMIM 268000) co-segregate in an X-linked pattern (Zito et al. *J Med Genet* 40:609-615, 2003; Moore et al., *J Med Genet* 43:326-333, 2006). *RPGR*, located on the X chromosome, encodes the retinitis pigmentosa GTPase regulator (Meindl et al. *Nat Genet* 13:35-42, 1996). Loss-of-functions mutations in *RPGR* can disrupt the structure of both photoreceptor-connecting cilia and motile cilia (Hong et al. *Inv Ophthalm. Vis Sci* 44:2413-2421, 2003), thus leading to a combined RP and PCD condition (Moore et al. 2006). Males hemizygous for *RPGR* mutations often display early onset retinal degeneration, hearing loss, recurrent sinusitis, and chronic chest infections. Female carriers of heterozygous *RPGR* mutations may also suffer from mild symptoms of PCD and/or RP, including late onset retinal degeneration, recurrent sinusitis minus chest infections, and progressive hearing loss. The *RPGR* gene encodes several alternatively spliced isoforms. These include *isoform A* (CCDS14246.1), consisting of 19 exons, and *isoform C* (CCDS35229.1), consisting of 15 exons. Exons 1-14 are the same for both isoforms. However, *isoform A* uses a cryptic donor splice site in exon 15, resulting in a short (152 nucleotides) exon 15 and inclusion of exons 16-19. By contrast, *isoform C* does not use the cryptic donor splice site, resulting in an extended exon 15 (also called ORF15 in the literature) with 1706 nucleotides of coding sequence (see Bader et al. *Invest Ophthalmol* 44:1458-1463, 2003 for a detailed description of the ORF15 exon). Importantly, because *isoform C* (with ORF15) is preferentially expressed in retina and *isoform A* (without ORF15) is expressed throughout the respiratory tract, mutations in ORF15 lead to X-linked RP without symptoms of PCD while mutations in exons 1-14 lead to XLRP with additional PCD symptoms.

**Description of This Particular Test:** This test involves bidirectional DNA sequencing of all 19 coding exons of *RPGR isoform A* (CCDS 14246.1), plus ~50 bp of flanking non-coding DNA on either side of each exon. This test does not include sequencing of *RPGR isoform C* (CCDS\_35229.1), which includes the ORF15 exon. For patients with only symptoms of X-linked Retinitis Pigmentosa, see Test #679. As indicated, we will sequence a single exon (Test #100; \$190) in family members of patients with a known mutation, or to confirm research results.

**Reference Sequences:** Genomic: NC\_000023.10 mRNA: NM\_000328.2 Protein: NP\_000319.1 CCDS 14246.1

**Indications for Test:** Candidates for this test are patients displaying X-linked inheritance of retinitis pigmentosa and symptoms of primary ciliary dyskinesia (Rozet et al. *J Med Genet* 39:284-285, 2002; Moore et al., 2006).

**Sensitivity of Test:** This test is predicted to detect a causative mutation in about 10% of patients with apparently X-linked PCD (Moore et al. 2006), or ~50-60% of all patients diagnosed with X-linked RP (Bader et al. 2003).

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

**Specimen Requirements:** See page 4 of Requisition Form.

<b>Price:</b>	<b>Sequencing of the <i>RPGR</i> Gene:</b>	<b>\$ 1090</b>
<b>CPT Codes:</b>		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x21	83898 \$ 330	Sequencing x21 83904 \$ 490
Separation x1	83894 \$ 70	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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