

Bardet-Biedl Syndrome via *BBS1* Gene Sequencing (Test #252)

Brief Description of Clinical Features: Bardet-Biedl syndrome (BBS) (OMIM# 209900) is a pleiotropic disorder characterized by retinal degeneration, obesity, post-axial polydactyly, cognitive impairment, hypogenitalism and renal and cardiovascular anomalies (Green et al. N Engl J Med 321:1002-1009, 1989; Elbedour et al. Am J Med Genet. 52:164-169, 1994). Bardet-Biedl syndrome 1 (BBS1) (OMIM# 209901) is the most common type of BBS (Mykytyn et al. Nat Genet 31:435-438, 2002; Mykytyn et al. Am J Hum Genet 72:429-437, 2003).

Genetics: BBS1 is primarily inherited as an autosomal recessive disorder, although complex inheritance has been reported in a few families (Katsanis et al. Science 293:2256-2259, 2001). Mutations in the *BBS1* gene cause BBS (Mykytyn et al. 2002). *BBS1* encodes BBS1 protein, which is localized to the basal bodies of the primary cilia and to the centrosomes (Kulaga et al. Nat Genet 36:994-998, 2004). BBS1 protein interacts with six other BBS proteins (BBS2, BBS4, BBS5, BBS7, BBS9 and BBS11) to form a complex known as the BBSome, which has a role in cilia maintenance and function (Nachury et al. Cell 129:1201-1213, 2007). A mix of missense, nonsense, frameshift and splicing mutations has been reported in *BBS1*. The M390R missense mutation is the most common causative mutation (Mykytyn et al. 2002; Mykytyn et al. 2003). BBS exhibits locus heterogeneity; at least 12 BBS genes have been identified (*BBS1*, *BBS2*, *BBS3*, *BBS4*, *BBS5*, *MKKS/BBS6*, *BBS7*, *TTC8/BBS8*, *BBS9*, *BBS10*, *TRIM32/BBS11* and *BBS12*) (Tobin and Beales, Genet Med 11:386-402, 2009). In addition, hypomorphic mutations in two Meckel-Gruber syndrome genes (*MKS1* and *CEP290*) were reported to be associated with BBS, representing *BBS13* and *BBS14* respectively (Leitch et al. Nat Genet 40:443-448, 2008).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all 17 coding exons (exon 1-17) of the *BBS1* gene plus ~50 bp of flanking non-coding DNA on each side. This test starts with sequencing exon 12 for the most common *BBS1* pathogenic mutation (p.M390R). If zero or one copies of p.M390R are found in exon 12, then we proceed with sequencing the remaining 16 exons. As indicated, we will also perform sequencing of any single exon (Test #100) or pair of exons (Test #200) for family members of patients with known mutations and to confirm previous research results (\$190-340 charge).

Reference Sequences: Genomic: NC_000011.9 mRNA: NM_024649.4 Protein: NP_078925.3 (CCDS 8142.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with BBS and family members of patients who have known *BBS1* mutations. Conclusive connections between clinical features and individual mutated *BBS* genes have not yet been made.

Sensitivity of Test: Mutations in the *BBS1* gene are the most frequent cause of BBS. *BBS1* mutations are estimated to cause approximately ~23% of BBS cases (Mykytyn et al. 2003; Katsanis Hum Mol Genet 13 Spec. No. 1:R65-71, 2004).

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.

Prices: Sequencing of the full *BBS1* gene \$ 890 Sequencing of only exon 12 of the *BBS1* gene \$190

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x16	83898 \$ 250	Sequencing x16	83904 \$ 370
Separation x1	83894 \$ 80	Interpretation/Report x2	83912 \$ 120

Accreditation Info: 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