

Bardet-Biedl Syndrome via *MKKS/BBS6* Gene Sequencing (Test #257)

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). McKusick-Kaufman syndrome (MKKS) (OMIM# 236700) is characterized by hydrometrocolpos secondary to vaginal atresia and bilateral postaxial polydactyly (McKusick et al. JAMA 189:813-816, 1964). Both MKKS and Bardet-Biedl syndrome 6 (BBS6) (OMIM# 604896) are caused by mutations in *MKKS/BBS6* gene (Stone et al. Nat Genet 25:79-82, 2000; Slavotinek et al. Nat Genet 26:15-16, 2000; Katsanis et al. Nat Genet 26:67-70, 2000).

Genetics: MKKS and BBS6 are inherited as autosomal recessive disorders, however complex inheritance has been reported in a few BBS families (Katsanis et al. Science 293:2256-2259, 2001). *MKKS/BBS6* encodes a chaperonin protein (MKKS/BBS6), which shows similarity to the alpha subunit of the *Thermoplasma acidophilum* thermosome chaperonin protein (Stone et al. 2000). MKKS/BBS6 protein interacts with two other CCT/TRiC chaperonin like BBS proteins, BBS10 and BBS12, to form a chaperonin complex that mediates BBSome complex assembly (Seo et al. PNAS 107:1488-1493, 2010). A mix of missense, nonsense, splicing and small deletion mutations has been reported in *MKKS/BBS6* (Slavotinek et al. 2000; Katsanis et al. 2000). 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 4 coding exons (exons 4-7) of the *MKKS/BBS6* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. As indicated, we will also perform sequencing of any single exon or pair of exons for family members of patients with known mutations and to confirm previous research results (\$190-340 charge).

Reference Sequences: Genomic: NC_000020.10 mRNA: NM_018848.2 Protein: NP_061336.1 (CCDS 13111.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with MKKS/BBS and the family members of patients who have known *MKKS/BBS6* mutations. Conclusive connections between clinical features and individual mutated *BBS* genes have not yet been made.

Sensitivity of Test: Mutations in the *MKKS/BBS6* gene are estimated to cause approximately 6% of BBS cases (Katsanis et al. Hum Mol Genet 13 Spec No 1:R65-R71, 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 <i>MKKS/BBS6</i> gene	\$ 580
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x8	83898 \$ 140	Sequencing x8 83904 \$ 220
Separation x1	83894 \$ 50	Interpretation/Report x1 83912 \$ 100

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

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