

Bardet-Biedl Syndrome via *TRIM32/BBS11* Gene Sequencing (Test #263)

Brief Description of Clinical Features: Bardet-Biedl syndrome (BBS) (OMIM# 209900) is 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).

Limb-girdle muscular dystrophy type 2H (LGMD2H) (OMIM# 254110) is a mild myopathy characterized by muscle weakness and wasting restricted to the proximal limbs (Frosk et al. Hum Mutat 25:38-44, 2005).

Both LGMD2H and Bardet-Biedl syndrome 11 (BBS11) (OMIM# 602290) are caused by mutations in *TRIM32/BBS11* gene (Forsk et al. 2005; Chiang et al. Proc Nat Acad Sci 103:6287-6292, 2006).

Genetics: LGMD2H and BBS are inherited as autosomal recessive disorders, although complex inheritance has been reported in a few BBS families (Katsanis et al. Science 293:2256-2259, 2001). *TRIM32/BBS11* encodes a tripartite motif (TRIM)-containing protein 32 (TRIM32). TRIM32 has domain structure composed of a RING finger, a B-box and a coiled-coil motif important for E3 ubiquitin ligase activity, along with five C-terminal NHL repeats important for protein-protein interaction (Kudryashova et al. J Molec Biol 354:413-424, 2005). Although the precise function of TRIM32 is not yet known, TRIM32 has been implicating in regulating components of the cytoskeleton (Kudryashova et al. 2005). A *TRIM32* missense mutation (Pro130Leu) has been reported in a BBS family (Chiang et al. 2006). 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 the only coding exon (exon 2) of the *TRIM32/BBS11* gene. The full coding region of this exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. As indicated, we will also perform sequencing of the relevant portion(s) of the exon for family members of patients with known mutations and to confirm previous research results (\$190-340 charge).

Reference Sequences: Genomic: NC_000009.11 mRNA: NM_012210.3 Protein: NP_036342.2 (CCDS 6817.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with BBS and the family members of patients who have known *TRIM32/BBS11* mutations. Conclusive connections between clinical features and individual mutated *BBS* genes have not yet been made.

Sensitivity of Test: Mutations in the *TRIM32/BBS11* gene are estimated to cause < 1% of BBS cases (Chiang et al. 2006).

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 *TRIM32/BBS11* gene \$ 490

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x6	83898 \$ 120	Sequencing x6	83904 \$ 170
Separation x1	83894 \$ 40	Interpretation/Report x1	83912 \$ 90

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

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