

Griscelli Syndrome-Type 2 (GS2) via Sequencing of the *RAB27A* Gene (Test #213)

Brief Description of Clinical Features: Griscelli syndrome (GS) is classified into three different subtypes, GS1 (OMIM 214450), GS2 (OMIM 607624), and GS3 (OMIM 609227), all of which are characterized by partial albinism, i.e. pigmentary dilution of the skin and hair. Patients with GS typically have large clumps of pigment irregularly distributed along hair shafts giving a silvery-gray appearance to hair color. GS1 is associated with severe primary neurologic defects while GS2 is associated with Hemophagocytic Lymphohistiocytosis (HLH / FHL) (see OMIM 267700). HLH is characterized by excessive, uncontrolled activation and proliferation of T cells and macrophages that infiltrate tissues and cause organ failure. Common symptoms of HLH include: fever, hepatosplenomegaly, pancytopenia, attenuated or absent NK cell function, and hemophagocytosis (Henter et al. *Pediatr Blood Cancer* 48:124-131, 2007). Griscelli Syndrome type 3 (GS3) is characterized by pigmentary dilution only. GS is commonly diagnosed between the ages of 4 months and 7 years.

Genetics: GS is an autosomal recessive disorder caused by mutations in *MYO5* (GS1), *RAB27A* (GS2) or *MLPH* (GS3). Mutations in these genes affect melanosome trafficking and with GS1 and GS2, affect additional vesicular transport events. For example, *RAB27A* encodes a small GTPase (Rab27a) that is required for both anchoring melanosomes in melanocytes and for cytolytic granule secretion in T cells and NK cells (reviewed in Van Gele et al. *Pigment Cell Melanoma Res* 22:268-282, 2009). Thus, GS2 patients develop HLH and partial albinism. To date about 30 causative mutations in *RAB27A* have been identified comprising small and large frameshift deletions, missense, and splice site mutations (Meschede et al. *Braz J Med Biol Res* 41:839-848, 2008). Some missense mutations have been shown to affect the Rab27a GTP-binding motif and protein-protein interaction domains (Menasche et al. *Blood* 101:2736-2742, 2003). Mutations in *RAB27A* do not affect T cell or NK cell numbers, but rather inhibit granule exocytosis in these cells similar to HLH / FHL genes. Rarely, mutations in *RAB27A* result in immunological deficiencies without hemophagocytosis (Aksu et al. *Am J Med Genet A* 116A:329-333, 2003).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all coding exons (exons 2-6) of the *RAB27A* gene plus ~ 50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence any single exon (Test #100) or two exons (Test #200) in family members of patients with known mutations, or to confirm research results (\$190-340).

Reference Sequences: Genomic: NC_000015.9 mRNA: NM_004580.3 Protein: NP_004571.2 (CCDS 10153.1)

Indications for Test: Patients with clinical features of GS2, FHL, or FHL-related disorders, and individuals with a family history of these disorders. FHL patients who test negative for mutations in *PRF1*, *UNC13D*, *STX11*, and *STXBP2* are also candidates. Conversely, GS2 patients who test negative for mutations in *RAB27A* may be candidates for all or a portion of FHL, GS1, GS3, CHS, and HPS2 DNA testing.

Sensitivity of Test: Sensitivity of this test is currently unknown.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 3-4 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *RAB27A* Gene \$490

CPT Codes							
Test	83890 x1	83891 x1	83898 x5	83904 x5	83894 x1	83912 x1	Totals
<i>RAB27A</i>	\$30	\$40	\$120	\$190	\$30	\$80	\$490

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

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