

Hermansky-Pudlak Syndrome Type 2 (HPS2) via Sequencing of the *AP3B1* Gene (Test #762)

Brief Description of Clinical Features: Hermansky-Pudlak Syndrome (HPS) (OMIM 203300) is characterized by tyrosinase-positive oculocutaneous albinism, significant reduction in visual acuity often complicated by nystagmus, and bleeding diathesis resulting in bruising, and sporadic and prolonged bleeding (Hermansky, Pudlak *Blood* 14:162-169, 1959). Hair color ranges from white to brown, and along with skin color, is typically a shade lighter than is seen in unaffected family members. HPS patients may develop granulomatous colitis, with onset usually in their teens, and/or pulmonary fibrosis, with onset typically in their thirties or forties (Gahl et al *N Engl J Med* 338:1258-1264, 1998). Similar characteristics are found with Chediak-Higashi Syndrome (CHS) (OMIM 214500). Both HPS and CHS are storage pool disorders. The cellular origin of disease is attributed to abnormal storage granules such as melanosomes, platelet-dense granules, and lysosomes. Granule cargo includes pigment proteins, signaling molecules, and enzymes and defects in granule biogenesis, structure, or function affect myriad downstream events. Micrographs of platelets from HPS patients often reveal a striking lack of dense granules whereas granulocytes of CHS patients contain giant, aberrant storage granules.

Genetics: HPS is an autosomal recessive disorder associated with the *HPS1*, *AP3B1*/(*HPS2*), *HPS3*, *HPS4*, *HPS5*, *HPS6*, *DTNBPI*/(*HPS7*), and *BLOC1S3*/(*HPS8*) genes. HPS is unusually common in Puerto Rico and is caused by unique mutations in *HPS1* and *HPS3* (Santiago et al *J Invest Dermatol* 126:85-90, 2006; Anikster et al *Nat Genet* 28:376-380, 2001). In non-Puerto Ricans, mutations in *AP3B1* (OMIM 603401) account for ~6% of documented HPS cases (Oh et al *Am J Hum Genet* 62:593-598, 1998) with the remaining cases being distributed as follows: *HPS1* ~50%, *HPS3* ~15%, *HPS4* ~12%, *HPS5* ~5%, *HPS6* ~4%, *DTNBPI*/(*HPS7*) ~1%, and *BLOC1S3*/(*HPS8*) ~2%. Patients with HPS2 have mutations in the *AP3B1* gene that encodes the β chain of the adaptor protein-3 (AP-3) complex. The AP-3 complex plays a role during budding of vesicles from the *trans* Golgi network and endosomal compartments and is essential for proper intracellular protein sorting and vesiculation (Simpson et al *The Journal of Cell Biology* 137:835 -845, 1997). Patients with HPS2 are more likely than other HPS patients to develop congenital neutropenia and are thus more susceptible to infections (Jung et al *Blood* 108:362-369, 2006). The cytotoxic T lymphocytes in HPS2 patients display impaired killing activity due to lytic granule abnormalities (Clark et al *Nat Immunol* 4:1111-1120, 2003). It is worth noting that of all HPS subtypes, HPS2 most closely resembles CHS.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 27 coding exons of the *AP3B1* 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). We also offer a Panel test (Test #760) for all eight HPS genes.

Reference Sequences: Genomic: NC_000005.9 mRNA: NM_003664.3 Protein: NP_003655.3 (CCDS 4041.1)

Indications for Test: Patients with symptoms or family history of HPS, CHS, or Griscelli Syndrome, patients with any degree of hypopigmentation or bleeding diathesis, and patients with morphologically abnormal granulocytes or platelets.

Sensitivity of Test: HPS2 accounts for ~6% of documented HPS cases among non-Puerto Ricans.

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.

Price:		Sequencing of the <i>AP3B1</i> Gene					\$1320	
CPT Codes								
Test	83890 x1	83891 x1	83898 x27	83904 x27	83894 x1	83912 x1	Total	
<i>AP3B1</i>	\$30	\$40	\$420	\$620	\$80	\$130	\$1320	

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

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