

Hermansky-Pudlak Syndrome Type 8 (HPS8) via Sequencing of the *BLOC1S3* Gene (Test #768)

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 *BLOC1S3*/(*HPS8*) (OMIM 609762) account for ~2% 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%, *AP3B1*/(*HPS2*) ~6%, *HPS3* ~15%, *HPS4* ~12%, *HPS5* ~5%, *HPS6* ~4%, and *DTNBPI*/(*HPS7*) ~1%. To date, the only documented mutation in *BLOC1S3* that causes HPS8 was reported in a large family with HPS; all were homozygous for c.448delC that results in a frameshift and premature protein termination (Morgan et al *Am J Hum Genet* 78:160-166, 2006). This family displayed the primary features of HPS, i.e. hypopigmentation, impaired visual acuity, and platelet dysfunction, but bleeding tendency was not apparent in some individuals, and no individuals were affected by granulomatous colitis or pulmonary fibrosis.

Description of This Particular Test: This test involves bidirectional DNA sequencing of the single coding exon of the *BLOC1S3* 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_000019.9 mRNA: NM_212550.3 Protein: NP_997715.1 (CCDS 12656.1)

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: HPS8 accounts for ~2% of documented HPS cases.

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 *BLOC1S3* Gene \$ 390

CPT Codes							
Test	83890 x1	83891 x1	83898 x3	83904 x3	83894 x1	83912 x1	Total
<i>BLOC1S3</i>	\$30	\$40	\$80	\$130	\$20	\$90	\$390

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

Contact: Dr. Michael Chicka, michael.chicka@preventiongenetics.com, www.preventiongenetics.com