

HPS1 and HPS3 Gene Analysis for Common Puerto Rican and Ashkenazi Variants in Hermansky-Pudlak Syndrome (HPS)

Disorder also known as: Albinism with hemorrhagic diathesis and pigmented reticuloendothelial cell; platelet delta-granule storage pool disease.

Clinical Features:

The disorder is characterized by oculocutaneous albinism, platelet delta-granule storage pool deficiency leading to bleeding diathesis, and lysosomal accumulation of ceroid lipofuscin. Patients have nystagmus and easy bruisability. Pulmonary fibrosis is a severe complication in many patients. Granulomatous colitis occurs in 10%-20% of patients. Nine different genes are known to cause HPS when mutated (HPS1 – HPS9). Many patients have ethnic-associated variants including a northwestern Puerto Rican HPS1 variant, a central Puerto Rican HPS3 variant, and an Ashkenazi HPS3 variant.

Genetics:

Autosomal recessive.

Test Methods:

The Puerto Rican HPS1 16 bp duplication is tested by PCR amplification and electrophoresis for fragment sizing. The Puerto Rican HPS3 3.9 kb deletion is tested by allele-specific PCR amplification and electrophoresis for fragment identification. The Ashkenazi HPS3 IVS5+1G>A variant is tested by bi-directional sequencing of exon 5 and its splice sites.

Test Sensitivity:

Tests for 2 specific variants, a 16 bp duplication in HPS1¹ and a 3.9 kb deletion in HPS3², identify more than 95% of Puerto Rican patients with Hermansky-Pudlak syndrome and can be used in the general population for carrier detection. The latter variant may have a tendency to occur independently in many different populations, but data is not yet available to determine the sensitivity of the test in people of non-Puerto Rican ethnicity. Testing for the IVS5 splice site variant in HPS3 in a study of five Ashkenazi Jewish HPS patients found that 3 were homozygous for that variant and 2 were compound heterozygotes for the splice variant and another variant in the HPS3 gene.³

References:

1. Oh, J., et al., Positional cloning of a gene for Hermansky-Pudlak syndrome, a disorder of cytoplasmic organelles, *Nat. Gen.*, 14:300-306, 1996.
2. Anikster, Y, et al. Variant in a novel gene causes a unique form of Hermansky-Pudlak syndrome in a genetic isolate of central Puerto Rico, *Nat. Gen.* 28:376-380, 2001.

3. Huizing, M., Hermansky-Pudlak syndrome Type 3 in Ashkenazi Jews and other non-Puerto Rican patients with hypopigmentation and platelet storage-pool deficiency, *Am J Hum Gen* 69:1022-32, 2001.