HPS1 and HPS3 Gene Analysis for Common Puerto Rican or 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
Test Code 188: Common Puerto Rican Variants (HPS1 gene 16 bp duplication and HPS3 gene 3.9 kb deletion) Using genomic DNA from the submitted specimen, the coding region of exon 15 of the HPS1 gene is PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all potentially pathogenic variants. Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines. The 3.9 kb deletion in the HPS3 gene associated with HPS in persons from the central region of Puerto Rico and elsewhere is analyzed by PCR and gel electrophoresis, and compared to positive and negative controls for this variant.

Test Code 189: Common Ashkenazi Jewish Variant (HPS3 gene IVS5+1G>A) Using genomic DNA from the submitted specimen, exon 5 and its splice sites in the HPS3 gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19 and analyzed for known familial sequence variant(s). Capillary sequencing or another appropriate method is used to confirm all potentially pathogenic variants. Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines.

TEST SENSITIVITY
Testing for the common Puerto Rican variants, a 16 bp duplication in HPS1and a 3.9 kb deletion in HPS3, identifies more than 95% of Puerto Rican patients with Hermansky-Pudlak syndrome and can be used in the general population for carrier detection.[1,2] 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]

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