

Hermansky-Pudlak Syndrome (HPS)

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

Genes: *AP3B1*, *AP3D1*, *BLOC1S3*, *BLOC1S6*, *DTNBP1*, *HPS1*, *HPS3*, *HPS4*, *HPS5*, and *HPS6*

Clinical Features:

Patients with Hermansky-Pudlak syndrome (HPS) will have oculocutaneous albinism, platelet delta-granule storage pool deficiency leading to bleeding diathesis, and lysosomal accumulation of ceroid lipofuscin material in the lysosomes. Albinism results in skin tones that can vary from white to olive and hair colors from white to brown, but pigment is typically lighter than family members. Reduced retinal pigment results in low vision with nystagmus and other eye disease. Bleeding diathesis, or the susceptibility to prolonged bleeding, causes easy bruisability, frequent nosebleeds in early life, and extended bleeding during menstruation and surgical procedures. Granulomatous colitis, characterized by inflammation of the large colon, presents at 15 years old on average and is severe in 15% of patients. Patients with HPS may also experience severe complications from pulmonary fibrosis and/or immunodeficiency.^{1,2,3}

Phenotype Correlations by Gene:

Variants in ten genes cause HPS and their protein products associate in 4 distinct but interacting complexes: AP-3, BLOC-1, BLOC-2, or BLOC-3. Patients with pathogenic variants affecting the same complex likely present with similar clinical symptoms.¹

AP-3 Deficiency (*AP3B1*, *AP3D1*): This subtype is associated with immunodeficiency in addition to the expected pigmentary and bleeding symptoms of HPS. Impaired NK-cell cytotoxicity and congenital neutropenia increase risks for severe infection in patients.^{4,5,6}

BLOC-1 Deficiency (*BLOC1S3*, *BLOC1S6*, *DTNBP1*): Approximately 12 patients have been described in the literature with variants causing BLOC-1 deficiency. While phenotype correlation has not been established, several individuals have been noted to have a silver/gold hair color that darkens with age and one patient has been reported with immunodeficiency.^{2,7,8}

BLOC-2 Deficiency (*HPS3*, *HPS5*, *HPS6*): The mildest subtype of HPS includes the common 3.9kb deletion seen in Puerto Rico and is sometimes not diagnosed until later in life; hypopigmentation in the eyes is more significant than in the skin which may be considered in

the normal range for a particular family. Bleeding tendencies are mild. Pulmonary fibrosis and immunodeficiency have not been reported in these patients.¹

BLOC-3 Deficiency (*HPS1*, *HPS4*): The most common subtype of HPS includes the 16bp duplication seen in Puerto Rico and presents with the classic phenotype of severe oculocutaneous albinism and bleeding diathesis. Onset of lethal pulmonary fibrosis typically begins in the 30's.¹ Significant granulomatous colitis is also common in patients with BLOC-3 deficiency.³

Genetics:

All 10 genes associated with HPS are inherited in an autosomal recessive manner.

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Test Sensitivity:

The prevalence of the disorder is approximately 1-9 per 1,000,000 worldwide; however, higher frequencies have been seen in certain founder populations. Northwestern Puerto Rico has a HPS type 1 prevalence of 1:1800, while in central Puerto Rico HPS type 3 is seen in 1:16,000 individuals.^{9,10} Founder mutations have been seen in multiple other populations, including Ashkenazi Jewish (*HPS3*)¹¹, Israeli-Bedouin (*HPS6*)¹, Swiss (*HPS1*)^{12,13}, and Japanese

(HPS1).^{12,14} Additional information about the general clinical sensitivity of each gene is included in the table below.

| Gene | Inheritance | Disease Associations | Sensitivity |
|----------------|-------------|-------------------------------|---|
| <i>AP3B1</i> | AR | HPS type 2, AP-3 Deficiency | ~10% of non-Puerto Rican individuals with HPS* |
| <i>AP3D1</i> | AR | HPS type 10, AP-3 Deficiency | <1% of individuals with HPS ¹⁵ |
| <i>BLOC1S3</i> | AR | HPS type 8, BLOC-1 Deficiency | <1% of individuals with HPS ² |
| <i>BLOC1S6</i> | AR | HPS type 9, BLOC-1 Deficiency | <1% of individuals with HPS ⁸ |
| <i>DTNBP1</i> | AR | HPS type 7, BLOC-1 Deficiency | <1% of individuals with HPS ⁷ |
| <i>HPS1</i> | AR | HPS type 1, BLOC-3 Deficiency | ~37% of non-Puerto Rican individuals and ~80% of Puerto-Rican individuals with HPS* |
| <i>HPS3</i> | AR | HPS type 3, BLOC-2 Deficiency | ~12% of non-Puerto Rican individuals and ~20% of Puerto-Rican individuals with HPS* |
| <i>HPS4</i> | AR | HPS type 4, BLOC-3 Deficiency | ~11.5% of non-Puerto Rican individuals with HPS* |
| <i>HPS5</i> | AR | HPS type 5, BLOC-2 Deficiency | ~9% of non-Puerto Rican individuals with HPS* |
| <i>HPS6</i> | AR | HPS type 6, BLOC-2 Deficiency | ~16.5% of non-Puerto Rican individuals with HPS* |

* Sensitivity based on approximately 278 individuals of non-Puerto Rican ancestry and 311 individuals with Puerto-Rican ancestry with HPS reported in the literature.¹⁶

References:

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