Hermansky-Pudlak Syndrome Panel

Versiti offers comprehensive genetic analysis to detect sequence variants and large deletions and duplications in all 10 genes known to cause autosomal recessive Hermansky-Pudlak syndrome. This panel can be ordered as:

- **Next Generation Sequencing (NGS) only;**
- **NGS with reflex to Array Comparative Genomic Hybridization (aCGH) Deletion/ Duplication if biallelic clinically significant variants are not detected by sequencing ;**
- **NGS with concurrent aCGH Deletion/ Duplication (both testing methodologies performed simultaneously); or**
- **Deletion/Duplication by aCGH only.**

Hermansky-Pudlak syndrome (HPS) is an autosomal recessive disorder affecting the trafficking of proteins into lysosomes and other cellular organelles, including pigment granules. Ten subtypes and their associated causative genes have been identified. HPS is characterized by oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder affecting dense granules. Pulmonary fibrosis, granulomatous colitis, immunodeficiency, and neurologic complications are associated with some but not all subtypes. The oculocutaneous albinism in some cases may be subtle and easily missed, especially in populations with lighter complexion; ophthalmoscopic evaluation to identify lateral nystagmus and reduced pigmentation of the iris and retina may be required as part of the clinical evaluation.

HPS is a rare disorder with a prevalence of 1 to 9 per million in the general population worldwide. However, the presence of founder variants dramatically increases the prevalence in specific populations. For example, in the northwestern Puerto Rican population the prevalence of HPS1 is 1 in 1,800 individuals, and in the central Puerto Rican population the prevalence of HPS3 is 1 in 16,000. Founder variants have also been described in the Ashkenazi Jewish, Swiss Alpine, and Israeli-Bedouin populations.

With other inherited disorders presenting with similar clinical features, genetic testing allows for precise diagnosis and accurate prognostication, essential for formulation of a monitoring and surveillance plan for early detection and management of extra-hematologic manifestations such as pulmonary fibrosis, granulomatous colitis, immunodeficiency and neurologic compromise that are seen in some, but not all subtypes of HPS. An accurate diagnosis provides information about the phenotype and prognosis, guides medical management decisions, assists with the identification of affected family members and allows for accurate genetic recurrence risk assessment. Misdiagnosis or failure of accurate subtyping can result in either unnecessary surveillance or inadequate monitoring for these additional medical complications, and can lead to significant morbidity and mortality in these patients.

The NGS panel evaluates for single nucleotide variants and small deletions and duplications, which are most commonly responsible for genetic disease. However, large deletions and duplications, also referred to as copy number variations (CNVs), are a known cause of genetic disorders, but can escape detection by next generation sequence analysis. Additional testing with aCGH Deletion/Duplication is available for all genes on this panel to evaluate for large deletions and duplications encompassing one or more exons, or affecting an entire gene, including the known founder variant in *HPS3*.

Refer to the table for further information about each gene in Hermansky-Pudlak Syndrome Panel, including the clinical phenotype, and inheritance pattern.

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Hermansky-Pudlak Syndrome Panel: gene, clinical phenotype, population-specific comments and inheritance pattern.			
Gene	Clinical Phenotype	Population-specific comments	Inheritance
AP3B1	**Hermansky-Pudlak syndrome type 2 (HPS2):** oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder, as well as pulmonary fibrosis and neutropenia.		Autosomal Recessive
AP3D1	**Hermansky-Pudlak syndrome type 10 (HPS10):** oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder, as well as neutropenia, seizures and developmental delay.		Autosomal Recessive
BLOC1S3	**Hermansky-Pudlak syndrome type 8 (HPS8):** oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder.		Autosomal Recessive
BLOC1S6	**Hermansky-Pudlak syndrome type 9 (HPS9):** oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder.		Autosomal Recessive
DTNBP1	**Hermansky-Pudlak syndrome type 7 (HPS7):** oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder.		Autosomal Recessive
HPS1	**Hermansky-Pudlak syndrome type 1 (HPS1):** oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder, as well as pulmonary fibrosis and granulomatous colitis.	Puerto Rican (northwestern), Swiss Alpine founder variants	Autosomal Recessive
HPS3	**Hermansky-Pudlak syndrome type 3 (HPS3):** mild ocular albinism and mild bleeding due to a platelet storage pool disorder.	Puerto Rican (central), Ashkenazi Jewish founder variants	Autosomal Recessive
HPS4	**Hermansky-Pudlak syndrome type 4 (HPS4):** oculocutaneous albinism and mild bleeding due to a platelet storage pool disorder, as well as pulmonary fibrosis and granulomatous colitis.	Frequently occurring European variant	Autosomal Recessive
HPS5	**Hermansky-Pudlak syndrome type 5 (HPS5):** mild ocular albinism and mild bleeding due to a platelet storage pool disorder.		Autosomal Recessive
HPS6	**Hermansky-Pudlak syndrome type 6 (HPS6):** mild ocular albinism and mild bleeding due to a platelet storage pool disorder.	Known Israeli-Bedouin founder variant	Autosomal Recessive

Indications for testing:

Hermansky-Pudlak Syndrome Panel (NGS and/or aCGH), order code 4875:

The Hermasky-Pudlak Syndrome panel should be considered for:

- Clarification and/or confirmation of the diagnosis and determination of the subtype in a patient with a clinical presentation compatible with Hermansky-Pudlak syndrome to allow for accurate prognostication and appropriate surveillance plan for variable extra-hematologic manifestations and early intervention to reduce morbidity and mortality.
- Identification of carriers with a family history of HPS of unclear molecular subtype

Single Gene Analysis (order code 4855) or Custom Blood Disorder Panel (Order Code 4850), (NGS and/or aCGH):

Analysis of genes included in this panel may also be ordered as a standalone Single Gene Analysis or as a Custom Blood Disorder Panel (2-10 genes), by NGS and/or by aCGH, as dictated by the patient's clinical and laboratory phenotype, as well as their ancestry, or to supplement previous genetic testing.

Targeted Familial Variant Analysis (order code 4970):

Targeted variant analysis for clinical diagnosis, carrier identification, or prenatal diagnosis can also be performed on any gene in the panel when the pathogenic variant(s) is known in the family. If the proband was not tested at Versiti, a control sample is preferred and may be required (please call the laboratory to discuss). If the familial variant is a large deletion or duplication, aCGH for the involved gene is required.

For clinical questions about laboratory tests and test utilization support, contact Versiti Client Services: (414) 937-6396 or 800-245-3117, Option 1, to be directed to our genetic counselors and clinical support team.

Test method:

NGS: This next-generation sequencing assay analyzes the complete coding region of 10 genes plus a minimum 30bp of non-coding DNA, including intron-exon boundaries, and is compared to the build GRCh37.p13 reference sequence. These targeted regions are captured by hybridization, amplified, and sequenced by massively parallel sequencing. Regions will have a minimum coverage of 50x and those regions with less than 50 sequencing reads or low quality coverage are supplemented with Sanger sequencing. All regions are covered by bidirectional analysis. Variants are identified by a customized bioinformatics pipeline, analyzed and comprehensively interpreted by our team of practicing hematologists with expertise in non-malignant hematology and laboratory diagnostics, scientists, and genetic counselors. All reported variants, including pathogenic, likely pathogenic, and variants of uncertain significance, are confirmed by Sanger sequencing. For prenatal testing, analysis of variable number tandem repeats (VNTR) is used to confirm results are not affected by maternal cell contamination.

aCGH: The specific genes are analyzed for copy number variations due to deletion or duplication by high density gene-focused array Comparative Genomic Hybridization. Probes are approximately 60bp in length and density of coverage in exonic regions is a minimum of 4 probes per 500 bp. Genomic DNA for the samples and gender-matched references are denatured, labeled with fluorescent dye and hybridized, the array is washed and scanned, and analysis is performed for the specific genes requested.

Assay sensitivity and limitations:

NGS: The analytical sensitivity of the NGS test is >99% for single nucleotide changes and insertions and deletions of less than 20 bp. NGS analysis is not designed to detect large deletions or duplications (>20 bp), or variants that are outside the regions sequenced. Low level mosaicism will not be detected by this sequencing methodology.

aCGH: Balanced chromosomal rearrangements (i.e., translocations, inversions) or point mutations that may be the cause of the clinical phenotype cannot be detected via aCGH. Any exonic deletion or duplication smaller than 500bp may not be detected. Low level of mosaicism will not be detected by aCGH. Probe performance could be affected by multiple SNPs in a given region. Breakpoints occurring outside the targeted gene(s) will not be defined.

Clinical Sensitivity

The clinical sensitivity of comprehensive genetic testing (NGS and aCGH) of the 10 genes known to be associated with HPS is highest in patients with confirmed oculocutaneous albinism by ophthalmologic examination and platelet delta granule deficiency on platelet transmission electron microscopy (whole mount). The large 3.9kb deletion in HPS3, which is one of the well-established founder pathogenic variants in the Puerto Rican population, can be detected by aCGH in our laboratory as it has not been validated for detection by NGS.

Reporting of Results

Results are classified and reported in accordance with ACMG next-generation sequencing and copy number variation standards and guidelines. Sequence variants and large deletions and duplications predicted to be pathogenic, likely pathogenic, and of uncertain significance will be reported; variants classified as likely benign or benign are typically not reported but such data are available upon request. Sequence variants are described using standard Human Genome Variation Society (HGVS) nomenclature (http://hgvs.org); copy number variants are described in accordance with the International System for Human Cytogenomic Nomenclature (ISCN).

Specimen Requirements

Parental/Patient/Pediatric: 3-5 mL Whole blood (EDTA tube, lavender top), 2-5 mL Bone marrow (EDTA tube, lavender top), 3-4 Buccal swabs, or ≥1ug of DNA at ≥50ng/uL of High Quality DNA.

Fetal: 7-15 mL amniotic fluid, 5-10 mg chorionic villi; back up culture of amniocytes or chorionic villi is highly recommended. Cultured: Two T25 flasks cultured amniocytes or chorionic villi ($2x10^6$ minimum). Maternal blood sample of 3-5 mL Whole blood (EDTA tube, lavender top) is requested for all prenatal samples for maternal cell contamination studies. For questions please contact the laboratory to discuss sample requirements.

SHIP

Shipping Requirements

Ship on an ice pack or at room temperature. Protect from freezing. Place the specimen and the requisition into plastic bags and seal. Insert into a Styrofoam container, seal and place into a sturdy cardboard box, and tape securely. Ship the package in compliance with your overnight carrier guidelines. Label with the following address:

Client Services/Diagnostic Laboratory
Versiti
638 N. 18th St
Milwaukee, WI, 53233

ORDER

Required Forms

Please complete all pages of the requisition form. Clinical history (including patient's ethnicity, clinical diagnosis, family history, and relevant laboratory findings) is necessary for optimal interpretation of genetic test results and recommendations. Clinical and laboratory history can either be recorded on the requisition form or clinical and laboratory reports can be submitted with the sample.

CPT Codes/Billing/Turnaround Time

Test code: 4875

For suggested CPT codes, visit the Versiti.org/test menu

Turnaround time: 21 days

The CPT codes provided are subject to change as more information becomes available. CPT codes are provided only as guidance to assist clients with billing.

For additional information related to shipping, billing or pricing, please contact Versiti Client Services: (414) 937-6396 or 800-245-3117, Option 1, or LabInfo@versiti.org

References

Hermansky-Pudlak syndrome references

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Variant interpretation references

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