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Hermansky-Pudlak Syndrome

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Summary

Clinical characteristics

Hermansky-Pudlak syndrome (HPS) is characterized by oculocutaneous albinism, a bleeding diathesis, and, in some individuals, pulmonary fibrosis, granulomatous colitis, and/or immunodeficiency. Ocular findings include nystagmus, reduced iris pigment, reduced retinal pigment, foveal hypoplasia with significant reduction in visual acuity (usually in the range of 20/50 to 20/400), and strabismus in many individuals. Hair color ranges from white to brown; skin color ranges from white to olive and is usually at least a shade lighter than that of other family members. The bleeding diathesis can result in variable degrees of bruising, epistaxis, gingival bleeding, postpartum hemorrhage, colonic bleeding, and prolonged bleeding with menses or after tooth extraction, circumcision, and/or other surgeries. Pulmonary fibrosis, colitis, and/or neutropenia have been reported in individuals with pathogenic variants in some HPS-related genes. Pulmonary fibrosis, a restrictive lung disease, typically causes symptoms in the early 30s and can progress to death within a decade. Granulomatous colitis is severe in about 15% of affected individuals. Neutropenia and/or immune defects occur primarily in individuals with pathogenic variants in *AP3B1* and *AP3D1*.

Diagnosis/testing

The clinical diagnosis of HPS can be established in a proband with hypopigmentation of the skin and hair, characteristic eye findings, and demonstration of absence of platelet delta granules (dense bodies) on electron microscopy. Identification of biallelic pathogenic variants in *AP3B1*, *AP3D1*, *BLOC1S3*, *BLOC1S5*, *BLOC1S6*, *DTNBP1*, *HPS1*, *HPS3*, *HPS4*, *HPS5*, or *HPS6* confirms the diagnosis if clinical features are inconclusive.

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Management

Treatment of manifestations: Correction of refractive errors and use of low vision aids; preferential seating in school; low-vision consultant as needed; UV-blocking sunglasses; surgery for strabismus as needed; protection from sun exposure with protective clothing and sunscreen; standard treatment for skin cancer; thrombin-soaked Gelfoam® for skin wounds with prolonged bleeding; medical alert bracelet and bleeding management plan; humidifier to reduce frequency of epistaxis; oral contraceptives and IUD for menorrhagia; DDAVP® (desmopressin acetate) for wisdom tooth extraction and invasive procedures; platelet or red blood cell transfusions for surgery or protracted bleeding; HLA-matched single-donor platelets as needed; maximize pulmonary function with prompt treatment of asthma and pulmonary infections; influenza, pneumococcal, and COVID-19 vaccines; regular moderate exercise; supplemental oxygen for advanced-stage pulmonary fibrosis; lung transplantation for end-stage pulmonary disease; steroids, other anti-inflammatory agents, and/or Remicade® for granulomatous colitis. Immunodeficiency, when present, is lifelong and granulocyte colony-stimulating factor responsive, and affected individuals benefit from an infection prevention plan.

Surveillance: Annual ophthalmologic examination including assessment for refractive errors; annual skin examination for evidence of sun-induced skin damage (e.g., solar keratoses [premalignant lesions], basal cell carcinoma, and squamous cell carcinoma); annual pulmonary function testing in those older than age 20 years; colonoscopy in those with symptoms of colitis (e.g., cramping, mucoid stools, hematochezia, melena); assessment for clinical and laboratory manifestations of immunodeficiency.

Agents/circumstances to avoid: Over-the-counter nonsteroidal anti-inflammatory products, aspirin-containing products, and other anticoagulants unless medically indicated; activities that increase the risk of bleeding; all tobacco and vaping products and inhalation of chemical and physical substances injurious to the lungs; unprotected and direct sun exposure.

Evaluation of relatives at risk: In families with *HPS3*-, *HPS5*-, or *HPS6*-related HPS (milder types of HPS in which hypopigmentation and nystagmus may not be clinically evident), it is appropriate to clarify the status of apparently asymptomatic at-risk sibs in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

Genetic counseling

HPS is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an HPS-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the HPS-causing pathogenic variants are identified in an affected family member, carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Hermansky-Pudlak syndrome (HPS) **should be suspected** in a proband with the following clinical, laboratory, and family history findings.

Clinical findings

- Nystagmus, low vision, photophobia, strabismus
- Skin and hair color lighter than other family members
- Increased bruising, epistaxis, gingival bleeding, and prolonged bleeding after minor procedures (e.g., circumcision, tooth extraction)

Laboratory findings

- Platelet aggregation testing showing impaired secondary aggregation response
- Prothrombin time, partial thromboplastin time, and platelet counts typically normal
- Absence of platelet delta granules (dense bodies) on whole mount electron microscopy

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The clinical diagnosis of HPS **can be established** in a proband with oculocutaneous albinism and absence of platelet delta granules (dense bodies), or the molecular diagnosis can be established in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in one of the genes listed in Table 1.

Clinical Diagnosis

Oculocutaneous albinism is established by finding hypopigmentation of the skin and hair on physical examination (especially when compared to other family members) associated with the following characteristic ocular findings:

- Nystagmus
- Reduced iris pigment with iris transillumination
- Reduced retinal pigment on fundoscopic examination
- Foveal hypoplasia associated with significant reduction in visual acuity

Absence of platelet delta granules (dense bodies) is identified by electron microscopy (preferably "whole mount" as opposed to contrasted ultra-thin sections or scanning electron microscopies) [Witkop et al 1989]. On stimulation of platelets, the dense bodies, which contain ADP, ATP, serotonin, calcium, and phosphate, release their contents to attract other platelets. This process constitutes the secondary aggregation response, which cannot occur in the absence of the dense bodies. There are normally four to eight dense bodies per platelet; there are no dense bodies in the platelets of individuals with HPS.

Molecular Diagnosis

The molecular diagnosis of HPS **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in one of the genes listed in Table 1.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic, and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic variants of uncertain significance (or of one known pathogenic variant and one variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel, targeted analysis) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see **Option 1**), whereas those with a phenotype indistinguishable from many other inherited disorders with either oculocutaneous albinism or platelet dense bodies are more likely to be diagnosed using genomic testing (see **Option 2**).

Option 1

A multigene panel that includes *AP3B1*, *AP3D1*, *BLOC1S3*, *BLOC1S5*, *BLOC1S6*, *DTNBP1*, *HPS1*, *HPS3*, *HPS4*, *HPS5*, *HPS6*, and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Targeted analysis for pathogenic variants can be performed first in individuals of Puerto Rican, Ashkenazi Jewish, or Israeli Bedouin ancestry (see Table 6).

- *HPS1* pathogenic variant c.1472_1487dup16 in individuals of **northwestern Puerto Rican** ancestry. Homozygosity for *HPS1* c.1472_1487dup16 is found in approximately 80% of affected individuals of Puerto Rican ancestry [Santiago Borrero et al 2006].
- *HPS3* deletion/duplication analysis for the common 3.9-kb deletion (g.339_4260del3904) in individuals of **central Puerto Rican** ancestry [Anikster et al 2001]. This deletion accounts for 20% of HPS-related pathogenic variants in Puerto Ricans [Santiago Borrero et al 2006].
- *HPS3* splice site variant c.1163+1G>A in individuals of **Ashkenazi Jewish** ancestry [Huizing et al 2001]
- *HPS6* frameshift variant c.1065dupG in individuals of **Israeli Bedouin** descent [Schreyer-Shafir et al 2006]

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Hermansky-Pudlak Syndrome

Gene [1]	Proportion of HPS Attributed to Pathogenic Variants in Gene [2]	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
AP3B1	~5%	~90%	~10% [6, 7]
AP3D1	~1%	100%	None reported [6]
BLOC1S3	~1%	80%	None reported [6]
BLOC1S5	~1%	100%	None reported [6]
BLOC1S6	~1%	100%	None reported [6]
DTNBP1	~1%	99%	1 individual [8]
HPS1	~55% [9]	~95%	~5% [6]
HPS3	~15% [10]	40%	60% [6, 10]
HPS4	~5%	100%	None reported [6]
HPS5	~5%	99%	2 individuals [6]

Table 1. continued from previous page.

Gene [1]	Proportion of HPS Attributed to Pathogenic Variants in Gene [2]	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
HPS6	~10% [11]	99%	2 individuals [6]
Unknown	~1%	NA	

NA = not applicable
1. See Table A. Genes and Databases for chromosome locus and protein.
2. There are approximately 770 individuals with HPS and biallelic HPS-related gene variants reported in the literature (as of January 2023).
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects large intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Data derived from [Huizing et al 2020] and the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
7. A homozygous chromosome 5 inversion with a breakpoint in *AP3B1* [Jones et al 2013] and several large chromosomal deletions in *AP3B1* have been reported.
8. A homozygous *DTNBP1* deletion of exon 6 was reported in one individual [Boeckelmann et al 2022].
9. Homozygosity for the *HPS1* c.1472_1487dup16 is found in affected individuals of northwest Puerto Rican ancestry. As of January 2023, approximately 260 affected individuals (~33% of all reported individuals with HPS) have been reported as homozygous for this variant [Santiago Borrero et al 2006, Huizing et al 2020]. Approximately 155 non-Puerto Rican individuals (~20% of all individuals with HPS) with a variety of *HPS1* variants are reported.
10. Homozygosity for an *HPS3* 3.9-kb deletion (g.339_4260del3904) is reported in approximately 70 affected individuals with HPS (~9% of all individuals with HPS) of central Puerto Rican ancestry. Approximately 45 non-Puerto Rican individuals (~6% of all individuals with HPS) with a variety of *HPS3* variants have been reported [Anikster et al 2001, Santiago Borrero et al 2006, Huizing et al 2020].
11. This includes 20 individuals of Israeli Bedouin descent homozygous for the c.1065dupG frameshift variant [Schreyer-Shafir et al 2006].

Clinical Characteristics

Clinical Description

Hermansky-Pudlak syndrome (HPS) is characterized by oculocutaneous albinism, a bleeding diathesis, and other organ involvement in specific subtypes [Huizing et al 2008]. Signs and symptoms of oculocutaneous albinism in HPS are variable but visual acuity generally remains stable.

Eyes. Nearly all children with HPS have nystagmus at birth, often noticed by the parents and the examining physician in infancy. Children with HPS may also have periodic alternating nystagmus, wandering eye movements, and lack of visual attention. The nystagmus can be very fast early in life and generally slows with time, but nearly all individuals have nystagmus throughout their lives. The development of pigment in the iris or retina does not affect the nystagmus. Nystagmus is most noticeable in lateral eye gaze, or when an individual is tired or anxious.

Iris color may remain blue or change to a green/hazel or brown/tan color. Iris transillumination can be complete or can show peripupillary clumps or streaks of pigment in the iris that appear like spokes of a wagon wheel. Fine granular pigment may develop in the retina.

Photophobia may accompany severe foveal hypoplasia.

Foveal hypoplasia is associated with significant visual acuity loss. Visual acuity, usually between 20/50 and 20/400, is typically 20/200 and usually remains constant after early childhood.

Individuals with HPS have increased crossing of the optic nerve fibers.

Alternating strabismus is found in many individuals with HPS and is generally not associated with the development of amblyopia.

Hair/skin. The hair color ranges from white to brown and can occasionally darken with age. Skin color can be white to olive but is generally at least a shade lighter than that of other family members.

Over many years, exposure of lightly pigmented skin to the sun can result in coarse, rough, thickened skin (pachydermia), solar keratoses (premalignant lesions), and skin cancer. Both basal cell carcinoma and squamous cell carcinoma can develop. Although skin melanocytes are present in individuals with HPS, melanoma is rare.

Some affected individuals have solar damage manifesting as actinic keratoses and nevi. Freckles, solar lentigines, and basal cell carcinoma also occur with increased frequency among individuals with HPS.

Bleeding diathesis. The bleeding diathesis of HPS results from absent or severely deficient dense granules in platelets; the alpha granule contingent is normal. Affected individuals experience variable bruising, epistaxis, gingival bleeding, postpartum hemorrhage, colonic bleeding, and prolonged bleeding during menstruation or after tooth extraction, circumcision, and/or other surgeries. Typically, cuts bleed longer than usual but heal normally. Bruising generally first appears at the time of ambulation. Epistaxis occurs in childhood and diminishes after adolescence. Menstrual cycles may be heavy and irregular. Affected individuals with colitis may bleed excessively per rectum. Exsanguination as a complication of childbirth, trauma, or surgery is extremely rare.

Pulmonary fibrosis. The fibrosis consists of progressive restrictive lung disease with an extremely variable time course. Symptoms usually begin in the 30s and may be fatal within a decade. Pulmonary fibrosis has been described largely in affected individuals from northwestern Puerto Rico (*HPS1*-related HPS), but also occurs in other individuals with pathogenic variants in *AP3B1*, *HPS1*, and *HPS4* [Gahl et al 2002, Gochuico et al 2012, Velázquez-Díaz et al 2021, Yokoyama & Gochuico 2021]. Some individuals with *HPS1*-related pulmonary fibrosis successfully underwent bilateral or single-lung transplantations [Yokoyama & Gochuico 2021, Benvenuto et al 2022]. Convincing evidence of pulmonary fibrosis has not been reported in affected individuals with pathogenic variants in other HPS-related genes.

Colitis. A bleeding granulomatous colitis resembling Crohn disease presents on average at age 17 years with wide variability [Gahl et al 1998, O'Brien et al 2021]. The colitis is severe in 15% of affected individuals and occasionally requires colectomy. Objective signs of colitis have been found in persons with pathogenic variants in *HPS1*, *HPS3*, *HPS4*, or *HPS6* [Hussain et al 2006, O'Brien et al 2021]. Although the colon is primarily involved in HPS, any part of the alimentary tract, including the gingiva, can be affected. HPS-related colitis may be responsive to corticosteroids, anti-inflammatory drugs, immune modulators, or anti-tumor necrosis factor alpha drugs [Schinella et al 1980, O'Brien et al 2021]. Partial or total colectomy was performed in some individuals with severe disease unresponsive to therapy [Schinella et al 1980, Gahl et al 1998, Hussain et al 2006].

Neutropenia. Neutropenia and/or additional immune defects (e.g., impaired NK cell cytotoxicity) have been associated with AP-3-deficient HPS, including individuals with pathogenic variants in *AP3B1* [Fontana et al 2006, de Boer et al 2017] or *AP3D1* [Ammann et al 2016, Mohammed et al 2019].

Other. Other features have been reported rarely in individuals with HPS, including cardiomyopathy and renal failure [Gahl et al 1998], thrombocytopenia and leukemia [Badolato et al 2012, Okamura et al 2018], or neurologic involvement [Okamura et al 2018, Michaud et al 2021].

Phenotype Correlations by Gene

All individuals with HPS exhibit oculocutaneous albinism (as a result of aberrant melanosome formation) and a bleeding diathesis (as a result of absent platelet delta granules). Other clinical features occur per subtype and are listed below; individuals with pathogenic variants in the same HPS protein complex of AP-3, BLOC-1, BLOC-2, or BLOC-3 exhibit similar clinical characteristics [Huizing et al 2008, Huizing et al 2020]. These complexes are described in Molecular Pathogenesis.

AP3B1, AP3D1 (AP-3 Deficiency)

Individuals with pathogenic variants in *AP3B1* or *AP3D1* exhibit immunodeficiency. They have an increased susceptibility to infections due to congenital neutropenia and impaired NK cell cytotoxicity. In vitro evidence suggests that the neutropenia is caused by mislocalization of granule proteins in neutrophils [de Boer et al 2017].

Some individuals with *AP3D1*-related HPS exhibited additional features not commonly seen in individuals with *AP3B1*-related HPS, including neurodevelopmental delay, seizures, or impaired hearing [Ammann et al 2016, Mohammed et al 2019, Frohne et al 2022]. It is not clear if these features are related to AP-3 complex subunit delta-1 deficiency.

BLOC1S3, BLOC1S5, BLOC1S6, DTNBP1 (BLOC-1 Deficiency)

Data are insufficient to determine whether individuals with BLOC-1 deficiency are prone to complications besides albinism, a bleeding diathesis, and colitis.

BLOC-1-deficient individuals appear to have a silver/blond/gold hair color at birth that may turn darker with age [Lowe et al 2013, Pennamen et al 2020]. No pulmonary defects have been reported in these individuals.

Some individuals exhibited additional features that should be monitored in other affected individuals. A female of northern European descent with *DTNBP1*-related HPS exhibited granulomatous colitis [Lowe et al 2013], a Portuguese female with *DTNBP1*-related HPS had recurrent bacterial infections with slightly reduced NK degranulation [Boeckelmann et al 2022]. Of the five reported individuals with *BLOC1S6*-related HPS, an Italian and a Japanese female had thrombocytopenia and leukemia [Badolato et al 2012, Okamura et al 2018], the Japanese female developed schizophrenia in her late 40s [Okamura et al 2018], a Chinese boy had abnormal brain waves by electroencephalogram [Liu et al 2021], and a Syrian girl had recurrent infections, abnormal psychomotor development, and dextrocardia [Michaud et al 2021].

HPS3, HPS5, HPS6 (BLOC-2 Deficiency)

Individuals with pathogenic variants in *HPS3*, *HPS5*, or *HPS6* are BLOC-2 deficient and generally have milder symptoms than those with BLOC-3 deficiency (pathogenic variants in *HPS1* or *HPS4*) [Huizing et al 2008]. The albinism in individuals with BLOC-2-related HPS can present with such minimal hypopigmentation that some individuals may be diagnosed with ocular albinism rather than oculocutaneous albinism. Visual acuity often approximates 20/100 or better.

Bleeding is also mild, and pulmonary fibrosis has not been observed in individuals with BLOC-2 deficiency.

Individuals with BLOC-2 deficiency can go undiagnosed for decades: a new diagnosis of *HPS5*-related HPS was described in a man age 92 years with light skin and hair, nystagmus, decreasing visual acuity with age, and a bleeding history. He is the oldest reported individual with HPS [Ringeisen et al 2013].

HPS1, HPS4 (BLOC-3 Deficiency)

Individuals with BLOC-3 deficiency exhibit a generally severe form of oculocutaneous albinism and bleeding diathesis [Huizing et al 2008].

BLOC-3 deficiency is associated with potentially lethal pulmonary fibrosis, a progressive restrictive lung disease. Individuals typically become symptomatic in their 30s and may die within a decade, unless transplanted [Gochuico et al 2012, Velázquez-Díaz et al 2021, Yokoyama & Gochuico 2021, Benvenuto et al 2022].

Significant granulomatous colitis occurs primarily in individuals with *HPS1*, *HPS3*, *HPS4*, or *HPS6* pathogenic variants [Hussain et al 2006, O'Brien et al 2021].

Genotype-Phenotype Correlations

Correlations between specific HPS-causing variants in any one gene and particular clinical presentations are not convincing.

Nomenclature

HPS may have been referred to as non-neuronal ceroid-lipofuscinosis to differentiate it from neuronal ceroid lipofuscinosis (Batten disease). In HPS, the nervous system appears to be spared.

Individuals with HPS with mild hypopigmentation and a bleeding disorder could be referred to as having "delta storage pool deficiency"; however, individuals with isolated delta storage pool deficiency do not have vision defects.

Prevalence

HPS is a rare disorder with an estimated worldwide prevalence of one to nine in 1,000,000 individuals (www.orpha.net).

The prevalence per subtype can differ because of founder variants. The prevalence of *HPS1*-related HPS in northwestern Puerto Rico is 1:1,800 [Santiago Borrero et al 2006].

HPS1-related HPS has also been reported in a small isolate in a Swiss village [Schallreuter et al 1993] and as a genetic isolate in Japan [Ito et al 2005].

HPS3-related HPS occurs as a genetic isolate in central Puerto Rico, where about 1:16,000 individuals are affected [Anikster et al 2001, Santiago Borrero et al 2006]. Newborn screening of 12% of the Puerto Rican population detected two homozygotes and 73 heterozygotes with the common g.339_4260del3904 variant (also referred to as the 3.9-kb deletion) [Torres-Serrant et al 2010].

Individuals with HPS have been identified in many other regions, including China, India, the Middle East, South America, and Western and Eastern Europe.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be caused by germline pathogenic variants in *AP3B1*, *AP3D1*, *BLOC1S3*, *BLOC1S5*, *BLOC1S6*, *DTNBP1*, *HPS1*, *HPS3*, *HPS4*, *HPS5*, or *HPS6*.

Differential Diagnosis

Albinism. The diagnosis of Hermansky-Pudlak syndrome (HPS) should be considered in anyone with oculocutaneous albinism or ocular albinism, as the bleeding diathesis can be mild, unrecognized, or previously disregarded. Pathogenic variants in HPS-related genes have been identified in next-generation sequencing studies of individuals with oculocutaneous albinism or ocular albinism [Lasseaux et al 2018, Hovnik et al 2021, Chan et al 2023]. Some would advocate screening all individuals with albinism for HPS by examining their platelets for absent dense bodies. Genes known to be associated with albinism are summarized in Table 2a.

Table 2a. Differential Diagnosis of Hermansky-Pudlak Syndrome: Disorders with Albinism

Gene(s)	Disorder	MOI	Clinical Features
DCT	OCA8 (OMIM 619165)	AR	• Characterized by ↓ or complete lack of melanin pigment in the skin, hair, & eyes. • Often presents w/white/blond/light hair, white or light skin that does not tan & is very susceptible to damage from the sun incl skin cancer, & fully translucent irises that do not darken w/age. • Ocular findings can include nystagmus, ↓ iris pigment w/iris translucency, ↓ retinal pigment, foveal hypoplasia w/significantly ↓ visual acuity, & misrouting of optic nerves resulting in alternating strabismus & ↓ stereoscopic vision. • All persons w/OCA have severe visual changes, but amount of skin, hair, & iris pigment can vary depending on gene (or type of OCA) & pathogenic variant involved.
LRMDA	OCA7 (OMIM 615179)		
OCA2	OCA2 (OMIM 203200)		
SLC24A5	OCA6 (OMIM 113750)		
SLC45A2	OCA4		
TYR	OCA1 (OMIM 203100, 606952)		
TYRP1	OCA3 (OMIM 203290)		
GPR143	X-linked ocular albinism (OMIM 300500)	XL	• Affected males have minor skin manifestations & congenital & persistent visual impairment. • Characterized by congenital nystagmus, ↓ visual acuity, hypopigmentation of iris pigment epithelium & ocular fundus, & foveal hypoplasia. • Significant refractive errors, ↓ or absent binocular functions, photophobia, & strabismus are common.

AR = autosomal recessive; MOI = mode of inheritance; OCA = oculocutaneous albinism; XL = X-linked

Disorders of platelet delta granules (dense bodies). Reviewed in Gunay-Aygun et al [2004], these disorders include Chediak-Higashi syndrome and Griscelli syndrome (see Table 2b).

Table 2b. Differential Diagnosis of Hermansky-Pudlak Syndrome: Disorders of Platelet Delta Granules

Gene(s)	Disorder	MOI	Clinical Features
LYST	Chediak-Higashi syndrome (CHS)	AR	• Significantly ↑ frequency of infection in childhood, partial OCA, & bleeding diathesis • Characterized by huge, fused, dysfunctional lysosomes & macromelanosomes. • Persons w/CHS always have giant intracellular granules in their neutrophils on peripheral blood smear (persons w/HPS never exhibit this finding). • ~85% of affected persons develop hemophagocytic lymphohistiocytosis or the accelerated phase of CHS, a finding that also sporadically occurs in *AP3B1*-related HPS. [1] • All affected persons – incl adolescents & adults w/atypical CHS & children w/classic CHS who have successfully undergone allogenic HSCT – develop neurologic findings.

Table 2b. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features
MLPH *MYO5A* *RAB27A*	Griscelli syndrome [2] (OMIM 214450)	AR	• Mild hypopigmentation & immunodeficiency • Can have the accelerated phase of lymphohistiocytosis • A distinguishing finding is silver-gray hair.

AR = autosomal recessive; HPS = Hermansky-Pudlak syndrome; HSCT = hematopoietic stem cell transplantation; MOI = mode of inheritance; OCA = oculocutaneous albinism
1. de Boer et al [2017]
2. Elejalde syndrome (OMIM 256710) is considered a type of Griscelli syndrome in which neurologic involvement (rather than immunodeficiency and lymphohistiocytosis) occurs.

Management

Clinical practice guidelines for Hermansky-Pudlak syndrome (HPS) have not been published; however, clinicians with expertise in HPS care have published management recommendations [Seward & Gahl 2013].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with HPS, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Hermansky-Pudlak Syndrome

System/Concern	Evaluation	Comment
Eyes	Complete ophthalmologic eval incl assessment of refractive error	The majority of persons w/ocular albinism have significant hyperopia (farsightedness) or myopia (nearsightedness) & astigmatism.
Skin	Skin exam for severity of hypopigmentation	
	Skin exam for evidence of skin damage & skin cancer	In persons age ≥12 mos
Bleeding	Assess history of bleeding issues.	Recommend comprehensive coagulation eval incl von Willebrand factor deficiency assays & platelet function assays.
Pulmonary	Assess for concomitant reactive airways disease unrelated to HPS & manifestations of pulmonary fibrosis.	
Colitis	Assess for manifestations of colitis.	Colonoscopy w/biopsy for persons w/signs & symptoms of colitis
Immunodeficiency	• Assess frequency of infections. • Laboratory assessment: WBC count & neutrophil function	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of HPS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral as needed.	

HPS = Hermansky-Pudlak syndrome; MOI = mode of inheritance; WBC = white blood count
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for HPS or its associated manifestations. Preventative and supportive care improves quality of life, maximizes function, and reduces complications. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. Treatment of Manifestations in Individuals with Hermansky-Pudlak Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Refractive errors	• Correction of refractive errors to improve visual acuity • Aids (e.g., handheld magnifying devices, bioptic lenses) as needed • Preferential seating in school • Low vision consultant as needed	Recommend UV-blocking sunglasses.
Strabismus	Surgery for strabismus is indicated when misalignment cannot be corrected by medical measures.	Surgery is not usually required & is not always successful.
Skin	Protection from sun to prevent burning, skin damage, & skin cancer: • Protective clothing (hats w/brims, long sleeves, pants, socks) for prolonged exposure • Sunscreen w/high SPF (45-50+) for sun-sensitive persons; SPF (15+) for less sun-sensitive persons	Recommendations are based on individual skin pigment & cutaneous response to sunlight. In very sun-sensitive persons, sun exposure of 5-10 mins can be damaging; in less sun-sensitive persons, exposure of ≥30 minutes is damaging.
	Standard treatments for skin cancer	
Bleeding	• Thrombin-soaked Gelfoam® can be used on minor wounds that fail to clot spontaneously. • Recommend medical alert bracelet that explicitly describes the functional platelet defect, as the standard tests for bleeding dysfunction (e.g., platelet count, prothrombin time, partial thromboplastin time) are normal in those w/HPS.	Recommend bleeding mgmt plan in coordination w/coagulation specialist, schools, family, & primary care providers.
Epistaxis	Humidifiers may ↓ frequency of nosebleeds.	
Menorrhagia	• Oral contraceptives & IUDs can ↓ menorrhagia. • Menorrhagia has been treated w/levonorgestrel-releasing intrauterine system [Kingman et al 2004] & recombinant factor VIIa [Lohse et al 2011].	Anti-fibrinolytics, such as aminocaproic acid & tranexamic acid, can ↓ severity of bleeding.
Surgical bleeding	• For more invasive trauma, such as wisdom tooth extraction, DDAVP® (desmopressin acetate), 0.3 µg/kg in 50 mL of normal saline, can be given as a 30- to 60-min IV infusion just prior to procedure. • For extensive surgeries or protracted bleeding, platelet or RBC transfusions may be required. • For elective surgical procedures w/estimated moderate or greater blood loss, HLA-matched single-donor platelets should be used. • Recommend having platelets on standby for all surgical procedures w/risk of significant bleeding.	Not all affected persons respond to DDAVP®, & responsiveness testing is recommended. [1]

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Pulmonary fibrosis	Maximize pulmonary function: • Prompt treatment of asthma & pulmonary infections • Influenza, pneumococcal, & COVID-19 vaccines • Regular moderate exercise • Optimized treatment for concomitant reactive airways disorders	Affected persons should be counseled to avoid all recreational inhalational products, chemical & physical substances (e.g., organic/inorganic fibers, volatile chemicals), & use of medications assoc w/ drug-induced pulmonary fibrosis (e.g., methotrexate, bleomycin, amiodarone, nitrofurantoin).
	Oxygen therapy for severe pulmonary disease	Oxygen therapy is life-sustaining for persons w/advanced-stage disease & helps forestall development of secondary pulmonary hypertension.
	Bilateral or single-lung transplantation if appropriate [2]	
Colitis	HPS-related colitis may respond to steroids & other anti-inflammatory agents. [3] Remicade® has also been used w/ benefit. [4]	HPS-related colitis can affect upper intestinal structures & is assoc w/ extraintestinal manifestations such as pyoderma gangrenosum.
Immunodeficiency	Typically responsive to granulocyte colony-stimulating factor	Recommend infection prevention plan in coordination w/infectious disease specialist, schools, family, & primary care providers.

IUD = intrauterine device; RBC = red blood cell
1. Cordova et al [2005]
2. Benvenuto et al [2022]
3. Mora & Wolfsohn [2011]
4. Erzin et al [2006], Felipez et al [2010]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with Hermansky-Pudlak Syndrome

System/Concern	Evaluation	Frequency
Eyes	Ophthalmologic exam incl assessment of refractive error	Annually
Skin	Skin exam for evidence of skin damage, solar keratoses (premalignant lesions), basal cell carcinoma, & squamous cell carcinoma	Annually; more frequently in persons w/concerning lesions or history of skin cancer
Pulmonary fibrosis	Pulmonary function testing	Annually in those age ≥20 yrs
	High-resolution chest CT to identify pulmonary fibrosis	In young adults w/*AP3B1*-, *HPS1*-, & *HPS4*-related HPS generally starting at age 30 yrs w/follow up as indicated based on PFT results & symptoms; if symptoms are suggestive, earlier imaging may be indicated.
Colitis	Colonoscopy in those w/abdominal cramping, ↑ mucus in stool, & rectal bleeding	As needed
Immunodeficiency	Assessment for clinical & laboratory manifestations of immunodeficiency	At each visit

PFT = pulmonary function testing

Agents/Circumstances to Avoid

The following should be avoided:

- All nonsteroidal anti-inflammatory medications and aspirin-containing products
- Therapeutic anticoagulants (should be used only if medically indicated)
- High-impact sports and activities that could increase the risk of bleeding
- Tobacco products (which decrease pulmonary function and may exacerbate pulmonary fibrosis)
- Other pulmonary toxicants (e.g., inorganic and organic fibers, volatile chemicals, polluted environments)
- Direct sun exposure without protection (e.g., protective clothing, sunscreen, and UV-blocking sunglasses)

Evaluation of Relatives at Risk

In individuals with *HPS1*- and *HPS4*-related HPS, the diagnosis will be apparent because the hypopigmentation and nystagmus are clinically evident.

In families with other types of HPS (caused by pathogenic variants in *AP3B1*, *AP3D1*, *BLOC1S3*, *BLOC1S5*, *BLOC1S6*, *DTNBP1*, *HPS3*, *HPS5*, or *HPS6*), some of which are milder types of HPS in which hypopigmentation and nystagmus may not be clinically evident, it is appropriate to clarify the status of apparently asymptomatic at-risk sibs in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

- If the pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known, platelet whole mount electron microscopy studies can be used to clarify the status of at-risk sibs.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancies should proceed normally for an affected mother or an affected fetus. Delivery, however, carries risk for bleeding in a woman with HPS; surveillance and a hematology consultation for anticipation of bleeding complications during delivery should be initiated once pregnancy is confirmed.

Therapies Under Investigation

No medications are currently approved by the US Food and Drug Administration as treatment for HPS.

Some medications for HPS-related pulmonary fibrosis have been investigated. Corticosteroid drugs were not effective and are not recommended for therapy [Vicary et al 2016]. Clinical trials investigating pirfenidone, an oral antifibrotic drug approved as treatment for idiopathic pulmonary fibrosis (IPF), were inconclusive [Gahl et al 2002, O'Brien et al 2011, O'Brien et al 2018]. Other antifibrotic therapies being studied as treatment for IPF, including tyrosine kinase inhibitors, are potential therapeutic candidates for HPS-related pulmonary fibrosis [Yokoyama & Gochuico 2021].

Gene therapy and gene editing are potential future treatments for HPS [Nieto-Alamilla et al 2022]. Preclinical studies of gene editing for *HPS1* variant c.1472_1487dup16 [Iyer et al 2019] and gene replacement of *HPS1* [Ikawa et al 2015] or *AP3B1* [Young et al 2012] are ongoing.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

In general, opaque contact lenses or darkly tinted lenses do not improve visual function. Dark glasses may be helpful for individuals with albinism, but many prefer to go without dark glasses because they reduce vision.

No successful therapy for or prophylaxis against HPS-related pulmonary fibrosis exists. Steroids are often tried but have no apparent beneficial effect.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hermansky-Pudlak syndrome (HPS) is inherited in an autosomal recessive manner.

Rarely, families with two-generation pseudodominant inheritance have been identified. Pseudodominance (i.e., an autosomal recessive condition present in individuals in two or more generations) may occur when an affected individual has children with a reproductive partner who is heterozygous (i.e., a carrier) for a pathogenic variant in the same HPS-associated gene.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an HPS-causing pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an HPS-causing pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an HPS-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has HPS or is a carrier (see Prevalence), offspring will be obligate heterozygotes (carriers) for a pathogenic variant in an HPS-related gene.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an HPS-causing pathogenic variant.

Carrier Detection

Carrier testing for at-risk family members requires prior identification of the *AP3B1*, *AP3D1*, *BLOC1S3*, *BLOC1S5*, *BLOC1S6*, *DTNBP1*, *HPS1*, *HPS3*, *HPS4*, *HPS5*, or *HPS6* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing for the reproductive partners of known carriers and for the reproductive partners of individuals affected with HPS should be considered, particularly if both partners are of the same ethnic background. Founder variants have been identified in individuals of Puerto Rican, Ashkenazi Jewish, European, Japanese, Swiss, and Israeli Bedouin ancestry (see Table 6).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the HPS-causing pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Hermansky-Pudlak Syndrome Network, Inc.**

  Phone: 800-789-9HPS

  Fax: 516-624-0640

  Email: info@hpsnetwork.org

  www.hpsnetwork.org

- **National Organization for Albinism and Hypopigmentation (NOAH)**

Phone: 800-473-2310 (US and Canada); 603-887-2310

Fax: 603-887-6049

Email: info@albinism.org

www.albinism.org

- **European Society for Immunodeficiencies (ESID) Registry**

  Email: esid-registry@uniklinik-freiburg.de

  ESID Registry

- **eyeGENE – National Ophthalmic Disease Genotyping Network Registry**

  Phone: 301-435-3032

  Email: eyeGENEinfo@nei.nih.gov

  https://eyegene.nih.gov/

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hermansky-Pudlak Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AP3B1	5q14.1	AP-3 complex subunit beta-1	AP3B1 database AP3B1base: Mutation registry for Hermansky-Pudlak syndrome 2 Albinism Database Mutations of the b3A subunit of the AP-3 complex gene (AP3B1)	AP3B1	AP3B1
AP3D1	19p13.3	AP-3 complex subunit delta-1		AP3D1	AP3D1
BLOC1S3	19q13.32	Biogenesis of lysosome-related organelles complex 1 subunit 3	BLOC1S3 database	BLOC1S3	BLOC1S3
BLOC1S5	6p24.3	Biogenesis of lysosome-related organelles complex 1 subunit 5	BLOC1S5 @ LOVD	BLOC1S5	BLOC1S5
BLOC1S6	15q21.1	Biogenesis of lysosome-related organelles complex 1 subunit 6	BLOC1S6 database	BLOC1S6	BLOC1S6
DTNBP1	6p22.3	Dysbindin	DTNBP1 database	DTNBP1	DTNBP1
HPS1	10q24.2	BLOC-3 complex member HPS1	Albinism Database Mutations of the Hermansky-Pudlak Syndrome-1 gene (HPS1)	HPS1	HPS1
HPS3	3q24	BLOC-2 complex member HPS3	HPS3 database Albinism Database Mutations of the Hermansky-Pudlak Syndrome-3 gene (HPS3)	HPS3	HPS3
HPS4	22q12.1	BLOC-3 complex member HPS4	HPS4 database	HPS4	HPS4

Table A. continued from previous page.

HPS5	11p15.1	BLOC-2 complex member HPS5	HPS5 database	HPS5	HPS5
HPS6	10q24.32	BLOC-2 complex member HPS6	HPS6 database	HPS6	HPS6

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Hermansky-Pudlak Syndrome (View All in OMIM)

203300	HERMANSKY-PUDLAK SYNDROME 1; HPS1
603401	ADAPTOR-RELATED PROTEIN COMPLEX 3, BETA-1 SUBUNIT; AP3B1
604310	BIOGENESIS OF LYSOSOME-RELATED ORGANELLES COMPLEX 1, SUBUNIT 6; BLOC1S6
604982	HPS1 BIOGENESIS OF LYSOSOMAL ORGANELLES COMPLEX 3, SUBUNIT 1; HPS1
606118	HPS3 BIOGENESIS OF LYSOSOMAL ORGANELLES COMPLEX 2, SUBUNIT 1; HPS3
606682	HPS4 BIOGENESIS OF LYSOSOMAL ORGANELLES COMPLEX 3, SUBUNIT 2; HPS4
607145	DYSTROBREVIN-BINDING PROTEIN 1; DTNBP1
607246	ADAPTOR-RELATED PROTEIN COMPLEX 3, DELTA-1 SUBUNIT; AP3D1
607289	BIOGENESIS OF LYSOSOME-RELATED ORGANELLES COMPLEX 1, SUBUNIT 5; BLOC1S5
607521	HPS5 BIOGENESIS OF LYSOSOMAL ORGANELLES COMPLEX 2, SUBUNIT 2; HPS5
607522	HPS6 BIOGENESIS OF LYSOSOMAL ORGANELLES COMPLEX 2, SUBUNIT 3; HPS6
608233	HERMANSKY-PUDLAK SYNDROME 2; HPS2
609762	BIOGENESIS OF LYSOSOME-RELATED ORGANELLES COMPLEX 1, SUBUNIT 3; BLOC1S3
614072	HERMANSKY-PUDLAK SYNDROME 3; HPS3
614073	HERMANSKY-PUDLAK SYNDROME 4; HPS4
614074	HERMANSKY-PUDLAK SYNDROME 5; HPS5
614075	HERMANSKY-PUDLAK SYNDROME 6; HPS6
614076	HERMANSKY-PUDLAK SYNDROME 7; HPS7
614077	HERMANSKY-PUDLAK SYNDROME 8; HPS8
614171	HERMANSKY-PUDLAK SYNDROME 9; HPS9
617050	HERMANSKY-PUDLAK SYNDROME 10; HPS10
619172	HERMANSKY-PUDLAK SYNDROME 11; HPS11

Molecular Pathogenesis

The proteins encoded by the eleven genes in which pathogenic variants are known to cause HPS associate into four HPS protein complexes, which are involved in cargo transport, cargo recycling, and cargo removal to maintain lysosome-related organelle (LRO) homeostasis [Huizing et al 2008, Bowman et al 2019]. The four complexes are the following:

- AP-3, a heterotetrameric complex of which two subunits, encoded by *AP3B1* and *AP3D1*, have pathogenic variants causing HPS [Dell'Angelica et al 1999, Ammann et al 2016]
- BLOC-1 (biogenesis of lysosome-related organelles complex 1), consisting of eight subunits [Falcón-Pérez et al 2002], four of which have pathogenic variants causing HPS: the protein products of *BLOC1S3*, *BLOC1S5*, *BLOC1S6*, and *DTNBP1*

- BLOC-2, including subunits encoded by *HPS3*, *HPS5*, and *HPS6* [Di Pietro et al 2004]
- BLOC-3, including subunits encoded by *HPS1* and *HPS4* [Martina et al 2003]

Genetic defects in HPS-related genes result in deficiency of the associated HPS protein complex, which leads to aberrant function of all LROs or only an individual LRO, resulting in a variety of clinical features. LROs affected in HPS include melanosomes in melanocytes (underlying pigmentation defects), platelet delta granules (underlying bleeding diathesis), lamellar bodies in alveolar type II cells (contributing to pulmonary fibrosis), and cytolytic granules in T cells and NK cells (contributing to immunodeficiency) [Huizing et al 2008, Bowman et al 2019, Li et al 2022].

Mechanism of disease causation. Loss of function

Table 6. Hermansky-Pudlak Syndrome: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change (Alias [2])	Predicted Protein Change	Comment [Reference]
HPS1	NM_000195.5 NP_000186.2	c.1472_1487dup16	p.His497GlnfsTer90	Founder variant in persons of northwestern Puerto Rican ancestry [Santiago Borrero et al 2006]
		c.972dupC	p.Met325HisfsTer128	Founder variant in persons of a Swiss Alpine village [Schallreuter et al 1993]
	NM_000195.5	c.398+5G>A (IVS5+5G>A)	--	Founder variant in persons of Japanese & Indian ancestry [Ito et al 2005]
HPS3	NG_009647.1	g.339_4260del3904 (3.9-kb del)	--	Founder variant in persons of central Puerto Rican ancestry [Anikster et al 2001]
	NM_032383.5	c.1163+1G>A (IVS5+1G>A)	--	Founder variant in persons of Ashkenazi Jewish ancestry [Huizing et al 2001]
HPS4	NM_022081.6 NP_071364.4	c.2089_2093dupAAGCA	p.Lys699SerfsTer5	Common variant in persons of European descent [Anderson et al 2003]
HPS6	NM_024747.6 NP_079023.2	c.1065dupG	p.Leu356ArgfsTer11	Founder variant in Israeli Bedouin persons [Schreyer-Shafir et al 2006]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Genes from Table 1 are in alphabetic order.
2. Variant designation that does not conform to current naming conventions

Chapter Notes

Author Notes

Dr Wendy J Introne, MD, is a pediatrician and medical and biochemical geneticist who performs clinical research on rare diseases.

Dr Marjan Huizing, PhD, is a cell biologist and geneticist who performs basic research on HPS and related disorders. She genetically subtyped more than 250 patients with HPS, studied their cells for the underlying cellular defects, and published extensively on the disease.

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- 25 May 2023 (wi) Revision: clarification of preferred method of electron microscopy in Establishing the Diagnosis
- 16 March 2023 (sw) Comprehensive update posted live
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- 26 October 2017 (sw) Comprehensive update posted live
- 11 December 2014 (me) Comprehensive update posted live
- 28 February 2013 (cd) Revision: deletion/duplication analysis available for *AP3B1*, *HPS3*, *HPS6*, and *BLOC1S6*; sequence analysis available for *BLOC1S6*
- 11 October 2012 (me) Comprehensive update posted live
- 8 July 2010 (cd) Revision: sequence analysis available clinically for mutations in *AP3B1* (*HPS2*), *HPS5*, *HPS6*, and *BLOC1S3* (*HPS8*)
- 4 May 2010 (me) Comprehensive update posted live
- 27 November 2007 (cd) Revision: sequence analysis available clinically for *HPS1* and *HPS4*; prenatal diagnosis available for *HPS4*.
- 21 March 2007 (me) Comprehensive update posted live
- 20 December 2004 (me) Comprehensive update posted live
- 2 January 2003 (tk) Comprehensive update posted live
- 24 July 2000 (me) Review posted live
- 27 January 2000 (wg) Original submission

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