



# Hermansky–Pudlak syndrome pulmonary fibrosis: a rare inherited interstitial lung disease

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**Hermansky–Pudlak syndrome (HPS) is an autosomal recessive disorder characterised by highly prevalent pulmonary fibrosis. HPS pulmonary fibrosis is a rare inherited interstitial lung disease that can serve as a model for studying fibrotic lung disorders.** <https://bit.ly/2ZWFR2Y>

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**ABSTRACT** Pulmonary fibrosis is a progressive interstitial lung disease of unknown aetiology with a poor prognosis. Studying genetic diseases associated with pulmonary fibrosis provides insights into the pathogenesis of the disease. Hermansky–Pudlak syndrome (HPS), a rare autosomal recessive disorder characterised by abnormal biogenesis of lysosome-related organelles, manifests with oculocutaneous albinism and excessive bleeding of variable severity. Pulmonary fibrosis is highly prevalent in three out of 10 genetic types of HPS (HPS-1, HPS-2 and HPS-4). Thus, genotyping of individuals with HPS is clinically relevant. HPS-1 tends to affect Puerto Rican individuals due to a genetic founder effect. HPS pulmonary fibrosis shares some clinical features with idiopathic pulmonary fibrosis (IPF), including dyspnoea, cough, restrictive lung physiology and computed tomography (CT) findings of fibrosis. In contrast to IPF, HPS pulmonary fibrosis generally affects children (HPS-2) or middle-aged adults (HPS-1 or HPS-4) and may be associated with ground-glass opacification in CT scans. Histopathology of HPS pulmonary fibrosis, and not IPF, shows vacuolated hyperplastic type II cells with enlarged lamellar bodies and alveolar macrophages with lipofuscin-like deposits. Antifibrotic drugs approved as treatment for IPF are not approved for HPS pulmonary fibrosis. However, lung transplantation has been performed in patients with severe HPS pulmonary fibrosis. HPS pulmonary fibrosis serves as a model for studying fibrotic lung disease and fibrosis in general.

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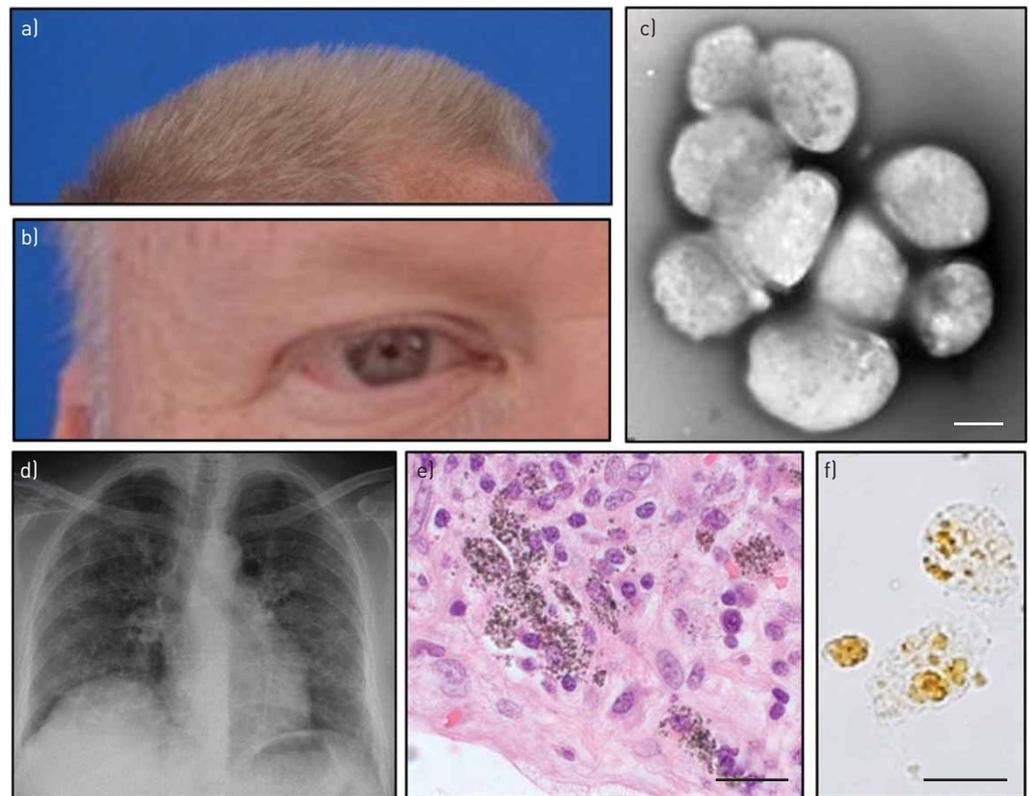
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## Introduction

Pulmonary fibrosis, a multifactorial, often fatal lung disease with limited treatment, is characterised by deposition of extracellular matrix protein and accumulation of fibroblasts, myofibroblasts and immune cells in the alveolar interstitium, leading to destruction of the pulmonary architecture [1–3]. The aetiology of pulmonary fibrosis is incompletely understood and several hypotheses regarding potential pathogenic mechanisms of disease have been posited [1–4]. Some data suggest that pulmonary fibrosis results from recurrent epithelial injury with aberrant repair or accelerated ageing [1–6]. Type II epithelial cell senescence and functional abnormalities, including endoplasmic reticulum stress, oxidative injury, mitochondrial dysfunction and impaired proteostasis, may alter alveolar homeostasis and contribute to the pathobiology of pulmonary fibrosis [1–4, 6–10]. Proposed mechanisms of disease include release of profibrotic mediators into the extracellular alveolar milieu, recruitment and activation of fibroblasts or myofibroblasts, epithelial–mesenchymal transition, and abnormal extracellular matrix turnover [1–4]. Several cytokines and growth factors are believed to contribute to the pathogenesis of pulmonary fibrosis, including transforming growth factor (TGF)- $\beta$ , connective tissue growth factor, platelet-derived growth factor, CCL2 (chemokine (C-C motif) ligand 2/monocyte chemoattractant protein-1), galectin-3, matrix metalloproteinases and interleukin-11 [1–4, 11, 12]. Dysregulation of these and other molecules may disrupt lung homeostasis and lead to development of pulmonary fibrosis.

Pulmonary fibrosis is a manifestation of several inherited disorders, including telomere disease, dyskeratosis congenita and Hermansky–Pudlak syndrome (HPS) [13–21]. HPS is a rare autosomal recessive disorder with locus heterogeneity that can serve as a model for investigating the pathogenesis of pulmonary fibrosis. HPS is characterised by oculocutaneous albinism, bleeding diathesis, inflammatory bowel disease and pulmonary fibrosis (figure 1) [16, 17, 22, 23]. HPS was initially described by Frantisek Hermansky and Paulus Pudlak in 1959 [24]. They reported two patients with oculocutaneous albinism, bleeding diathesis due to platelet dysfunction and reticular cells with pigment deposits in the bone marrow. Since the initial report, 10 genetic types of HPS have been identified and each is associated with a



**FIGURE 1** Clinical features of Hermansky–Pudlak syndrome (HPS). a, b) Hypopigmentation of a) hair and b) skin and iris of a Puerto Rican male. c)  $\delta$ -granules are absent in platelets from a patient with HPS-1 imaged using whole-mount transmission electron microscopy. Scale bar: 2  $\mu$ m. d) Bilateral interstitial infiltrates are found in a chest radiograph of a 50-year-old female with HPS pulmonary fibrosis. e) Fibrotic lung tissue stained with haematoxylin and eosin and f) unstained renal epithelial cells isolated from urine derived from a subject with HPS-1 show abnormal intracellular deposits. Scale bar: 20  $\mu$ m.

defect in biogenesis of lysosome-related organelles complex (BLOC)-1 (HPS-7, HPS-8 and HPS-9), BLOC-2 (HPS-3, HPS-5 and HPS-6), BLOC-3 (HPS-1 and HPS-4) or adapter protein (AP)-3 complex (HPS-2 and HPS-10) (table 1) [17, 22, 25–34]. The worldwide prevalence of HPS is approximately 1–9 per million individuals, but prevalence per HPS genetic type can be different in subpopulations due to genetic founder effects. Four HPS genetic types are associated with the development of interstitial lung disease (ILD) or pulmonary fibrosis. Most middle-aged adults with HPS-1 or HPS-4 and children or young adults with HPS-2 develop progressive and generally fatal pulmonary fibrosis [16, 17, 20, 21, 35]. In addition, one child with HPS-10 was reported to have ILD [33]. Given the high prevalence of fibrotic lung disease, understanding the pathogenesis of pulmonary fibrosis in these HPS genetic types can provide insights into the aetiology of fibrosis, which is incompletely understood. In this review, we summarise the current understanding of the genetics, pathobiology, clinical features and management of HPS pulmonary fibrosis.

### Genetics of HPS pulmonary fibrosis

10 types of HPS have been identified and each is associated with variants in a specific gene (table 1) [17, 22, 34]. Pulmonary fibrosis develops in individuals with HPS-1 [16], HPS-2 [20, 35] or HPS-4 [21]; ILD was described in a young boy with HPS-10 [33].

#### HPS-1

The *HPS1* gene, identified by positional cloning in 1996 by Oh *et al.* [36], is 30.5 kb with 20 exons and is found on chromosome 10q24.1–q25.1. *HPS1* encodes a 700-amino-acid protein with a molecular weight of 79.3 kDa. HPS1 and HPS4 proteins interact to form BLOC-3 [37, 38]. Although the function of BLOC-3 has not been fully elucidated, BLOC-3 is a Rab32/38 guanine nucleotide exchange factor, and promotes membrane recruitment of Rab32 and Rab38 [39]. BLOC-3 was found to activate Rab32/38, which regulates melanogenesis in melanocytes *in vitro* [40]. Given that HPS1 and HPS4 proteins are subunits of the same complex, their clinical manifestations are similar, including the development of pulmonary fibrosis in middle-aged adults.

67 *HPS1* variants located throughout the entire gene have been reported in association with HPS-1 [34]. The variants include frameshift, missense, nonsense, insertion, deletion and splice site variants. A common *HPS1* variant is c.1472\_1487dup16-bp. This 16-bp duplication in exon 15 of *HPS1* is generally found in affected individuals who originate from the northwest region of Puerto Rico [16]. Due to a genetic founder effect, the prevalence of HPS-1 in northwest Puerto Rico is approximately 1 per 1800 individuals; 1 in 22 Puerto Ricans in the region is a carrier of this *HPS1* variant [41]. Approximately 257 individuals with HPS-1 are reported to be Puerto Rican and tend to be homozygous for the c.1472\_1487dup16-bp *HPS1* variant; many Puerto Rican individuals with HPS-1 are unreported [34].

Notably, HPS-1 also affects individuals of other ethnicities and nationalities. Approximately 129 non-Puerto Rican individuals with numerous variants in *HPS1* have been reported; none of these individuals were homozygous for the c.1472\_1487dup16-bp *HPS1* variant [34]. Genetic isolates of HPS-1 were reported in Japan and Switzerland [42, 43]. Caucasian, African-American, non-Puerto Rican Latino, European, Middle Eastern, Pakistani, Afghan, Ukrainian, Russian, subcontinental Indian and Chinese individuals with HPS-1 have also been reported [34, 44–48]. Although multiple pathogenic *HPS1* variants were identified, genotype–phenotype correlations with pulmonary fibrosis or other disease manifestations in HPS-1 have not been reported.

TABLE 1 Hermansky–Pudlak syndrome (HPS)-associated genes, loci, proteins and complexes

HPS type	Gene <sup>#</sup>	Locus	Protein	Complex
HPS-1	<i>HPS1</i>	10q23.1	HPS1	BLOC-3
HPS-2	<i>AP3B1</i>	5q14.1	AP-3 complex β3A subunit	AP-3
HPS-3	<i>HPS3</i>	3q24	HPS3	BLOC-2
HPS-4	<i>HPS4</i>	22q11.2–q12.2	HPS4	BLOC-3
HPS-5	<i>HPS5</i>	11p15–p13	HPS5	BLOC-2
HPS-6	<i>HPS6</i>	10q24.3	HPS6	BLOC-2
HPS-7	<i>DTNBP1</i>	6p22.3	Dysbindin	BLOC-1
HPS-8	<i>BLOC1S3</i>	19q13	BLOC-1 subunit 3	BLOC-1
HPS-9	<i>PLDN</i>	15q15	Pallidin	BLOC-1
HPS-10	<i>AP3D1</i>	19p13.3	AP-3 complex δ1 subunit	AP-3

AP: adaptor protein; BLOC: biogenesis of lysosome-related organelles complex. <sup>#</sup>: see [www.genecards.org](http://www.genecards.org) for aliases.

### HPS-2

HPS-2 is associated with biallelic variants in *AP3B1*, located on chromosome 5q14.1 [25]. *AP3B1* encodes the  $\beta 3A$  subunit of the AP-3 complex, which is involved with membrane formation and intracellular vesicle trafficking. To date, approximately 35 individuals with HPS-2 have been reported in the literature; their ethnicities are varied [34]. No Puerto Rican cases of HPS-2 have been described. 29 pathogenic variants throughout *AP3B1* have been reported and there were no founder mutations or frequently occurring *AP3B1* variants [34]. Northern blot analysis from tissues with nonsense variants shows absent *AP3B1* transcript, consistent with nonsense-mediated mRNA decay [49]. In addition to neutropenia and immunodeficiency, children or young adults with HPS-2 can develop ILD or pulmonary fibrosis [20, 35, 49, 50].

### HPS-4

HPS-4 is associated with biallelic pathogenic variants in the *HPS4* (also known as *BLOC3S2*) gene, located on chromosome 22q12.1 [21]. 32 pathogenic variants located throughout *HPS4* have been reported [34]. Almost half of these are nonsense variants and result in truncated HPS4 protein [34]. Approximately 36 individuals with HPS-4 have been reported of various ethnicities, including Ashkenazi-Jewish, European, South Asian, Chinese and Japanese [27, 34]. A c.2089\_2093dupAAGCA variant in *HPS4* was reported in individuals of European descent [21, 27]. *HPS4* contains 14 exons and encodes a 76.9-kDa protein, which interacts with the HPS1 protein in BLOC-3 [37, 38]. Reduced levels of the HPS4 protein destabilise BLOC-3 and result in low levels of HPS1 [45, 51]. Clinical manifestations of HPS-4 resemble those of HPS-1, including progressive pulmonary fibrosis [21].

### Pathobiology of HPS

Defective formation of lysosome-related organelles and abnormal intracellular vesicle trafficking are mechanisms that contribute to the clinical manifestations of HPS (figure 2) [22, 52]. Each HPS-causing gene encodes a protein which is a subunit of a cytoplasmic complex involved in these functions. Hetero-oligomeric complexes involved in the pathobiology of HPS include BLOC-1, BLOC-2, BLOC-3 and the AP-3 complex. HPS gene products are ubiquitously expressed, and defects in these cellular processes manifest in various cells and organ systems.

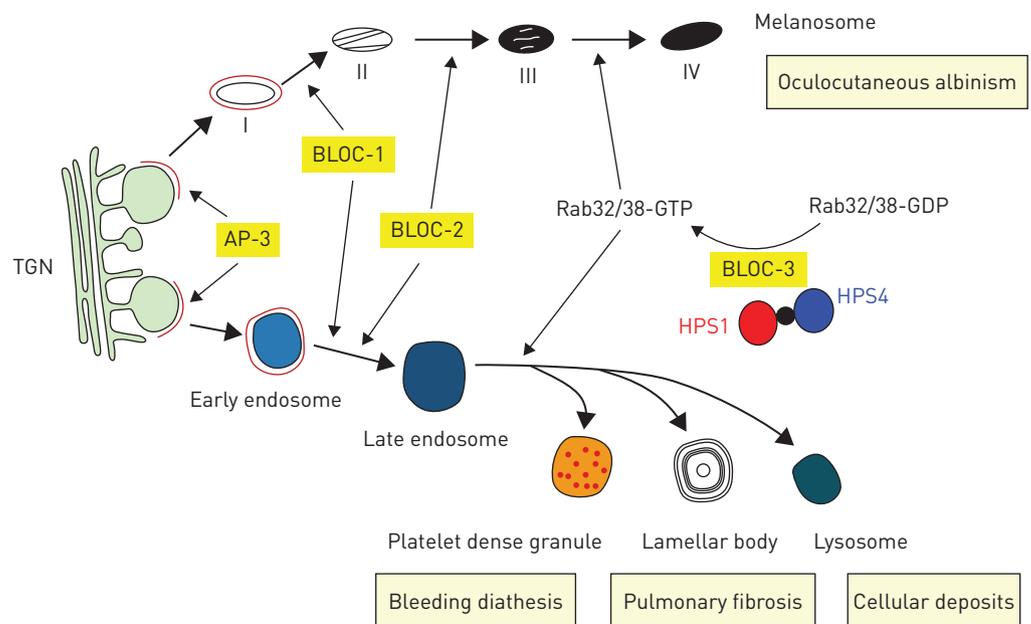


FIGURE 2 Relationships of protein complexes involved in Hermansky-Pudlak syndrome (HPS), biogenesis of intracellular organelles and clinical manifestations of disease. Four stages (I-IV) of melanosome maturation and platelet  $\delta$ -granule (dense granule), lamellar body and lysosome formation *via* the endosomal pathway from the TGN are shown. Defects in these vesicles are associated with oculocutaneous albinism, bleeding diathesis, pulmonary fibrosis and excessive cellular deposits in HPS. Protein complexes associated with HPS, including AP-3, BLOC-1, BLOC-2 and BLOC-3, and a Rab32/38 guanine nucleotide exchange factor comprised of HPS1 and HPS4 protein subunits, are involved in the formation of melanosomes, platelet  $\delta$ -granules, lamellar bodies and lysosomes. TGN: trans-Golgi network; AP: adaptor protein; BLOC: biogenesis of lysosome-related organelles complex.

### ***Oculocutaneous albinism***

Melanosomes are lysosome-related organelles involved in the synthesis and storage of melanin. Melanosomes are found in melanocytes and retinal pigment epithelial cells in the eye, and improper biogenesis of these organelles in HPS causes oculocutaneous albinism. The severity of oculocutaneous albinism is variable and generally dependent upon HPS genetic type [22]. For example, individuals with HPS-1 and HPS-4 typically have pronounced pigment defects. Their skin, hair and eye colour are generally light (figure 1a and b). Visual acuity is poor and many people with HPS-1 are legally blind. In contrast, people with other HPS genetic types have milder oculocutaneous albinism.

### ***Bleeding diathesis***

$\delta$ -granules are lysosome-related organelles in platelets and their contents (*i.e.* calcium, ADP, ATP and serotonin) contribute to blood clotting [53]. Specifically,  $\delta$ -granules are involved in platelet recruitment and the secondary aggregation response, which is abnormal in individuals with platelet  $\delta$ -granule deficiency. Each platelet generally contains three to eight  $\delta$ -granules; however, platelets in individuals with HPS are devoid of  $\delta$ -granules (figure 1c) [54]. The absence of platelet  $\delta$ -granules in HPS causes easy bruisability and excessive bleeding. Patients with HPS may experience severe or frequent epistaxis, pronounced bleeding with loss of deciduous teeth, menorrhagia in females, haematochezia associated with HPS inflammatory bowel disease and excessive blood loss with clinical biopsies or surgery [55].

### ***Pulmonary fibrosis***

In the lung, lamellar bodies in alveolar type II epithelial cells are surfactant-containing lysosome-related organelles, and accumulation of enlarged lamellar bodies in type II cells is a histopathological feature of murine models of HPS and individuals with HPS pulmonary fibrosis [56–58]. Light microscopy analysis of HPS pulmonary fibrosis lung tissue shows foamy-appearing alveolar macrophages and hyperplastic type II cells, and electron microscopy images demonstrate type II cells engorged with several enlarged lamellar bodies. Intracellular ceroid lipofuscin may accumulate in alveolar macrophages, which are found in high concentrations in murine models of HPS and patients with HPS-1 with and without pulmonary fibrosis [19, 59–61]. Foamy alveolar macrophages were also reported in a patient with HPS-5, which is an HPS genetic type that is not known to be associated with pulmonary fibrosis [62].

Macrophages, mast cells and other immune cells may be involved in a distal lung inflammatory response associated with high concentrations of cytokines and chemokines in the alveolar milieu [59–61, 63]. Levels of CCL2, CCL3 (macrophage inflammatory protein-1 $\alpha$ ) and granulocyte–macrophage colony-stimulating factor are increased in bronchoalveolar lavage (BAL) fluid from patients with HPS-1 with and without pulmonary fibrosis, suggesting that a pro-inflammatory alveolar microenvironment may precede the development of fibrotic lung disease in HPS-1 [61]. Alveolar macrophages isolated from BAL fluid derived from patients with HPS-1 were shown to spontaneously secrete high concentrations of CCL2, CCL3 and CCL5 (RANTES (regulated on activation, normal T-cell expressed and secreted)) [61]. This constitutive activation of HPS-1 alveolar macrophages was downregulated *in vitro* by pirfenidone, which is an antifibrotic drug approved as treatment for idiopathic pulmonary fibrosis (IPF) [61]. Notably, alterations in the peripheral blood immunome were detected in patients with HPS pulmonary fibrosis, which suggests that dysregulation of the immune system is not restricted to the lung in this disorder [64].

Despite these advances, the mechanisms contributing to HPS pulmonary fibrosis are not fully defined, and it is unclear how intracellular trafficking defects and abnormal biogenesis of lysosome-related organelles cause fibrotic lung disease. It is also unknown why pulmonary fibrosis develops in specific HPS genetic types and not others. However, further investigations into the mechanisms of disease are being facilitated by the development of *in vitro* type II cell and lung organoid models of HPS, and studies utilising *in vivo* murine models of HPS and human lung tissue have demonstrated that alveolar type II epithelial cells play a central role in the pathobiology of pulmonary fibrosis [65–68]. Experiments utilising bone marrow transplantation and transgenic type II cell-specific correction of the HPS defect in HPS murine models demonstrated that type II cells are involved with regulation of alveolar macrophage activation and susceptibility to pulmonary fibrosis [67]. In addition, dysregulation of type II cells in murine models of HPS or patients with HPS was reported, including aberrant endoplasmic reticulum stress response, impaired autophagy, defective surfactant secretion and altered phospholipid content [69–72]. Type II cells in HPS also exhibit high expression of CCL2, other cytokines, inducible nitric oxide synthase and galectin-3 [60, 68, 73]. Excessive CCL2 production by type II cells in HPS mice was associated with high concentrations of alveolar macrophages, which produce increased levels of TGF- $\beta$ , a profibrotic protein. Targeted deletion of CCL2 in type II cells normalised alveolar macrophage concentration, downregulated TGF- $\beta$  production by macrophages and ameliorated bleomycin-induced pulmonary fibrosis [68]. Galectin-3, a  $\beta$ -galactoside-binding lectin with pleiotropic effects, also has profibrotic effects in HPS, and was shown to promote epithelial apoptosis, fibroblast proliferation and myofibroblast differentiation, and

M2-like differentiation of macrophages [74]. In HPS, galectin-3 contributes to exaggerated injury and fibroproliferative repair by altering the effects of chitinase 3-like-1 protein, another mediator of pulmonary fibrosis in HPS [74, 75].

Fibroblasts and myofibroblasts, effector cells capable of secreting extracellular matrix proteins, are not known to contain lysosome-related organelles, but they are involved in the pathogenesis of HPS pulmonary fibrosis. Although the origin of these mesenchymal cells is uncertain, it is postulated that various mechanisms, including epithelial–mesenchymal transformation, proliferation of resident fibroblasts, altered myofibroblast de-differentiation and recruitment of circulating bone marrow-derived fibrocytes, may contribute to expansion of the alveolar interstitial cell population and to maintenance of a profibrotic milieu [76–79]. A cross-sectional study demonstrated high peripheral blood fibrocyte concentrations in patients with HPS pulmonary fibrosis, but not in HPS patients without lung disease or normal controls [79]. A longitudinal study showed that episodic increases in circulating fibrocytes were associated with death from HPS pulmonary fibrosis [79]. These findings indicate that peripheral blood fibrocyte concentration is associated with clinical outcome and suggest that fibrocytes may have a role in the pathobiology of disease. In addition, alterations in levels and activity of matrix metalloproteases in HPS may have a role in dysregulated turnover of extracellular matrix protein in the lung [80].

## Clinical features of HPS pulmonary fibrosis

### *Clinical features*

Symptoms of HPS pulmonary fibrosis are similar to those of other fibrotic lung disorders, including IPF. Individuals with HPS pulmonary fibrosis typically present with progressive dyspnoea on exertion or chronic cough [16, 55, 81, 82]. Children with HPS-2 also experience recurrent infections and neutropenia responsive to granulocyte colony-stimulating factor, and may develop spontaneous pneumothorax [17, 20, 35]. Symptoms generally manifest in the fourth decade of life in individuals with HPS-1, in middle-aged adults with HPS-4, or in children or young adults with HPS-2 [16–18, 20, 21, 35, 55, 81]. In contrast, patients with IPF usually present with symptoms of disease when they are older than 50 years of age (table 2) [83–86].

Physical examination findings include oculocutaneous albinism with variable pigmentation. Horizontal nystagmus, photophobia, iris transillumination and poor visual acuity are present in most patients [55, 82]. Ecchymoses may be found on the extremities, trunk or face. Auscultation of the chest reveals coarse inspiratory bilateral rales initially in the lung bases that progress to involve additional areas. Acrocyanosis and digital clubbing may be found in individuals with severe lung disease.

### *Lung function testing*

Consistent with pulmonary function testing measurements in patients with fibrosing lung disease, lung function values in individuals with HPS pulmonary fibrosis have a broad range and typically correlate with severity of disease [18]. Patients with early HPS pulmonary fibrosis may have normal values. Spirometry in

TABLE 2 Clinical features of Hermansky–Pudlak syndrome (HPS) pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF)

	HPS-1 or HPS-4 pulmonary fibrosis	HPS-2 pulmonary fibrosis	IPF
<b>Onset of pulmonary symptoms</b>	Middle age	Children or young adults	>50 years of age
<b>Acute exacerbations</b>	Yes	Unknown	Yes
<b>Oculocutaneous albinism</b>	Yes	Yes	No
<b>Nystagmus</b>	Yes	Yes	No
<b>Excessive bleeding</b>	Yes	Yes	No
<b>HRCT scan finding of ground-glass opacification</b>	Yes	Yes	No
<b>Type II epithelial cell enlargement</b>	Yes	Yes	No
<b>Giant lamellar bodies</b>	Yes	Yes	No
<b>Foamy alveolar macrophages</b>	Yes	Unknown	No
<b>Ceroid lipofuscin tissue deposition</b>	Yes	Yes	No
<b>Pulmonary histopathology</b>	UIP, NSIP, DAD	UIP, NSIP, DIP	UIP

HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; DAD: diffuse alveolar damage; DIP: desquamative interstitial pneumonitis.

symptomatic patients may show reduced forced vital capacity (FVC) with normal airflow; individuals with coexisting asthma may have small or large airways airflow obstruction responding to an inhaled bronchodilator. Lung volume measurements in individuals with HPS pulmonary fibrosis generally show restriction; diffusing capacity of the lung for carbon monoxide ( $D_{LCO}$ ) is typically reduced [18, 55]. FVC, forced expiratory volume in 1 s, total lung capacity, vital capacity and  $D_{LCO}$  can decrease to similar extents in affected patients [18]. Rate of decline in lung function may initially vary in patients with mild HPS pulmonary fibrosis [87]. However, serial pulmonary function tests in some patients with severe disease receiving placebo in a clinical trial demonstrated progression of disease, with 12–15% annual rates of decline in FVC % pred values [88]. Reduced oxygen saturation with exertion or at rest may be found in patients with severe HPS pulmonary fibrosis [55, 81].

### Imaging

HPS pulmonary fibrosis and IPF have some common radiographic features, but some of their findings differ (table 2). In patients with HPS pulmonary fibrosis, chest imaging with conventional or high-resolution computed tomography (HRCT) scans is more sensitive than using chest radiographs; individuals with mild findings of HPS pulmonary fibrosis on HRCT scans had normal findings on chest radiographs [19]. Bilateral reticulonodular interstitial infiltrates, fibrosis and pleural thickening can be found on chest radiographs (figure 1d). Conventional or HRCT scan findings in patients with HPS pulmonary fibrosis can include bilateral reticulations and septal thickening predominantly involving basilar subpleural regions of the lung in early disease and diffusely involving the lung parenchyma in severe disease (figure 3). Other HRCT scan findings include peri-bronchovascular thickening, traction bronchiectasis and honeycombing. Ground-glass opacities, which are generally atypical in IPF, are found in HRCT scan images of patients with HPS pulmonary fibrosis. In a cohort of six children with HPS-2, ground-glass opacities were found in all initial CT scans [35]. Analyses of HPS pulmonary fibrosis HRCT imaging findings and pulmonary function values showed that radiographic scores correlate inversely with FVC [19].

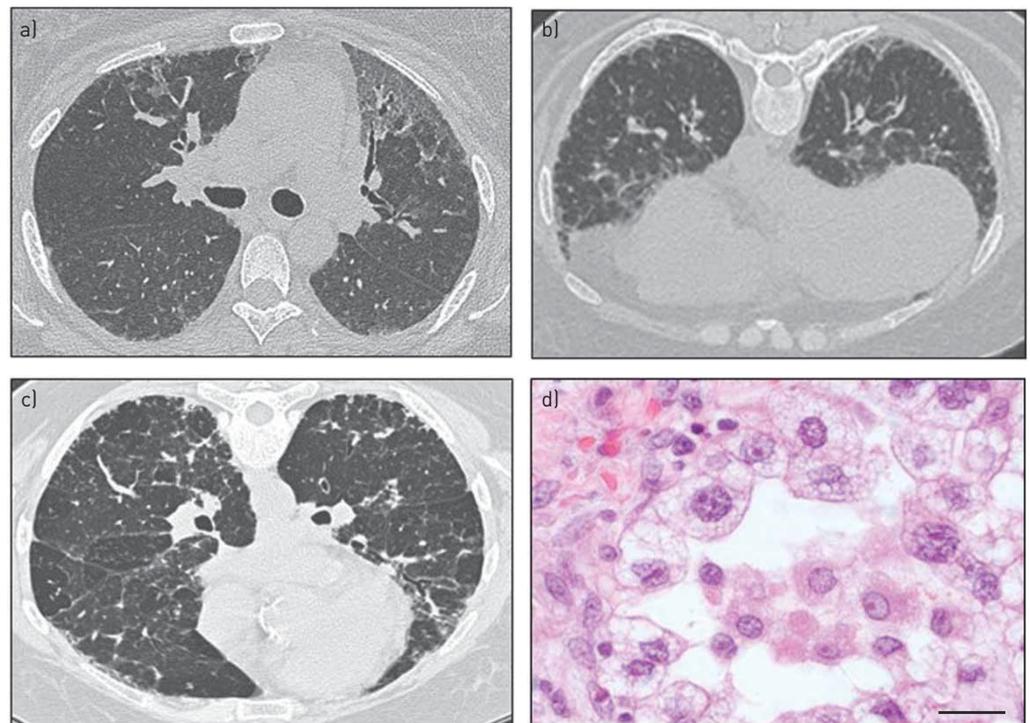


FIGURE 3 Computed tomography (CT) scan and histopathological images of Hermansky-Pudlak syndrome (HPS) pulmonary fibrosis. a) Supine and b) prone CT scan images of a 47-year-old subject with moderate HPS pulmonary fibrosis show bilateral ground-glass opacities, reticulations and honeycombing. c) CT scan image of a 38-year-old subject with HPS pulmonary fibrosis demonstrates bilateral ground-glass opacities, traction bronchiectasis, reticulations and honeycombing. d) Aggregates of foamy alveolar macrophages, vacuolated hyperplastic type II alveolar epithelial cells containing enlarged lamellar bodies, and interstitial accumulation of cells and extracellular matrix are found in lung tissue from a subject with HPS pulmonary fibrosis. Haematoxylin and eosin staining. Scale bar: 20  $\mu$ m.

### **Histopathology**

Some histopathology features of HPS pulmonary fibrosis are found in other fibrosing lung disorders, but there are some distinctive histological findings of HPS pulmonary fibrosis. Thickening of the interalveolar septa and alveolar interstitium due to accumulation of extracellular matrix proteins, immune cells, fibroblasts and myofibroblasts is found in HPS pulmonary fibrosis and IPF. In addition, type II cell hyperplasia, fibroblastic foci and temporal heterogeneity are histological features of both disorders [89]. Enlargement of airspaces due to cystic destruction of lung parenchyma and dense fibrosis can also be seen in HPS pulmonary fibrosis and IPF. Usual interstitial pneumonia, a histological hallmark of IPF, and nonspecific interstitial pneumonia histological patterns were reported in patients with HPS-1 and HPS-2; desquamative interstitial pneumonitis was reported in children with HPS-2 [35, 84, 89–93]. However, foamy-appearing alveolar macrophages that sometimes contain ceroid lipofuscin deposits and vacuolated type II cells with enlarged lamellar bodies are characteristics of HPS pulmonary fibrosis (figure 3). Electron microscopy imaging of lung tissue can show multiple giant lamellar bodies in type II cells [58].

### **Natural history of disease**

HPS pulmonary fibrosis is a chronic progressive ILD that often culminates in lung transplantation or death due to respiratory failure, typically in middle-aged adults with HPS-1 or HPS-4, or in children and young adults with HPS-2. Natural history of disease data from individuals with HPS-1 show that pulmonary fibrosis affecting middle-aged adults progresses at variable rates [88]. Cross-sectional analysis of FVC measurements *versus* age at 5-year intervals demonstrated a bimodal distribution in a cohort of individuals with HPS. Nadirs of FVC were found in patients with HPS at ages 36–40 and 56–60 years, suggesting that some patients progress at an earlier age, and hence more rapidly, than others [16]. However, longitudinal studies comparing rates of disease progression in individuals with HPS pulmonary fibrosis based on age of disease onset are not reported. Data from subjects with HPS pulmonary fibrosis randomised to receive placebo in clinical trials investigating pirfenidone as treatment showed that individuals with mild or moderate disease have inconsistent rates of disease progression [87, 88]. Approximate survival of three individuals 37–47 years of age with severe disease was <20 months after reaching a FVC of 50% predicted [88]. Rapid progression of fibrosis on HRCT scans was reported in children with HPS-2 [35]. Lung transplantations were performed in patients with severe HPS-1 at 27–57 years of age [90, 94–98]. Acute exacerbations of pulmonary fibrosis associated with rapid worsening of dyspnoea, decline in lung function and development of diffuse ground-glass opacities on HRCT scan were reported in some individuals with HPS-1 and HPS-4 [89, 90, 94, 99]. Histopathology of explanted tissue from a lung transplant recipient with HPS-1 who experienced an acute exacerbation revealed usual interstitial pneumonia with diffuse alveolar damage [90].

## **Diagnosis, management and treatment of HPS pulmonary fibrosis**

### **Diagnosis**

The diagnosis of HPS is established in an individual with oculocutaneous albinism and an increased tendency to bleed or easy bruisability who has pathogenic biallelic variants in genes associated with HPS. Targeted genetic sequencing or next-generation sequencing is emerging as a method to identify genetic variants and diagnose HPS in patients with clinical manifestations of disease [34, 47, 62, 100, 101]. Platelet whole-mount electron microscopy demonstrating absent  $\delta$ -granules is consistent with HPS [16, 54, 82, 102, 103]. Although platelet electron microscopy is used to diagnose HPS, this test requires specialised expertise and is available at limited clinical laboratories [82, 102]. Pulmonary fibrosis in individuals with HPS is diagnosed by CT scan findings. Given the high prevalence of pulmonary fibrosis in HPS, lung biopsy is usually not recommended to establish a diagnosis of HPS pulmonary fibrosis and is relatively contraindicated due to patients' increased tendency to bleed [102]. Although foamy alveolar macrophages are found in patients with HPS, there is generally no role for bronchoscopy in diagnosing HPS pulmonary fibrosis.

### **Clinical management**

Clinical management involves preventive care for asymptomatic individuals with HPS genetic types associated with pulmonary fibrosis, supportive care for those with symptomatic HPS pulmonary fibrosis and lung transplantation for patients with severe disease [55]. Genetic counselling may be beneficial for families affected with HPS.

Individuals with HPS-1, HPS-2, HPS-4 and possibly HPS-10 are at risk for development of pulmonary fibrosis. Avoidance of respiratory irritants, including smoke inhalation, is recommended. Routine maintenance of health, including regular exercise, balanced nutrition, proper weight management, treatment of comorbid illness, and vaccinations against influenza and pneumococcus, is recommended. Lung transplantation is a viable option for individuals with severe HPS pulmonary fibrosis and

optimisation of each patient's candidacy as a potential transplant recipient should be pursued throughout their lives [94]. Minimising the risk of skin cancer by avoiding the sun or using high-calibre sunblock as well as routine dermatology evaluations to screen for skin cancer and to remove suspicious lesions are recommended [55, 104]. Alloimmunisation is another potential barrier to lung transplantation for some patients with an increased bleeding tendency [94]. To minimise alloimmunisation, it is preferable to use procoagulant drugs to prevent or treat haemorrhage for mild bleeding if possible. For patients who require platelet or blood transfusion, irradiated single-donor leukoreduced platelets are recommended and, in some instances, human leukocyte antigen-matched platelets may be indicated [94].

Patients with symptomatic HPS pulmonary fibrosis may benefit from pulmonary rehabilitation or supplemental oxygen for hypoxaemia [55]. A 6-min walk test using a portable oximeter should be considered as hypoxaemia may be detected only during exertion in patients with mild HPS pulmonary fibrosis. Overnight pulse oximetry measurements are recommended in patients with moderate HPS pulmonary fibrosis to detect nocturnal hypoxaemia during sleep.

#### **Medical treatment**

No medications are currently approved by the US Food and Drug Administration as treatment for HPS pulmonary fibrosis. Corticosteroid drugs have not been shown to be effective and are not recommended for therapy [81]. Two clinical trials investigating pirfenidone, an oral antifibrotic drug approved as treatment for IPF, have been conducted [87, 88, 105–107]. Pirfenidone inhibits TGF- $\beta$ , and incubation of alveolar macrophages from patients with HPS-1 with pirfenidone significantly reduced inflammatory cytokine secretion and downregulated their constitutive activation [61, 108–110]. The first randomised, placebo-controlled trial showed that pirfenidone slowed the rate of lung function decline in a subset of subjects with mild or moderate HPS pulmonary fibrosis [88]. A second trial was conducted to study the efficacy of pirfenidone in subjects with mild or moderate disease [87]. This randomised, placebo-controlled trial was stopped due to futility and hence was unable to determine whether or not pirfenidone is an effective treatment for HPS pulmonary fibrosis. Pirfenidone was tolerated by most subjects enrolled in these trials, but taken together, results regarding efficacy were inconclusive [87, 88]. Notably, three subjects enrolled in the first protocol elected to receive open-label pirfenidone for several years and longitudinal analyses demonstrated that pirfenidone may have ameliorated their HPS pulmonary fibrosis [111]. Currently, pirfenidone is not approved as treatment for HPS pulmonary fibrosis.

Nintedanib, a tyrosine kinase inhibitor, is an antifibrotic drug approved as treatment for IPF, ILD associated with systemic sclerosis or chronic fibrosing ILD with a progressive phenotype [112–116]. Clinical trials showed that nintedanib reduced the rate of FVC decline in patients with any of these conditions compared with placebo [112–114]. A potential adverse effect of nintedanib is bleeding, which is a theoretical concern for patients with HPS who may experience excessive bleeding due to platelet dysfunction [16, 17]. Although nintedanib is not specifically approved as treatment for HPS pulmonary fibrosis, nintedanib is approved as treatment for patients with progressive fibrotic lung disease caused by different underlying conditions [114, 115].

#### **Lung transplantation**

Despite an increased tendency to bleed, patients with HPS pulmonary fibrosis have successfully undergone single- or double-lung transplantation [90–95]. Pre-transplant multidisciplinary planning involves early referral to a regional transplant centre. Consultation with a haematologist is recommended to determine an appropriate management plan to prevent and treat bleeding. Therapeutic options include procoagulant drugs (*e.g.* desmopressin and aminocaproic acid) and platelet transfusions, and plans should be individualised based on the severity of each patient's platelet dysfunction and their response to procoagulant medications. Consultation with a gastroenterologist is recommended for individuals with coexisting inflammatory bowel disease. Patients with HPS pulmonary fibrosis have progressive disease and mechanical ventilation can be used as a temporising supportive measure in lung transplant candidates with respiratory failure. Extracorporeal membrane oxygenation with full anticoagulation was also successfully employed in patients with end-stage HPS pulmonary fibrosis who were actively listed for lung transplant [90, 94, 97, 98]. Lung transplant recipients with HPS should receive standard of care post-transplant, including immunosuppressive medications and surveillance bronchoscopies with biopsies [94]. However, patients undergoing endoscopic biopsies may need prophylactic treatment against bleeding. Recurrence of pulmonary fibrosis in lung transplant recipients with underlying HPS has not been reported [94].

#### **Future therapy**

Future therapy for HPS pulmonary fibrosis may involve antifibrotic drugs or novel approaches to treatment. Antifibrotic therapies are being studied in clinical trials as treatment for IPF and pulmonary

fibrosis associated with other underlying conditions, and these drugs are potential candidate medications to investigate as treatment for HPS pulmonary fibrosis. In addition, patients with HPS-1 have variants in the same gene (*i.e.* *HPS1*) and many patients originating from Puerto Rico are homozygous for the same c.1472\_1487dup16-bp *HPS1* variant. Thus, gene therapy and gene editing are potential treatments for HPS. A pre-clinical proof-of-principle study showed that the *HPS1* defect in dermal melanocytes from patients with HPS-1 was corrected by transducing the cells with a lentiviral vector containing an *HPS1* construct [117]. After transduction, the HPS-1 melanocytes expressed HPS1 protein and pelleted cells became darker, thereby showing molecular and functional correction of the *HPS1* gene. Another pre-clinical study involving fibroblasts demonstrated that high levels of galectin-3, a profibrotic protein, in HPS-1 lung fibroblasts normalised following transfection with an *HPS1* construct [73]. Furthermore, *in vivo* transgenic correction of *Ap3b1* in type II epithelial cells in mice with an HPS-2 defect conferred protection from bleomycin-induced pulmonary fibrosis [67]. Other investigators demonstrated that gene editing with *Streptococcus pyogenes* Cas9 nuclease corrected the c.1472\_1487dup16-bp *HPS1* microduplication variant in HPS-1 B-lymphoblastoid cells [118]. These promising proof-of-principle results suggest that gene therapy and gene editing are possible strategies as future treatment for HPS pulmonary fibrosis.

### Conclusions

HPS pulmonary fibrosis is a rare autosomal recessive disorder with an enigmatic and complex pathogenesis of disease. Investigations into the pathobiology of HPS pulmonary fibrosis are facilitated by the availability of *in vitro* and *in vivo* pre-clinical models of disease. Pulmonary fibrosis develops in individuals with HPS-1, HPS-2 or HPS-4 and is highly prevalent in individuals with HPS-1, who have pathogenic biallelic variants in *HPS1*. Given these unique attributes, HPS pulmonary fibrosis serves as a model for studying fibrotic lung disorders and fibrosis in general.

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