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# Rare Etiologies of Interstitial Lung Disease: Focus on Hermansky-Pudlak Syndrome

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## Abstract

**Background:** Interstitial lung diseases (ILDs) are a diverse group of disorders leading to progressive pulmonary fibrosis. Rare genetic forms such as Hermansky--Pudlak syndrome (HPS) provide insight into disease mechanisms.

**Aim:** To summarize current knowledge on HPS-associated interstitial lung disease (HPS-ILD).

**Material and methods:** A literature review was conducted using PubMed with key terms related to HPS and pulmonary involvement. Selected references were also screened.

**Results:** HPS-ILD results from defects in intracellular trafficking, leading to epithelial dysfunction, immune activation, and fibrosis. It shares features with idiopathic pulmonary fibrosis but occurs earlier and has a genetic basis. Diagnosis relies on clinical features, imaging, and genetic testing. Treatment is mainly supportive, with lung transplantation as the only effective option in advanced disease.

**Conclusions:** HPS-ILD is a valuable model of fibrotic lung disease, highlighting the role of epithelial injury and the need for targeted therapies.

**Keywords:** *Hermansky--Pudlak syndrome; interstitial lung disease; pulmonary fibrosis; rare diseases*

### 1. Introduction

Interstitial lung diseases (ILDs) comprise a heterogeneous group of disorders characterized by inflammation and progressive pulmonary fibrosis, ultimately leading to impaired gas exchange (1--4). Rare forms, particularly genetic conditions, provide important insight into disease mechanisms (13). This review focuses on Hermansky-Pudlak syndrome (HPS), a rare

autosomal recessive disorder associated with lysosome-related organelle dysfunction and a high risk of developing pulmonary fibrosis (3,13).

HPS is clinically defined by oculocutaneous albinism, bleeding diathesis and in selected subtypes (HPS-1, HPS-2, HPS-4), progressive interstitial lung disease(32,62). The underlying pathogenesis involves defects in intracellular trafficking, leading to alveolar epithelial dysfunction, immune activation and excessive extracellular matrix deposition (32,82,91). HPS-associated ILD shares similarities with idiopathic pulmonary fibrosis but presents earlier and has a distinct genetic background(32,77,81).

Diagnosis is based on clinical features, genetic testing and high-resolution computed tomography(35), while lung biopsy is generally avoided due to bleeding risk (32). Treatment remains limited, with supportive care as the mainstay and lung transplantation as the only effective option in advanced disease(13).

HPS-ILD represents a valuable model for understanding fibrotic lung diseases and highlights the need for further research into targeted and gene-based therapies.

## 2. Research materials and methods

The literature review was conducted using articles retrieved from the PubMed database. The search strategy was based on a combination of key terms related to Hermansky--Pudlak syndrome and pulmonary involvement, including Hermansky--Pudlak syndrome, HPS, pulmonary fibrosis, interstitial lung disease, interstitial pneumonia, interstitial pneumonitis, and diffuse parenchymal lung disease. Review articles, systematic reviews and meta-analyses were excluded. Additionally, relevant publications cited in the reference lists of the initially identified articles were manually screened and included where appropriate to ensure a comprehensive evaluation of the available evidence.

2.2.Procedure / Test protocol / Skill test trial / Measure / Instruments.

Not applicable --literature review.

2.3. Data collection and analysis / Statistical analysis.

Not applicable -- literature review.

2.3.1. Statistical Software.

Not applicable -- literature review.

2.3.2. AI.

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition and linguistic refinement, rather than replacing human judgment in the analytical process.

2.3.3. Statistical Methods.

Not applicable -- literature review.

## 3. Rare Etiologies of ILD - General Overview

Pulmonary fibrosis is a hallmark of many ILDs and involves excessive deposition of extracellular matrix proteins, along with accumulation of fibroblasts, myofibroblasts and immune cells in the alveolar space. (1--4) This process disrupts normal lung architecture and is often triggered by repeated epithelial injury, especially to alveolar cells type II. Abnormal repair, cell senescence, oxidative stress, mitochondrial dysfunction and impaired protein homeostasis all contribute to disease progression (1--10). Profibrotic mediators such as TGF-β, connective tissue growth factor, platelet-derived growth factor, CCL2, galectin-3, matrix metalloproteinases and IL-11 further drive fibroblast activation and extracellular matrix remodeling (1--5,11,12)

### 3.1 Genetic and Monogenic ILDs

Inherited forms of pulmonary fibrosis, though rare, provide insight into disease mechanisms. (13). Familial pulmonary fibrosis (FPF) occurs in two or more first-degree relatives and accounts for less than 5% of IPF cases (14). It typically shows autosomal dominant inheritance with incomplete penetrance and symptoms usually appear in the sixth decade, although preclinical lung changes may be detectable years earlier (15--17).

The genetic background is diverse. Some FPF cases are linked to telomere-related disorders such as dyskeratosis congenita, caused by mutations in TERT, TERC, RTEL1, PARN, DKC1,

or TINF2 (15,18--21). Others involve surfactant protein mutations (SFTPC, SFTPA2), while some families have unknown genetic causes (22,23). These inherited forms highlight that pulmonary fibrosis can result from specific molecular defects affecting epithelial integrity and repair mechanisms (13).

### 3.2 Immune Dysregulation in Rare ILDs

Immune system abnormalities are also implicated in rare ILDs (13). In both FPF and Hermansky-Pudlak syndrome (HPS) studies have shown that immune cells are activated before clinical fibrosis develops. This includes increased numbers of activated CD4+ T-cells, B-cells and alveolar macrophages, as well as elevated cytokines in the peripheral blood Imaging may show ground-glass opacities reflecting early alveolar inflammation and bronchoalveolar lavage often reveals immune cell infiltration and activated macrophages (13,17,24,25). These findings suggest that immune activation is an early contributor to fibrotic processes rather than just a consequence.

### 3.3 Lysosomal and Storage Disorders

Hermansky-Pudlak syndrome (HPS) is an example of a rare ILD linked to lysosomal and organelle dysfunction (4,13). HPS is an autosomal recessive disorder with defects in lysosome-related organelles, including the BLOC-1, BLOC-2, BLOC-3 and adaptor protein-3 complexes (26--28). Clinically, HPS manifests as oculocutaneous albinism, bleeding tendencies and, in some subtypes, inflammatory bowel disease and progressive pulmonary fibrosis (4,13)

Pulmonary fibrosis develops in specific HPS subtypes: HPS-1 and HPS-4 usually in middle-aged adults and HPS-2 earlier in life (4,13,29--31). Because the genetic defects are well-defined, HPS serves as a model for studying how organelle dysfunction, epithelial injury and immune dysregulation contribute to fibrosis.

### 3.4 Summary

In summary, rare ILDs---including genetic, immune-mediated and lysosomal disorders---demonstrate that pulmonary fibrosis often results from a combination of epithelial injury, abnormal repair, immune activation and extracellular matrix remodeling (1--10,13). These conditions, though uncommon, are valuable for understanding the mechanisms that may also apply to more common fibrosing ILDs like IPF.

The next section will focus specifically on Hermansky-Pudlak syndrome, its genetic subtypes and the mechanisms underlying its pulmonary manifestations, providing a deeper look into one of the most informative rare ILDs.

## 4. Hermansky-Pudlak Syndrome (HPS)

### 4.1 Epidemiology

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder associated with a high prevalence of pulmonary fibrosis, although its global distribution indicates that it affects diverse populations worldwide (32--34). Cases have been reported across multiple regions, including India, China, Japan, Western Europe, the Middle East and Latin America, highlighting that the disease is not restricted to a single ethnic group Additional data from international registries further confirm its presence in countries such as the United States, Canada, Australia, Israel and several South American nations.(32--36).

Despite its global occurrence, HPS shows a striking geographic clustering in Puerto Rico, where it is significantly more common due to a founder effect. In the northwest region of the island, the prevalence of the HPS-1 subtype is estimated at approximately 1 in 1,800 individuals, accounting for around 50% of all reported cases worldwide. (32,35,37,38). Additionally, about 1 in 21 individuals in this region are carriers of the founder mutation, a 16 base pair duplication in exon 15 of the *HPS1* gene (35,38). In central Puerto Rico, another subtype, HPS-3, occurs with a lower prevalence of approximately 1 in 4,000 individuals (36).

Outside Puerto Rico, the genetic background of HPS appears more heterogeneous. Studies have shown that non-Puerto Rican Hispanic patients do not carry the common Puerto Rican founder mutation but instead present with different mutations in genes such as *HPS1*, *HPS4* and *HPS5* (35,36). Certain populations also show subtype-specific patterns; for example, HPS-3 has been reported more frequently among Ashkenazi Jewish individuals (35,39).

Although HPS is considered a rare disease globally, affecting approximately 500,000 to 1,000,000 individuals worldwide, its true prevalence may be underestimated (32). This may be partly due to variable clinical expression, especially in milder subtypes. Supporting this, one study suggested that up to 35% of individuals within a German albino population could represent mild forms of HPS, indicating potential underdiagnosis (35,39,40).

In terms of outcomes, HPS is associated with reduced life expectancy, typically ranging from 40 to 50 years. Mortality is high, with more than 70% of patients dying from complications directly related to the disease, including pulmonary fibrosis. (32,41).

Overall, the epidemiology of HPS is characterized by global distribution with strong regional clustering, significant genetic heterogeneity and likely underrecognition in milder cases. These features highlight the importance of improved awareness and screening, particularly in populations with known founder mutations or atypical presentations.

### 4.2 Genetics and Pathophysiology

Hermansky-Pudlak syndrome (HPS) is a genetically heterogeneous disease, consisting of at least ten subtypes (HPS-1 to HPS-10). Each is caused by mutations in corresponding genes (*HPS1-HPS10*). The protein products of these genes are involved in the formation and function of lysosome-related organelles (LROs), such as melanosomes, platelet dense bodies, lamellar bodies and cytotoxic T-cell granules (35,42,43). Defects in these organelles explain the characteristic clinical features of HPS, for example hypopigmentation and platelet storage deficiency (35,44).

At the molecular level, HPS proteins assemble into four major multi-subunit complexes: BLOC-1, BLOC-2, BLOC-3 and adaptor protein-3 (AP-3), all of which are involved in intracellular membrane trafficking and protein sorting required for LRO biogenesis (26,29,45,46). BLOC-1 consists of multiple subunits including proteins encoded by genes mutated in HPS-7, HPS-8 and HPS-9 (28,35,47,48). BLOC-2 is composed of HPS-3, HPS-5, and HPS-6 (35,36,49), while BLOC-3 includes HPS-1 and HPS-4 (35,50). The AP-3 complex, a heterotetramer involved in vesicular transport from endosomes, contains subunits encoded by *AP3B1* and *AP3D1*, which are mutated in HPS-2 and HPS-10, respectively (35,45).

These complexes cooperate in directing proteins away from degradative lysosomal pathways toward specialized organelles such as melanosomes. For example, BLOC-1, BLOC-2 and AP-3 are involved in trafficking components necessary for melanosome formation. (35,51--53). BLOC-3 acts as a guanine nucleotide exchange factor (GEF) for Rab32 and Rab38, small GTPases that regulate intracellular transport processes. These Rab proteins are essential for the delivery of key enzymes, such as tyrosinase and TYRP1, to developing melanosomes and disruption of this pathway leads to the hypopigmentation seen in HPS (32,35,54).

The clinical phenotype of HPS depends largely on which complex is affected. Mutations within the same complex tend to produce similar clinical features (26,45,49). In general, defects in BLOC-1 and BLOC-2 are associated with milder phenotypes, while BLOC-3 (HPS-1 and HPS-4) and AP-3 (HPS-2) deficiencies are linked to more severe disease, including pulmonary fibrosis (35,45). This is why classification based on affected complexes is often more clinically useful than classification based on individual genes (26,45,49)

The pathophysiology of pulmonary fibrosis in HPS is not fully understood (35). However, several mechanisms have been proposed based on cellular and animal studies. In alveolar type II (AT2) cells, which are responsible for surfactant production, Rab38 plays an important role in the formation and maintenance of lamellar bodies (55,56). Deficiency of Rab38 leads to

abnormal lamellar body structure and altered surfactant composition, which disrupts alveolar homeostasis and contributes to progressive lung fibrosis, particularly in HPS-1 and HPS-4 (35).

In addition, defects in intracellular trafficking and organelle biogenesis affect not only epithelial cells but also immune cells. Although the exact mechanisms remain unclear, abnormalities in macrophages and monocytes have been suggested and may contribute to inflammatory processes such as granulomatous colitis (35). Due to the rarity of the disease and limitations in human tissue studies, much of the current understanding comes from murine models, which replicate key aspects of HPS pathology (57).

Overall, HPS represents a disorder of intracellular trafficking and organelle dysfunction, where defects in LRO biogenesis lead to multisystem manifestations. The link between specific genetic defects and clinical severity---especially pulmonary fibrosis in BLOC-3 and AP-3 deficiencies---provides important insight into the mechanisms connecting cellular dysfunction with progressive lung disease (45,58--60).

### 4.3 Clinical Phenotype

Hermansky-Pudlak syndrome (HPS) is a multisystem disorder with variable clinical presentation. All subtypes are characterized by oculocutaneous albinism (OCA) and platelet storage pool deficiency, while additional manifestations depend on the specific genetic subtype (61). More severe complications, including pulmonary fibrosis, are mainly associated with HPS-1, HPS-2 and HPS-4, whereas other subtypes tend to have milder clinical courses (32,62).

#### *4.3.1 Oculocutaneous Albinism*

OCA results from impaired melanosome function and leads to reduced pigmentation of the skin, hair and eyes(63). The severity varies, with more pronounced hypopigmentation in HPS-1 and HPS-4 (4). Patients often present with nystagmus and reduced visual acuity (4,35,64)

Skin hypopigmentation increases the risk of UV-related damage, including sunburn and skin cancers(44).

#### *4.3.2 Bleeding Diathesis*

Bleeding tendency in HPS is caused by the absence of platelet δ-granules, which impairs normal clot formation(65). Symptoms usually begin in childhood and include epistaxis, easy bruising, prolonged bleeding after minor trauma and menorrhagia (61).

Management includes avoiding anticoagulant medications and using desmopressin or platelet transfusions in more severe cases(35,66).

*4.3.3 Gastrointestinal and Immune Manifestations*

Granulomatous colitis, resembling Crohn's disease, occurs mainly in HPS-1, HPS-4 and HPS-6 and affects about 15% of patients (35,66). Treatment follows standard inflammatory bowel disease protocols (67).

Immunodeficiency is primarily seen in HPS-2 and is associated with neutropenia and impaired function of cytotoxic T cells and NK cells (35,68).

*4.3.4 Pulmonary Fibrosis*

Pulmonary fibrosis is the most severe complication of HPS and occurs mainly in HPS-1, HPS-2 and HPS-4 (32). It closely resembles idiopathic pulmonary fibrosis in both clinical and histological features (32,35)

In HPS-1, nearly all patients develop fibrosis, typically between 30 and 40 years of age (61). The disease is progressive, leading to respiratory failure, with an average survival of around 3 years after diagnosis (32,35,69).

Pathologically, abnormalities in alveolar type II cells, enlarged lamellar bodies and increased inflammatory cell activity are observed (4,70).

*4.3.5 Clinical Variability and Case-Based Observations*

Clinical presentation of HPS may vary significantly even within the same family. Case reports describe individuals presenting early in life with hypopigmentation, recurrent epistaxis, infections and other systemic features (71).

Familial clustering has also been documented, including cases with multiple affected siblings showing albinism, bleeding disorders and pulmonary fibrosis. In such families, pulmonary fibrosis and interstitial lung disease may be identified in several members, sometimes leading to premature death(72). These observations highlight the variability of disease expression and the importance of genetic background and inheritance patterns in HPS.

*4.3.6 Summary*

The clinical phenotype of HPS includes hypopigmentation, bleeding diathesis, gastrointestinal involvement, immune abnormalities and pulmonary fibrosis, reflecting underlying defects in lysosome-related organelles (4,35,73--76). Pulmonary fibrosis remains the main cause of mortality in affected patients (35).

## 5. Hermansky-Pudlak Associated Interstitial Lung Disease (HPS-ILD)

Hermansky-Pudlak associated interstitial lung disease (HPS-ILD) represents one of the most severe complications of HPS and is primarily observed in patients with HPS-1, HPS-2 and HPS-4 (32,77). Although not all individuals carrying these mutations develop pulmonary fibrosis, these subtypes account for the majority of cases(78).

### 5.1 Clinical Features

HPS-ILD closely resembles idiopathic pulmonary fibrosis (IPF) in both clinical and histological presentation (32,77). Patients typically present with progressive dyspnoea on exertion and chronic cough, which gradually worsen over time (4,32,61,79,80). As the disease progresses, dyspnoea may occur at rest and require supplemental oxygen(32).

The age of onset is an important distinguishing feature. HPS-associated pulmonary fibrosis usually develops earlier, most commonly between 30 and 40 years of age, compared to IPF, which typically occurs after 50 years(69,72,81).

Physical examination may reveal features of underlying HPS, including oculocutaneous albinism, nystagmus and ecchymoses (61,80). Pulmonary findings include bilateral inspiratory crackles, initially at the lung bases, with progression over time, as well as digital clubbing and signs of advanced disease (4).

Despite similarities to IPF, survival differs. Patients with HPS-associated pulmonary fibrosis may live approximately 10 years after diagnosis, whereas IPF historically has a poorer prognosis, with around 50% survival at 3 years(32,38,72,80).

### 5.2 Pathogenesis

The pathogenesis of HPS-ILD is not fully understood, but current evidence suggests a central role of epithelial cell dysfunction (82). Injury to alveolar epithelial cells, combined with abnormalities in intracellular trafficking, leads to cellular stress, apoptosis and impaired repair mechanisms (32,82).

This results in recruitment and activation of fibroblasts and myofibroblasts, which drive excessive extracellular matrix deposition and fibrosis (32). Multiple mechanisms may contribute to the origin of these cells, including epithelial-mesenchymal transition, proliferation of resident fibroblasts and recruitment of circulating fibrocytes (83--85).

Alveolar type II epithelial cells appear to play a central role in disease development. These cells contain lamellar bodies, a type of lysosome-related organelle and their dysfunction leads to abnormal surfactant handling and structural changes in the alveoli (86). Histologically, this

is reflected by enlarged lamellar bodies, hyperplastic type II cells and accumulation of foamy alveolar macrophages (56,87,88).

### 5.3 Role of Inflammation and Immune Dysregulation

There is strong evidence that inflammation precedes fibrosis in HPS-ILD (88). Bronchoalveolar lavage fluid from patients shows increased numbers of alveolar macrophages and elevated levels of cytokines and chemokines(88).

Activated macrophages secrete mediators such as CCL2, CCL3 and GM-CSF, contributing to a pro-inflammatory microenvironment (4,88). Elevated CCL2 levels have been associated with disease progression (89,90).

In addition, dysregulation is not limited to the lung, as alterations in the peripheral immune system have also been observed (13).

### 5.4 Fibrotic Mechanisms

Fibroblasts and myofibroblasts are key effector cells responsible for extracellular matrix deposition in HPS-ILD(91). Increased numbers of circulating fibrocytes have been identified in patients with pulmonary fibrosis and are associated with worse outcomes (92).

Additional profibrotic mediators, such as galectin-3, promote epithelial apoptosis, fibroblast proliferation and myofibroblast differentiation (93). Dysregulation of matrix metalloproteinases may further contribute to abnormal extracellular matrix turnover(94).

### 5.5 Additional Considerations

Certain clinical features may be associated with increased risk of pulmonary fibrosis in HPS. For example, ocular albinism and older age have been linked to higher risk, while nystagmus may be associated with lower risk (78).

Although histological similarities exist between HPS-ILD and IPF, lung biopsy is generally contraindicated due to the high risk of bleeding associated with platelet dysfunction in HPS(38,72). Diagnosis is therefore primarily based on clinical features and genetic testing (72).

### 5.6 Summary

HPS-ILD is a progressive fibrosing lung disease that shares many features with IPF but differs in genetic background, earlier onset and underlying mechanisms (38,62,72). The disease is driven by a combination of epithelial dysfunction, immune activation and fibroblast-mediated matrix deposition, ultimately leading to respiratory failure.

## 6. Radiology

Radiological imaging plays a key role in the detection and assessment of HPS-associated interstitial lung disease (HPS-ILD). High-resolution computed tomography (HRCT) is more sensitive than chest radiography, especially in early stages, where chest X-rays may still appear normal (24).

### 6.1 Chest Radiography and HRCT Findings

On chest radiographs, common findings include bilateral reticulonodular interstitial infiltrates, fibrosis and pleural thickening (95,96). However, HRCT is the preferred modality for evaluating early and subtle changes (95,96).

Typical HRCT findings include:

- bilateral reticulations and interlobular septal thickening, predominantly in subpleural and basal regions (4,32)
- ground-glass opacities (GGO), which are relatively common in HPS-ILD (78).
- traction bronchiectasis and honeycombing in more advanced disease (4,96).
- peribronchovascular thickening and diffuse parenchymal involvement in later stages (4,96).

Ground-glass opacities are particularly notable, as they are less typical in idiopathic pulmonary fibrosis (IPF) but frequently observed in HPS-ILD(97).

### 6.2 Disease Progression and Patterns

Radiological abnormalities often begin in peripheral and subpleural regions and progress centrally as the disease advances(4). Severity can be graded based on the extent of involvement, ranging from minimal reticular changes to diffuse disease affecting most of the lung parenchyma (95).

Importantly, radiographic severity correlates inversely with pulmonary function parameters such as forced vital capacity (FVC), reflecting disease progression (4,24).

### 6.3 Radiology-Pathology Correlation

Radiological findings are supported by pathological observations, including ceroid deposition and inflammatory cell infiltration(78). The most common CT patterns reported are ground-glass opacities, reticulation and traction bronchiectasis (78).

### 6.4 Differential Diagnosis and Diagnostic Considerations

Although imaging findings overlap with other interstitial lung diseases such as IPF and nonspecific interstitial pneumonia (NSIP), certain features may help differentiate HPS-

ILD(91,95,96). For example, the presence of ground-glass opacities and earlier age of onset may suggest HPS-ILD rather than IPF (97).

Lung biopsy is generally not recommended due to bleeding risk associated with platelet dysfunction (32,96). Therefore, diagnosis relies on a combination of clinical features, imaging and genetic testing (96).

### 6.5 Summary

Radiological evaluation, particularly HRCT, is essential in the diagnosis and monitoring of HPS-ILD. Characteristic findings include ground-glass opacities, reticulations and traction bronchiectasis, with disease progression from peripheral to diffuse involvement (96). Imaging findings, in conjunction with clinical and genetic data, form the basis for diagnosis and disease assessment.

## 7. Diagnostics

The diagnosis of Hermansky-Pudlak syndrome (HPS) is based on a combination of clinical features, laboratory findings, imaging and increasingly, genetic testing (61,98).

**7.1 Clinical Suspicion** Initial suspicion typically arises in individuals presenting with oculocutaneous albinism and bleeding tendency (4,98--100). Many patients are identified early due to hypopigmentation, while others are diagnosed later after complications such as easy bruising or excessive bleeding (32,101).

Ophthalmologic findings, including reduced visual acuity, nystagmus and iris transillumination, may also prompt further evaluation (32,102).

### 7.2 Platelet and Laboratory Diagnostics

A key diagnostic feature is platelet storage pool deficiency. The gold standard test is whole-mount electron microscopy demonstrating absence of platelet δ-granules (4,38,79,80).

Alternative tests, such as platelet aggregation studies, may be used but are less specific (32,103). Bleeding time is often prolonged but is not recommended for diagnostic purposes due to low specificity (32,101).

### 7.3 Genetic Testing

Genetic testing plays an increasingly important role in confirming diagnosis and determining HPS subtype (4,32).

Next-generation sequencing or targeted gene panels can identify pathogenic biallelic variants in HPS-related genes(4,99,100). Case-based data demonstrate the use of whole exome

sequencing to detect disease-causing mutations and confirm autosomal recessive inheritance (104).

However, not all patients have identifiable mutations, suggesting that additional disease-causing genes may exist (105).

### 7.4 Imaging and Diagnosis of Pulmonary Involvement

Pulmonary fibrosis in HPS is primarily diagnosed using high-resolution computed tomography (HRCT) (24,35).

Early HRCT findings include septal thickening, ground-glass opacities and mild reticulation, while advanced disease shows bronchiectasis, honeycombing and diffuse fibrosis (24,35). HRCT is more sensitive than chest radiography and allows monitoring of disease progression (24,35).

Pulmonary function tests are also used to assess disease severity, typically showing restrictive impairment and reduced diffusing capacity (104).

### 7.5 Additional Diagnostic Considerations

Bronchoscopy has limited diagnostic value and is mainly used for research purposes (4,32).

Lung biopsy is generally contraindicated due to bleeding risk associated with platelet dysfunction (4,32).

Diagnosis of HPS-ILD therefore relies on integration of clinical presentation, imaging findings and genetic confirmation (106).

### 7.6 Summary

The diagnostic approach to HPS combines clinical recognition of albinism and bleeding diathesis, confirmation of platelet abnormalities and genetic testing, with HRCT playing a central role in identifying pulmonary involvement (4,24,35).

## 8. Treatment

**8.1 Clinical management and preventive care** Clinical management of HPS and HPS-associated pulmonary fibrosis (HPS-PF) includes both preventive strategies in asymptomatic individuals and supportive care in symptomatic patients (4,61). Individuals at risk, particularly those with HPS-1, HPS-2 and HPS-4, should avoid exposure to respiratory irritants such as cigarette smoke (4,107). Maintenance of general health through regular physical activity, balanced nutrition and management of comorbidities is recommended. Preventive measures also include vaccinations against influenza and pneumococcal infections (107). Due to

oculocutaneous albinism, patients require protection from ultraviolet radiation and regular dermatological screening to reduce the risk of skin malignancies (108). Genetic counselling is also an important component of long-term management (4).

**8.2 Supportive and symptomatic treatment** Supportive treatment plays a key role in patients with established pulmonary disease. Oxygen supplementation is indicated in patients with hypoxaemia (109) and may be required both at rest and during exertion as the disease progresses (61). Pulmonary rehabilitation can improve exercise tolerance and quality of life (4,61).

Monitoring of disease progression includes functional assessment such as the 6-minute walk test, which may reveal exertional hypoxaemia even in early disease. Overnight pulse oximetry is recommended in moderate disease to detect nocturnal desaturation (4).

Infection prevention is essential and appropriate vaccination strategies should be implemented (32). Due to platelet dysfunction, patients should avoid medications that impair platelet aggregation, such as aspirin and nonsteroidal anti-inflammatory drugs. Management of bleeding complications and careful monitoring during invasive procedures are also necessary components of care. (32,41,61).

**8.3 Pharmacological treatment** At present, no pharmacological therapies have been specifically approved for the treatment of HPS pulmonary fibrosis. Corticosteroids have not demonstrated clinical benefit and are therefore not recommended (24,110,111).

Pirfenidone, an antifibrotic agent that inhibits transforming growth factor-β (TGF-β), has been investigated as a potential treatment (112--114)*)*. Clinical trials have shown mixed results: some studies suggested a slower decline in lung function in selected patients with mild to moderate disease, whereas others failed to demonstrate significant benefit (81). Long-term observational data indicate that some patients may experience stabilization or slower disease progression with prolonged therapy. Overall, the efficacy of pirfenidone in HPS-PF remains inconclusive (35).

Nintedanib, a tyrosine kinase inhibitor with antifibrotic properties, has shown efficacy in reducing lung function decline in other fibrotic interstitial lung diseases (115--118). However, its use in HPS patients is limited due to the increased risk of bleeding associated with platelet dysfunction (63).

**8.4 Experimental and future therapies** Given the genetic basis of HPS, gene therapy represents a potential future treatment strategy. Experimental studies have demonstrated the

possibility of correcting gene defects in vitro using viral vectors. However, significant challenges remain, particularly regarding effective delivery of genetic material to alveolar epithelial cells in vivo. Therefore, gene therapy is not yet applicable in clinical practice (119).

**8.5 Lung transplantation** Lung transplantation remains the only effective life-extending therapy for patients with advanced HPS pulmonary fibrosis. Early referral to a transplant centre is recommended to optimize eligibility. (13).

Despite the presence of bleeding diathesis, successful single- and double-lung transplantations have been performed in patients with HPS (120--123). Pre-transplant evaluation requires a multidisciplinary approach, including consultation with a hematologist to develop strategies for bleeding prevention. Management may include the use of desmopressin, antifibrinolytic agents, or platelet transfusions (107,120,124,125).

Importantly, recurrence of pulmonary fibrosis after lung transplantation in HPS patients has not been reported (107).

**8.6 Limitations and clinical observations** Clinical responses to treatment vary significantly between patients. In some cases, pirfenidone has not demonstrated clinical benefit and disease progression may continue despite therapy (126). The use of alternative antifibrotic agents such as nintedanib may be limited by complications including bleeding risk or pneumothorax (126,127).

Complications such as pneumothorax may indicate rapid disease progression and poor prognosis (126).

In patients with HPS-2, additional management strategies may be required due to immunodeficiency; granulocyte colony-stimulating factor (G-CSF) can be used to treat neutropenia and reduce infection risk (97).

## 9. Discussion

Hermansky-Pudlak syndrome (HPS) represents a unique model within rare interstitial lung diseases, integrating genetic, cellular and immunological mechanisms that lead to pulmonary fibrosis (3,13). As discussed, HPS-associated ILD shares clinical and radiological features with idiopathic pulmonary fibrosis (IPF), but differs in genetic background, earlier onset and systemic manifestations (32,77,81).

A key finding of this review is the central role of intracellular trafficking defects and lysosome-related organelle dysfunction. Mutations affecting BLOC-3 and AP-3 complexes impair alveolar type II cell function, leading to abnormal surfactant processing and epithelial

injury (35,55). These processes are consistent with broader ILD mechanisms, including epithelial damage, impaired repair and cellular stress responses (1--10). Thus, HPS supports the concept that epithelial dysfunction is a primary driver of fibrosis.

Immune dysregulation also plays an important role. Evidence indicates that immune activation, including macrophage accumulation and cytokine release, occurs early in disease development(13,88). This suggests that inflammation contributes to the initiation and progression of fibrosis rather than being merely a secondary phenomenon.

Radiologically, HPS-ILD demonstrates overlapping but distinguishable features compared to other ILDs. High-resolution computed tomography (HRCT) is essential for diagnosis and monitoring, particularly given the contraindication to lung biopsy due to bleeding risk (24,35,96). The integration of imaging, clinical features and genetic testing is therefore crucial for accurate diagnosis (96).

Despite advances in understanding disease mechanisms, treatment options remain limited. Current management is largely supportive, including oxygen therapy and pulmonary rehabilitation (3,61). Antifibrotic therapies such as pirfenidone and nintedanib have shown inconsistent efficacy in HPS(35,63) and lung transplantation remains the only effective life-extending therapy for advanced disease (13).

Importantly, HPS highlights the heterogeneity of fibrotic lung diseases. Variability in clinical presentation and progression, even within the same subtype, suggests the influence of additional genetic and environmental factors (71,72). This underscores the need for individualized approaches to diagnosis and management.

## 10. Future Directions

Future research in HPS and HPS-associated pulmonary fibrosis should focus on both improving understanding of disease mechanisms and developing effective targeted therapies.

One of the most promising areas is gene-based therapy. Given the monogenic nature of HPS, gene therapy and gene editing represent rational and potentially curative approaches. Preclinical studies have already demonstrated successful correction of HPS-related defects in vitro using lentiviral vectors and CRISPR/Cas9 technology, restoring protein function and normal cellular phenotype. Additionally, animal models have shown that genetic correction in alveolar epithelial cells can protect against fibrosis, further supporting the feasibility of this approach (3). However, significant challenges remain, particularly in achieving efficient and safe delivery of genetic material to lung tissue in vivo.

Another important direction involves the development of novel antifibrotic therapies. While current drugs such as pirfenidone and nintedanib have limited efficacy in HPS, ongoing research into fibrotic pathways---including TGF-β signaling, galectin-3 and other profibrotic mediators---may lead to more effective targeted treatments. Combination therapies addressing multiple pathways simultaneously may be required to achieve meaningful clinical benefit (3).

There is also a need for improved biomarkers and disease monitoring strategies. Current assessment relies heavily on imaging and pulmonary function tests, which may not detect early disease or subtle progression. Ongoing clinical trials aim to identify biomarkers that can better predict disease onset and progression, potentially enabling earlier intervention (32).

From an epidemiological and clinical perspective, further studies are required to better understand the natural history and heterogeneity of HPS. Due to the rarity of the disease, multicenter collaborations and international registries will be essential to collect sufficient data. These efforts will also facilitate well-designed randomized clinical trials, which are currently limited by small patient populations (32).

Finally, improvements in clinical care infrastructure are needed. The establishment of specialized multidisciplinary centers can enhance diagnosis, management and follow-up of patients with HPS. This is particularly important in regions with higher disease prevalence, such as Puerto Rico, where access to lung transplantation and specialized care may be limited.

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