Hermansky-Pudlak syndrome

Overview of clinical and molecular features and case report of a new HPS-1 variant

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Review

Inherited platelet function disorders (IPFDs) encompass a heterogeneous group of haemorrhagic diseases caused by congenital defects of platelets function affecting various elements of the platelet physiology (membrane receptors, intraplatelet signalling proteins, granules), and leading to different clinical manifestations (1–3). Platelets have three types of secretory granules that differ in their number, content and function. Each single platelet has between 50 and 80 alpha (α) granules, containing adhesion molecules like P-selectin, cytokines, coagulation and fibrinolytic factors, complement molecules and growth factors. Dense (δ) granules, much less frequent (only 3–8 per platelet) contain small molecules like calcium, nucleotides (ADP, ATP), serotonin and pyrophosphate. Platelets have also lysosomes containing different proteolytic enzymes and glycosidases (4).

Congenital defects regarding the number and/or content of platelet granules include a range of disorders with variable reduction in the number and content of such granules (Table 1). In this review we will focus on the Hermansky-Pudlak syndrome (HPS), which is one of the most severe congenital disorders of δ-platelet

Keywords
Hermansky-Pudlak syndrome, inherited platelet disorders, dense granules

Summary
Hermansky-Pudlak syndrome (HPS) is a rare, autosomal recessive disorder affecting lysosome-related organelles (LRO), including dense platelet granules. HPS causes oculo-cutaneous hypopigmentation, bleeding diathesis and granulomatous colitis or pulmonary fibrosis. To date, there is no curative treatment and the clinical management depends on the severity of symptoms. A prompt diagnosis of HPS patients could improve their quality of life and clinical management. However, the absence of a specific platelet function test, the wide molecular heterogeneity, and the lack of phenotype-genotype correlations hamper the rapid diagnosis. Nine subtypes of HPS have been identified as a result of mutations in nine genes that codify for proteins involved in formation and shuttle of the LRO. The molecular characterization of patients and knowledge derived from animal models of HPS contribute to the understanding of biogenesis and function of the LRO. This paper describes a patient with a novel homozygous nonsense mutation causing HPS and provides a review of the literature focusing on recent advances in the molecular characterization and physiopathology of HPS.

Schlüsselwörter
Hermansky-Pudlak-Syndrom, erbliche Blutgerinnungsstörung, dichte Granula

Zusammenfassung
Das Hermansky-Pudlak-Syndrom (HPS) ist eine seltene, autosomal-rezessive Krankheit, die Ly-
granules, and report a patient with a novel homozygous mutation in \( \text{HPS1} \) causing this disorder.

**Hermansky-Pudlak syndrome (HPS)**

The HPS, so called in honour of the two Czechoslovak pathologists who first described it (5), encompasses a group of clinically and biologically heterogeneous disorders with sensible differences in their molecular base. It is an inherited disease due to the congenital alteration of lysosome-related subcellular organelles, like delta granules in platelets or melanosomes in melanocytes.

Patients with HPS are also characterized by haemorrhagic diathesis with variable degree of severity depending on platelet alteration, and oculocutaneous albinism (tyrosinase positive) with nystagmus, and visual acuity loss. Many patients show other severe clinical manifestations depending on the HPS subtype (i.e. pulmonary fibrosis, granulomatous colitis, neutropenia, immunodeficiency and neurological symptoms) (6–9).

As it happens in the majority of IPFDs, the incidence of HPS is not accurately known and less than 1000 cases have been described all around the world (1). Noteworthy HPS is particularly prevalent in Puerto Rico, especially in the north of the country, where 1/1800 people are affected. Two founding-effect mutations are responsible of this high HPS rate in Puerto Rico, a 16-bp duplication in exon 15 of the \( \text{HPS1} \) gene and a 3.9 kb deletion in \( \text{HPS3} \). These mutations are not especially prevalent in other countries (8, 9). To the best of our knowledge, only two Spanish HPS patients have been reported, and only the one previously described by our group had a molecular diagnosis (10, 11).

**Physiopathology, genetics**

Congenital \( \delta \)-granule disorders, including HPS, arise from genetic disorders involving formation and/or intracellular traffic of the lysosome-related organelles (LRO). LRO, a family to which platelet \( \delta \)-granules belong, are a heterogeneous group of membranous vesicles sharing with lysosomes their synthesis pathways, certain membrane components and their acid pH. However, LRO differ from lysosomes in their morphology, composition and function. Different types of LRO are selectively present in cells like melanocytes, platelets, T-lymphocytes, neutrophils and pulmonary epithelial cells (►Tab. 2), contributing importantly to their specialised function (12, 13).

During the last decades, we have witnessed many remarkable advances in the knowledge of the basics of formation, function and molecular pathology of LRO, including HPS. Today, it is known that different subtypes of HPS (HPS-1 to HPS-9) arise from quite numerous mutations located in up to nine genes: \( \text{HPS1}, \text{AP3B1}, \text{HPS3}, \text{HPS4}, \text{HPS5}, \text{DTNBPI}, \text{BLOC1S3} \) and \( \text{BLOC1S6} \) (7–9, 12) (►Tab. 3). Except \( \text{AP3B1} \), the rest of these genes encode proteins with an unknown function that are part of Biogenesis of Lysosome-related Organelles Complexes (BLOC), which are very ubiquitous structures located both anchored to cellular membrane and in a soluble cytoplasmic form (►Fig. 1) (13).

BLOC-1 regulates the traffic of vesicles in the endosomal system through its union to actin filaments of the cytoskeleton and participates in the early endosomal membrane and LROs fusion through its union to SNARE proteins. BLOC-1 interacts with other complexes like AP3 and BLOC-2 (12). Mutations in BLOC-1 proteins are very infrequent, resulting in HPS-7, HPS-8 and HPS-9 subtypes that represent mild forms of HPS with limited clinical manifestations. So far, only 6 molecular alterations in subunits of this complex have been reported, two nonsense mutations in \( \text{BLOC1S6} \) causing HPS-9 (14, 15), one frameshift change and a simple deletion in \( \text{BLOC1S3} \) leading to HPS-8 (16, 17), and two nonsense mutations in \( \text{DTNBPI} \) in two patients with HPS-7 (18, 19).

BLOC-2 complex is a heterotrimer consisting of HPS3, HPS5 and HPS6 (►Fig. 1), although the involvement of other not yet identified proteins is not ruled out (12). BLOC-2 interacts with BLOC-1 in the early endosomes and binds microtubules, clathrins and SNARE proteins to move throughout the cytoplasm. BLOC-2 complex is involved in transport of LRO components (e.g. TYR and TYRP1 enzymes in melanosomes from early endosomes to final LROs). BLOC-2 seems to be also involved in the secretion of lysosomes and other related granules, as suggested by the low lysosome secretion in mice platelets with HPS-5 and HPS-6 (12). Patients with molecular alterations affecting BLOC-2 (HPS3, HPS5 and HPS6 genes) have a mild HPS phenotype (HPS-3, HPS-5, HPS-6) with moderate bleeding, variable hypopigmentation and sporadic granulomatous colitis, but do not show pulmonary fibrosis (7–9, 12). To our knowledge, 9 molecular alterations have been reported in HPS3 (20–23), 11 in HPS5 (8, 24–26) and 9 in HPS6 (24, 27, 28). Most of them are frameshift or nonsense mutations affecting the function of BLOC-2. As mentioned, there is a 3.9 kb deletion in HPS3 with founder effect in the central area of Puerto Rico, where HPS-3 affects 1:4000 native people (20).

BLOC-3 complex is a heterodimer formed by HPS1 and HPS4, which shares no homology with other known proteins. The N- and C-termini of HPS1 interacts with the N-terminal and middle region of HPS4 to form the complex (29). Similar to other BLOCs, the precise function of BLOC-3 is not well known, but it is believed to be involved in lysosome and late endosome biogenesis and transport (12). Mutations in HPS1 and HPS4 affecting BLOC-3 are the most frequent and the ones that give rise to the more severe forms of HPS, i.e. HPS-1 and HPS-4. In addition to other typical complications of this syndrome as hypopigmentation and haemorrhagic diathesis, these patients commonly suffer from granulomatous colitis (>30% cases) and pulmonary fibrosis (>80% cases in HPS-1 subtype). The reason for lung affection is unclear, but it probably reflects the relevant role of BLOC-3 in the biogenesis and function of lamellar bodies of pneumocytes (9, 12, 13). The clinical phenotype of HPS-4 is very similar to HPS-1 one, although usually less severe.

The HPS1 gen, located in 10q24.2 is the most frequently mutated: 31 mutations have been described, including 2 amino acid change single mutations (p.L239P and p.L668P) and a majority of frameshift changes and nonsense mutations (8, 11, 20, 21, 13).
Tab. 1 Congenital defects in platelets granules

<table>
<thead>
<tr>
<th>affected granules</th>
<th>name</th>
<th>clinical and laboratory phenotype</th>
<th>inheritance</th>
<th>genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>α and δ</td>
<td>α and δ storage pool disease</td>
<td>• normal or discretely diminished platelets count&lt;br&gt;• normal platelet morphology&lt;br&gt;• α and/δ granules defect by electron microscopy&lt;br&gt;• LTA down&lt;br&gt;• granular protein release impairment measured by flow cytometry&lt;br&gt;• mild bleeding usually in the context of high haemorrhagic risk situations</td>
<td>AR/AD</td>
<td>-</td>
</tr>
<tr>
<td>α</td>
<td>grey platelet syndrome (GPS)</td>
<td>• moderate thrombocytopenia (30–100 x 10^9/l)&lt;br&gt;• large and grey platelets&lt;br&gt;• LTA N or ↓&lt;br&gt;• Some patients show a selective defect in GPVI and activation by collagen.&lt;br&gt;• defect in α-granular proteins in biochemical assays (e. g. β-TG, PDGF)&lt;br&gt;• selective absence of α-granules in thin-section electron microscopy&lt;br&gt;• clinical:&lt;br&gt;  – early bone marrow fibrosis&lt;br&gt;  – mild haemorrhagic episodes usually associated with high risk situations (e. g. dental procedures under antiaggregant treatment, surgery, delivery, trauma)&lt;br&gt;  – occasional splenomegaly</td>
<td>AR/AD</td>
<td>NBEAL2</td>
</tr>
<tr>
<td>Quebec syndrome (QS)</td>
<td></td>
<td>• moderate thrombocytopenia (&lt;100 x 10^9/l), normal morphology&lt;br&gt;• LTA N or ↓&lt;br&gt;• impaired procoagulant platelet activity&lt;br&gt;• enhanced fibrinolytic activity&lt;br&gt;• defect in α-granular proteins showed in FC (P-selectin, factor V)&lt;br&gt;• clinical:&lt;br&gt;  – cutaneous-mucose and post-surgery haemorrhagic episodes&lt;br&gt;  – clinical response to fibrinolytic inhibitors&lt;br&gt;  – absence of clinical response to platelet transfusion</td>
<td>AD</td>
<td>PLAU</td>
</tr>
<tr>
<td>δ</td>
<td>Hermansky-Pudlak syndrome (HPS)</td>
<td>• normal platelet count and morphology&lt;br&gt;• selective defect of δ-granules by electron microscopy&lt;br&gt;• LTA N or ↓&lt;br&gt;• decrease in radiolabeled hydroxytryptamine and mepacrine uptake and reduced release of CD63 by flow cytometry&lt;br&gt;• clinical:&lt;br&gt;  – oculocutaneous albinism&lt;br&gt;  – lysosomal accumulation of ceroid lipofuscin,&lt;br&gt;  – pulmonary fibrosis,&lt;br&gt;  – granulomatous colitis</td>
<td>AR</td>
<td>HPS1–HPS9</td>
</tr>
<tr>
<td>Chediak-Higashi syndrome (CHS)</td>
<td></td>
<td>• normal platelet count and morphology&lt;br&gt;• selective defect of δ-granules by electron microscopy&lt;br&gt;• LTA N or ↓&lt;br&gt;• decrease in radiolabeled hydroxytryptamine and mepacrine uptake and reduced release of CD63 by flow cytometry&lt;br&gt;• clinical:&lt;br&gt;  – oculocutaneous albinism,&lt;br&gt;  – large peroxidase positive lysosomal granules in neutrophils and other non-haematopoietic cells&lt;br&gt;  – impaired NK and cytotoxic T lymphocyte function&lt;br&gt;  – In most patients haemophagocytic lymphohistiocytosis is lethal unless allogenic transplantation is performed.</td>
<td>AR</td>
<td>LYST</td>
</tr>
<tr>
<td>Griscelli syndrome (GS)</td>
<td></td>
<td>• normal platelet count and morphology&lt;br&gt;• selective defect of δ-granules by electron microscopy&lt;br&gt;• clinical:&lt;br&gt;  – albinism,&lt;br&gt;  – silver hair,&lt;br&gt;  – neurological defects,&lt;br&gt;  – lymphohistiocytosis,&lt;br&gt;  – diminished NK cell and T-lymphocyte cytotoxic function</td>
<td>AR</td>
<td>RAB27, MYO5A, MLPH</td>
</tr>
<tr>
<td>as syndromic deficiency</td>
<td></td>
<td>• normal platelet count&lt;br&gt;• reduced second aggregation wave&lt;br&gt;• absence of δ-granules by electron microscopy</td>
<td>AD/AR</td>
<td>-</td>
</tr>
</tbody>
</table>

LTA: light transmission aggregometry (weak agonists and low concentrations: including ADP, epinephrine and collagen); LTA N: LTA normal; LTA ↓: reduced aggregation or absence of second wave; AR: autosomic recessive; AD: autosomic dominant; β-TG: β-thromboglobulin; PDGF: platelet-derived growth factor
### Tab. 2 Main of intracellular lysosome related organelles (LRO), function and pathological consequences of their defects

<table>
<thead>
<tr>
<th>LRO</th>
<th>function</th>
<th>cell</th>
<th>pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>melanosomes</td>
<td>• biosynthesis and storage of intracellular melanin</td>
<td>melanocytes, iris cells and retina cells</td>
<td>oculocutaneous hypopigmentation</td>
</tr>
<tr>
<td>δ granules</td>
<td>storage molecules involved in the coagulation cascade</td>
<td>platelets and megakaryocytes</td>
<td>haemorrhagic diathesis</td>
</tr>
<tr>
<td>cytolytic granules</td>
<td>intracellular degradation of macromolecules</td>
<td>T-cytotoxic lymphocytes and NK-cells</td>
<td>immunodeficiency, viral infections</td>
</tr>
<tr>
<td>azurophil granules</td>
<td>storage of lytic enzymes for bacterial destruction involved in pathological processes including inflammation</td>
<td>neutrophils and eosinophils</td>
<td>neutropenia, immunodeficiency, bacterial infections</td>
</tr>
<tr>
<td>basophil granules</td>
<td>• storage of histamine, serotonin, heparin, IL-4 and lyosomal proteases</td>
<td>basophils and mast cells</td>
<td>immunodeficiency, allergies</td>
</tr>
<tr>
<td>lamellar bodies</td>
<td>storing and secretion of surfactants for pulmonary function</td>
<td>type II pneumocytes</td>
<td>pulmonary fibrosis</td>
</tr>
<tr>
<td>major histocompatibility complex class II compartments</td>
<td>processing and incorporating antigens to cell membranes</td>
<td>B lymphocytes, macrophages, dendritic cells and other antigen presenting cells</td>
<td>immunodeficiency</td>
</tr>
<tr>
<td>neuromelanin granules</td>
<td>neuromelanin storage</td>
<td>brain stem catecholaminergic neurons</td>
<td>unknown</td>
</tr>
<tr>
<td>ruffled borders</td>
<td>storage, activation and secretion acid hydrolases, used for bone resorption and remodeling</td>
<td>osteoclasts</td>
<td>osteoporosis</td>
</tr>
<tr>
<td>Weibel-Palade bodies</td>
<td>storage and regulation of the secretion of haemostatic and proinflammatory factors (von Willebrand factor, P-selectin)</td>
<td>endothelial cells</td>
<td>haemorrhagic diathesis</td>
</tr>
<tr>
<td>synaptic vesicles</td>
<td>neutrotransmitters storage</td>
<td>neurons</td>
<td>abnormal behaviour</td>
</tr>
</tbody>
</table>

### Tab. 3 Responsible genes for different types of HPS (in human and mouse model) and mutations

<table>
<thead>
<tr>
<th>human sub-type HPS</th>
<th>protein complex</th>
<th>gene</th>
<th>NCBI RefSeq</th>
<th>chromosome location</th>
<th>mutations number</th>
<th>references</th>
<th>murine model</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS-1</td>
<td>BLOC-3</td>
<td>HPS1</td>
<td>NM_000195</td>
<td>10q24.2</td>
<td>32</td>
<td>(8, 11, 20, 30–45)</td>
<td>Pale ear</td>
</tr>
<tr>
<td>HPS-2</td>
<td>AP-3</td>
<td>AP3B1</td>
<td>NM_003664</td>
<td>5q14.1</td>
<td>12</td>
<td>(52–58)</td>
<td>Pearl</td>
</tr>
<tr>
<td>HPS-3</td>
<td>BLOC-2</td>
<td>HPS3</td>
<td>NM_032383</td>
<td>3q24</td>
<td>9</td>
<td>(20–23)</td>
<td>Cocoa</td>
</tr>
<tr>
<td>HPS-4</td>
<td>BLOC-3</td>
<td>HPS4</td>
<td>NM_022081</td>
<td>22q12.1</td>
<td>13</td>
<td>(8, 46–50)</td>
<td>Light ear</td>
</tr>
<tr>
<td>HPS-5</td>
<td>BLOC-2</td>
<td>HPS5</td>
<td>NM_181507</td>
<td>11p15.1</td>
<td>11</td>
<td>(8, 24–26)</td>
<td>Ruby eye-2</td>
</tr>
<tr>
<td>HPS-6</td>
<td>BLOC-2</td>
<td>HPS6</td>
<td>NM_024747</td>
<td>10q24.32</td>
<td>9</td>
<td>(24, 27, 28)</td>
<td>Ruby eye</td>
</tr>
<tr>
<td>HPS-7</td>
<td>BLOC-1</td>
<td>DNTBP1</td>
<td>NM_032122</td>
<td>6p22.3</td>
<td>2</td>
<td>(18, 19)</td>
<td>Sandy</td>
</tr>
<tr>
<td>HPS-8</td>
<td>BLOC-1</td>
<td>BLOC1S3</td>
<td>NM_212550</td>
<td>19q13.32</td>
<td>2</td>
<td>(16, 17)</td>
<td>Reduced pigmentation</td>
</tr>
<tr>
<td>HPS-9</td>
<td>BLOC-1</td>
<td>BLOC1S6</td>
<td>NM_012388</td>
<td>15q21.1</td>
<td>2</td>
<td>(14, 15)</td>
<td>Pallid</td>
</tr>
<tr>
<td>-</td>
<td>BLOC-1</td>
<td>BLOC1S5</td>
<td>NM_001199323</td>
<td>6p24.3</td>
<td>-</td>
<td>-</td>
<td>Muted</td>
</tr>
<tr>
<td>-</td>
<td>BLOC-1</td>
<td>BLOC1S4</td>
<td>NM_018366</td>
<td>4p16.1</td>
<td>-</td>
<td>-</td>
<td>Cappuccino</td>
</tr>
<tr>
<td>-</td>
<td>BLOC-1</td>
<td>BLOC1S1</td>
<td>NM_001487</td>
<td>19p13.11</td>
<td>-</td>
<td>-</td>
<td>Kxd1-KO</td>
</tr>
<tr>
<td>-</td>
<td>AP-3</td>
<td>AP3D1</td>
<td>NM_001261826</td>
<td>19p13.3</td>
<td>-</td>
<td>-</td>
<td>Mocha</td>
</tr>
<tr>
<td>-</td>
<td>HOPS</td>
<td>VPS33A</td>
<td>NM_022916</td>
<td>12q24.31</td>
<td>-</td>
<td>-</td>
<td>Buff</td>
</tr>
<tr>
<td>-</td>
<td>Rab geranylgeranyl transferase alpha</td>
<td>RABBGTA</td>
<td>NM_004581</td>
<td>14q11.2</td>
<td>-</td>
<td>-</td>
<td>Gunmetal</td>
</tr>
</tbody>
</table>
The aforementioned 16-pb duplication in exon 15 of \textit{HPS1} with founder effect in northwest of Puerto Rico causes an extraordinary high prevalence or HPS-1 in this island. This HPS subtype is also common in Japanese, Chinese, Caucasian and non-Puerto Rican people, and it has been reported in few European cases (8, 9, 12, 13). Regarding the HPS-4 subtype, up to 13 mutations have been described in the \textit{HPS4} gen, mostly nonsense and frameshift (8, 46–50).

Unlike other genes causing HPS, \textit{AP3B1} codifies the \(\beta_3\) subunit, namely \(\text{AP}3\beta_1\), of the adapter complex 3 (AP-3). This complex, synthesized in the Golgi apparatus, consists of four subunits that are differently combined in a form of AP-3 distributed very ubiquitously and a second AP-3 form with specific cerebral location. Both are believed to act in the recognition and selection of specific proteins such as LAMP or TYR that are necessary to the formation of new vesicles and for their transport throughout endosome/lysosome pathways (51).

Molecular defects in \textit{AP3B1} give rise to HPS-2, which is the only HPS subtype presenting with lymphohistiocytosis and immunodeficiency, and with a lower grade of albinism, hypopigmentation and bleeding. Immunodeficiency in HPS-2 patients has been related with the role of AP-3 in the formation and transport of lytic T lymphocyte granules (9, 12, 51). Up to 12 mutations in \textit{AP3B1} have been identified in HPS-2 patients, mainly frameshift and nonsense mutations (52–58).

Despite the high number of patients with different HPS subtypes and the wide amount of mutations identified, there is not a clear evidence of the link between these mutations and the severity of the clinical manifestations in each subtype of patients. It is important to mention that the genes described above might not be the only ones involved in HPS. Indeed, since the 1970’s murine models of HPS have been developed involving up to 15 candidate genes, and in some cases, the equivalent human genes are still unknown (\textit{▶Tab. 3}). Research in these murine models have shed light on the biogenesis and function of LROs, and are promising to allow for better clinical characterization of these patients, including novel aspects like drug susceptibility and resistance to atherosclerosis (9, 13, 59).

**Diagnostic approach**

While the clinical identification of many patients with HPS is facilitated by the typical symptomatology accompanying the bleeding diathesis, the laboratory demonstration of a platelet dysfunction related to a \(\delta\)-granules deficiency, and the identification of the underlying molecular alteration can be difficult to obtain. In some, but not all, HPS patients, the semi-automatic PFA-100 test can show prolonged closures times (60), and light transmission aggregometry (LTA) is usually diminished and lack the second aggregation wave with weak platelet agonists such as ADP or epinephrine. However, neither PFA-100 nor platelet LTA are specific tests, so normal results do not exclude the diagnosis of HPS (9, 61, 62).

Therefore, some additional tests are especially relevant to specifically evaluate the quantitative or functional defect of \(\delta\)-granules, such as quantification of nucleotides content by luminaggregometry or luminescence, the passive uptake of mepacrine and the assessment of CD63 expression by flow cytometry, or radioactive assays to determine the uptake/release of \(^{14}\text{C\text{-}}\text{5-hydro-}\)
xytriptamine (63). Visual demonstration of δ-granules by electron microscopy (EM) remains the gold standard in HPS diagnosis (9). This can be performed by a simple whole mount assay with little manipulation of samples that allow to distinguish δ-granules as black dots due to their high density, or by a more complex EM analysis of platelet ultrastructure (thin sections) giving valuable information about the number and possible alterations in the morphology of these granules (64).

The molecular diagnosis may not be that simple; as previously stated mutations in nine genes (HPS1, AP3B1, HPS3, HPS4, HPS5, HPS6, DTNBPI, BLOC1S3 and BLOC1S6) cause HPS in humans. The large number of HPS culprit genes (>118 exons) and the lack of genotype-phenotype correlation, hamper the molecular diagnosis of HPS. For many years, the standard approach for the molecular diagnosis of HPS has been based on a HPS candidate gene analysis, considering HPS1 the most frequently affected gene and also potential clinical characteristics of patients such as greater severity, presuming a diagnosis to HPS-1 or HPS-4, or a immunodeficiency, which suggests HPS-2. This approach, arbitrary in some aspects, might not always be successful.

Additionally, there may be disease-causing genes not yet identified, this disorder could be often underdiagnosed and patients not be molecularly characterized. Current high-throughput DNA specific technologies provide a good alternative to address the molecular diagnosis of these patients. Several techniques like microsatellite genetic screening or next generation sequencing are being implemented in this setting (15, 17, 19).

Management of HPS patients

Similar to other IPFDs, the clinical management and treatment of patients with HPS must be done in specialised centres, individualised according to the severity of its clinical manifestations (62, 65). To date, no curative treatment exists and the use of aggressive alternatives like haematopoietic cell transplantation is restricted to very severe cases and must be preceded by an exhaustive risk-benefit evaluation(65). Patients should be advised to pay meticulous attention to oral and dental care, and to avoid drugs known as interfering with platelet function (such as aspirin, other nonsteroidal anti-inflammatory agents, or serotonin reuptake inhibitors) and intramuscular injections. Mild bleeding episodes might be effectively treated with antifibrinolytic agents. Desmopressin is not always useful in this context and it has the additional disadvantage of increasing the vasoconstriction due to high serotonin levels present in some patients with δ-granules deficiency. There is also limited experience in the use of recombinant factor VII in HPS. Platelet transfusion must be restricted to major bleeding episodes or previous to major surgery procedures, and in these cases the platelet products must be ideally HLA compatible to minimize the risk of alloimmunization (9, 65).

Case report

A man (age: 28 years) with a family history of parental consanguinity was referred to our center with a clinical suspicion of HPS. He is the second of three children, and while the first brother is healthy, the youngest sister was diagnosed with juvenile idiopathic scoliosis. History revealed megaureter due to ureter ostium stenosis at birth. The patient suffered from excessive bleeding following urological surgery, as well as other haemorrhagic episodes, including epistaxis requiring cauteronization, and excessive bleeding from small wounds. Examinations revealed oculocutaneous albinism, and nystagmus.

Diagnosis

The haemoglobin and the white blood cell count were in range, and platelets were 159 x 10⁹/l. Platelet function studies with the platelet function analyzer (PFA-100) demonstrated increased ADP (111 seconds; reference range, 57–100 seconds) and epinephrine (>300 seconds; reference range, 81–131 seconds) closure times. Platelet dysfunction was confirmed with platelet aggregometry studies that showed monophasic response after exposure to ADP (5 μmol/l), and markedly impaired aggregation in response to epinephrine (5 μmol/l), and 2 μg/ml collagen. There was an obvious decrease in the total uptake of 14C-5-hydroxyxytriptamine (54% of control values). In addition, upon stimulation with 25 μmol/l TRAP we observed an important reduction in the platelets flow cytometric externalization of fluorescein-labelled CD63 (15.7% positivity in patient vs 73.6% in control) and negative mepacrine test in the patient. These findings are consistent with a storage pool deficiency with reduced dense bodies and consequent defects of secretion-dependent aggregation. Whole mount electron microscopy revealed no δ-granules in the patient’s platelets (Fig. 2).

Based on the clinical presentation and haematological findings consistent with...
HPS, we aimed to molecularly characterize this patient. We first considered studying HPS1, as he did not exhibit neutropenia or immunodeficiency, characteristic of HPS-2, and that he did present bleeding manifestations that are not typical of HPS-9. The entire coding region (20 exons and flanking regions) of HPS1, the most frequent gene being affected in HPS, were sequenced by Sanger method. Patient was found to be homozygous for a novel nonsense mutation c.844 G>T, p.Glu204Stop located in exon 7. His parents were both found to be heterozygous for this mutation.

Follow-up
At present our patient is alive and well, except for mild bleeding, has not developed granulomatous enteropathic disease or pulmonary fibrosis, and his psychomotoric development is normal.

To our knowledge, this is the second case of molecular characterization of a HPS patient in Spain, with the previous patient also being described by our group (11). In that case, the patient was found to be a compound heterozygous, with the maternal allele inherited containing the insC974 mutation and a de novo mutation in exon 5 of the paternal allele also affecting HPS1, and he suffered from severe mental retardation, which is not characteristic of this disorder (11).

Conclusion
Despite, there is no curative approach for Hermansky-Pudlak syndrome, increased awareness and early identification of HPS patients may be useful for clinical management. With a high degree of clinical suspicion, the study of this disease, its causative genes and the phenotype associated is of enormous interest to both cell biology and medicine.

Conflict of interest
The authors declare that they have no conflict of interest.

References
I. Sánchez-Guiu et al.: Hermansky-Pudlak syndrome


