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Gene of the issue: Genetic Variants Associated with Hermansky-Pudlak Syndrome

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Hermansky-Pudlak syndrome (HPS), a rare autosomal recessive disorder characterized by defective biogenesis of lysosome-related organelles (LROs), affects approximately 1-9 per 1,000,000 individuals worldwide (www.orpha.net) [1]. Individuals with HPS manifest with a bleeding diathesis and oculocutaneous albinism; some also develop inflammatory bowel disease, pulmonary fibrosis, and/or neutropenia [1, 2]. The diagnosis of HPS is established in a patient with a compatible clinical presentation by demonstrating absent platelet delta granules by whole mount electron microscopy (Figure 1) and/or identifying bi-allelic pathogenic variants in an HPS-associated gene.

HPS displays locus heterogeneity; to date, ten genes associated with HPS are identified (Table I). Each HPS-associated gene encodes a protein subunit of either Biogenesis of Lysosome-related Organelles Complex (BLOC)-1, BLOC-2, BLOC-3, or the Adaptor Protein-3 (AP-3) complex [3]. These multi-subunit complexes are involved in formation of LROs, such as delta granules in platelets and melanosomes in melanocytes [3, 4]. All HPS types manifest with a bleeding diathesis and oculocutaneous albinism. Individuals with BLOC-1 (HPS types 7, 8, or 9) or BLOC-2 (HPS types 3, 5, or 6) related HPS generally exhibit mild clinical symptoms, including mild hypopigmentation. Individuals with BLOC-3 (HPS types 1 or 4) or AP-3 (HPS types 2 or 10) related HPS have more pronounced pigment defects of the skin, hair, and eyes and often have severe ancillary symptoms including progressive pulmonary fibrosis, inflammatory bowel disease, or neutropenia [2, 3].

HPS is a rare disorder affecting people of different ethnicities, including African American, Ashkenazi-Jewish, Chinese, Indian, Israeli Bedouin, Japanese, Latino, and Western European [1]. The prevalence of each HPS type varies due to founder mutations (Table I). HPS type 1 is the most common type, with Puerto-Rican, Swiss and Japanese genetic isolates [5–7]. In northwest Puerto Rico, the prevalence of HPS type 1 is 1 in 1,800, and approximately 80% of affected individuals from this region are homozygous for a 16-base

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Declaration of interest

The authors report no conflicts of interest.

pair duplication (c.1470_1486dup16) in *HPS1* [5, 8]. Other *HPS1* variants also occur in Puerto Rican patients with HPS type 1 [9]. HPS type 3 is common in central Puerto Rico, where about 1 in 4,100 individuals are affected due to a 3,904-bp deletion in *HPS3* [8, 10]. Disease-causing variants in the 10 HPS genes are reported in the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), Albinism Database (http://www.ifpcs.org/albinism/), and AP3B1base (http://structure.bmc.lu.se/idbase/AP3B1base/) (Table I). There may be other HPS genes that have not yet been identified in humans, and it is possible that genetic testing of patients with excessive bleeding (and minor hypopigmentation) of unknown etiology may lead to the discovery of new genes associated with HPS.

Individuals with HPS have an increased tendency to bleed which is attributed to a platelet delta storage pool deficiency. Delta granules are absent in platelets from individuals with HPS (Figure 1), which causes impairment of secondary aggregation, prolongation of bleeding times, and abnormal alpha granule secretion [4, 11,12]. Platelet delta and alpha granules arise from megakaryocyte multivesicular bodies, but ultrastructural studies show normal distribution, quantity, and size of alpha granules in patients with HPS (Figure 1) [13], suggesting that HPS gene products function in biogenesis of delta granules, and not alpha granules.

Individuals with HPS exhibit easy bruisability and increased bleeding. Excessive blood loss can be seen with medical procedures, dental extractions, or surgery, and trauma can cause significant hemorrhage [2]. Ecchymoses may be unusual in size or location, and they may be in various stages of resolution [2]. Venipuncture sites may bleed for prolonged periods. Children with HPS may experience severe epistaxis or pronounced bleeding with loss of deciduous teeth [2]. Individuals with inflammatory bowel disease may bleed excessively per rectum [2, 14, 15]. The inflammatory bowel disease of HPS affects some pediatric and adult patients [2, 15]. Clinical manifestations and therapy are generally similar to those for Crohn’s disease, including treatment with anti-tumor necrosis factor alpha drugs for severe disease and surgical bowel resection for cases refractory to medical treatment [15]. Menorrhagia, menometrorrhagia, and post-partum hemorrhage requiring transfusion of platelets or packed red blood cells can occur in female patients [2, 16, 17].

A bleeding diathesis is found in HPS patients irrespective of genetic type, other phenotypic features are dependent upon HPS type. Recurrent infections due to neutropenia and/or immunodeficiency may develop in patients with HPS types 2 or 10, and neutropenia generally responds to treatment with G-CSF [18, 19]. Pulmonary fibrosis is diagnosed in patients with HPS types 1, 2, or 4 [2, 3, 20]. Adults with HPS type 1 may present with progressive fibrotic lung disease in middle age, and children and young adults with HPS type 2 may develop pulmonary fibrosis [2, 3, 20]. Results of clinical trials investigating pirfenidone as treatment for HPS pulmonary fibrosis were inconclusive [21, 22], and thus medical therapy approved as treatment for HPS pulmonary fibrosis is not available. Single or double lung transplantation has been successfully performed on several patients with HPS, and it remains an option for certain candidates with severe HPS pulmonary fibrosis [23].

Desmopressin, pro-coagulants (e.g., aminocaproic acid, tranexamic acid), or platelet transfusion may be used as prophylaxis or treatment for excessive bleeding in patients with HPS [24, 25]. Response to desmopressin can be variable between and within patients with HPS, and some patients may not respond to desmopressin [16, 25]. Platelets are effective in preventing or treating bleeding in patients with HPS. However, platelets should be transfused judiciously. Donor organs were not found for some lung transplant candidates with severe HPS pulmonary fibrosis who were sensitized from prior blood product transfusions [23]. Thus, interventions such as transfusion of leukoreduced single donor platelets or blood products to limit alloimmunization should be implemented in patients with HPS who are at risk of developing pulmonary fibrosis.

Overall, HPS is a rare disorder associated with several genetic variants and phenotypic heterogeneity. Despite the spectrum of molecular and clinical features in HPS, genotype-phenotype associations have not been reported. Progress in genetic analyses including use of next-generation sequencing or panel-based platforms may improve the ability to diagnose patients with HPS and facilitate the identification of novel genes associated with HPS. Ultimately, these scientific advances may result in an expansion of the current understanding of HPS.

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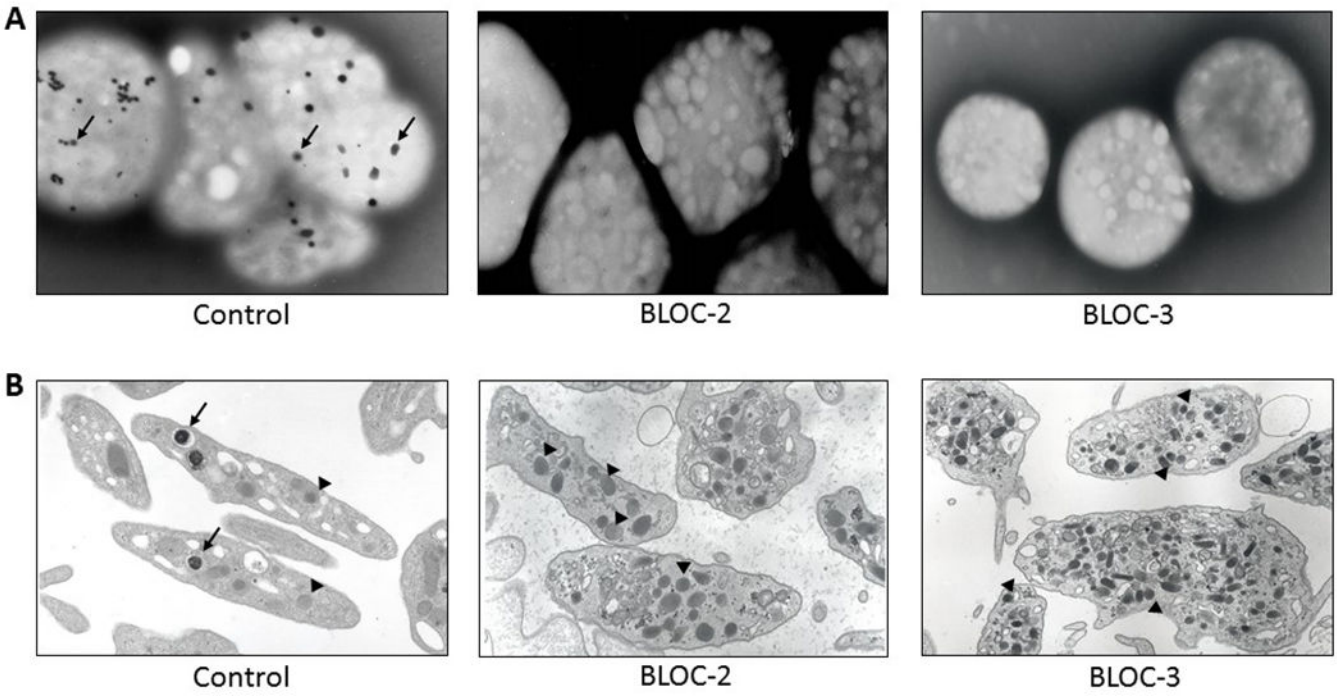

Figure 1.

Ultrastructural imaging of platelets.

A: Whole mount electron micrographs of control platelets (×4000), each containing several delta granules (arrows) and platelets of HPS patients with defects in BLOC-2 or BLOC-3 (×6000), each showing absence of delta granules.

B: Thin section micrographs of platelets from control and HPS patients with defects in BLOC-2 or BLOC-3. Control platelets (×16000) contain delta granules (arrows), which are lacking in BLOC-2 (x20000) and BLOC-3 (x22000) defective platelets. Other cytoplasmic components include alpha granules (arrowheads), which appear similar in size, number and shape in BLOC-2 and BLOC-3 defective platelets compared to control platelets.

Table I.

Genes Associated with Hermansky-Pudlak Syndrome[1]

HPS type	Gene	GeneID; mRNA[2] (# exons)	Locus	Protein	Protein ID[2] (# aa; Mw)	Complex	~ # variants reported[3]
HPS-1	*HPS1*	ID:3257; NM_000195 (20 exons)	10q24.2	HPS1	NP_000186 (700 aa; 79.3 kD)	BLOC-3	64
HPS-2	*AP3B1*	ID:8546; NM_003664 (27 exons)	5q14.1	AP-3 Beta 3A subunit	NP_003655 (1094 aa; 121.3 kD)	AP-3	38
HPS-3	*HPS3*	ID:84343; NM_032383 (17 exons)	3q24	HPS3	NP_115759 (1004 aa; 113.7 kD)	BLOC-2	23
HPS-4	*HPS4*	ID:89781; NM_022081 (14 exons)	22q12.1	HPS4	NP_071364 (708 aa; 76.9 kD)	BLOC-3	30
HPS-5	*HPS5*	ID:11234; NM_181507 (23 exons)	11p15.1	HPS5	NP_852608 (1129 aa; 127.4kD)	BLOC-2	31
HPS-6	*HPS6*	ID:79803; NM_024747 (1 exon)	10q24.32	HPS6	NP_079023 (775 aa; 83.0 kD)	BLOC-2	40
HPS-7	*DTNBP1*	ID:84062; NM_032122 (10 exons)	6p22.3	Dysbindin	NP_115498 (351 aa; 39.5 kD)	BLOC-1	3
HPS-8	*BLOC1S3*	ID:388552; NM_212550 (2 exons)	19q13.32	BLOC-1 subunit 3	NP_997715 (202 aa; 21.3 kD)	BLOC-1	4
HPS-9	*PLDN*	ID:26258; NM_001311255 (5 exons)	15q21.1	Pallidin	NP_001298184 (177 aa; 20.3 kD)	BLOC-1	2
HPS-10	*AP3D1*	ID:8943; NM_001261826 (32 exons)	19p13.3	AP-3 delta subunit	NP_001248755 (1215 aa; 136.7 kD)	AP-3	1

Abbreviations: aa, amino acids; AP, Adaptor Protein; BLOC, Biogenesis of Lysosome-related Organelles Complex; kD, kilodaltons; Mw, molecular weight.

[1] As of July 2019

[2] Genbank accession numbers of the mRNA and protein product encoding the longest isoform (often transcript variant 1), its number of exons, amino acids and predicted protein molecular weight.

[3] Reported in the Human Gene Mutation Database (Professional 2019.1; http://www.hgmd.cf.ac.uk/) and additional literature reports.