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Severe Bleeding with Subclinical Oculocutaneous Albinism in a Patient with a Novel *HPS6* Missense Variant

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Abstract

Hermansky-Pudlak syndrome (HPS), a rare autosomal recessive disorder, manifests with oculocutaneous albinism and a bleeding diathesis. However, severity of disease can be variable and is typically related to the genetic subtype of HPS; HPS type 6 (HPS-6) is an uncommon subtype generally associated with mild disease. A Caucasian adult female presented with a history of severe bleeding; ophthalmologic examination indicated occult oculocutaneous albinism. The patient was diagnosed with a platelet storage pool disorder, and platelet whole mount electron microscopy demonstrated absent delta granules. Genome-wide SNP analysis showed regions of homozygosity that included the *HPS1* and *HPS6* genes. Full length *HPS1* transcript was amplified by PCR of genomic DNA. Targeted next-generation sequencing identified a novel homozygous missense variant in *HPS6* (c.383T>C; p.V128A); this was associated with significantly reduced *HPS6* mRNA and protein expression in the patient's fibroblasts compared to control cells. These findings highlight the variable severity of disease manifestations in patients with HPS, and illustrate that HPS can be diagnosed in patients with excessive bleeding and occult oculocutaneous

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albinism. Genetic analysis and platelet electron microscopy are useful diagnostic tests in evaluating patients with suspected HPS.

Keywords

Hermansky-Pudlak syndrome; platelet delta granules; oculocutaneous albinism

Introduction:

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder characterized by improper formation, processing, or trafficking of lysosome-related organelles, including melanosomes and platelet delta granules (Huizing, 2008). Ten genetic subtypes of HPS have been identified; eight are associated with genes encoding proteins in the Biogenesis of Lysosome-related Organelles Complex (BLOC)-1 (HPS-7, HPS-8, HPS-9), BLOC-2 (HPS-3, HPS-5, HPS-6), or BLOC-3 (HPS-1, HPS-4), and two are associated with genes encoding subunits of the Adaptor Protein-3 complex (HPS-2, HPS-10)(Huizing, 2017).

Cellular defects in HPS lead to diverse disease manifestations, including oculocutaneous albinism and a bleeding tendency secondary to a platelet storage pool deficiency (Huizing, 2008; Huizing, 2017; Gahl, 1998). Granulomatous colitis resembling Crohn's disease can affect a subpopulation of patients with HPS, and some disease manifestations are limited to specific HPS subtypes (Huizing, 2017). For example, pulmonary fibrosis develops in patients with HPS-1, -2, and -4, and immunodeficiency with natural killer cell dysfunction and neutropenia manifest in patients with HPS-2 (Huizing, 2017; Gochuico, 2012; Gil-Krzewska, 2017).

In this study, we report a patient who presented with severe bleeding tendency. Although oculocutaneous albinism was subclinical, ophthalmologic examination showed mild pigmentation defects and poor foveal development. A novel homozygous missense variant in *HPS6* associated with absent platelet delta granules and reduced cellular levels of *HPS6* mRNA and protein was identified in this patient.

Materials and Methods:

Editorial Policies and Ethical Considerations

The patient provided written informed consent to protocols 95-HG-0193 (clinicaltrials.gov NCT00001456, "Clinical and Basic Investigations into Hermansky-Pudlak Syndrome") and 04-HG-0211 (clinicaltrials.gov NCT00084305, "Procurement and Analysis of Specimens from Individuals with Pulmonary Fibrosis"). The research was conducted prospectively; the clinical studies were approved by the institutional review board of the National Human Genome Research Institute.

Clinical testing was performed at Regional Cancer Center, Johnson City, Tennessee and the National Institutes of Health Clinical Center, Bethesda, Maryland. Platelet aggregation was measured by the absorbance method using the AggRam system (Helena Laboratories, Beaumont, TX). High-resolution computed tomography scans of the chest, pulmonary

function tests, and platelet electron microscopy were performed as described (Rouhani, 2009; Ferreira, 2017).

Genetic Testing

Next Generation Sequencing (NGS) was performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory using a targeted panel (Agilent Technologies, Santa Clara, CA) encompassing 9 HPS genes (i.e., *HPS1*, *AP3B1*, *HPS3*, *HPS4*, *HPS5*, *HPS6*, *DTNBP1*, *BLOC1S3*, *BLOC1S6*). Large scale single-nucleotide polymorphism (SNP) analysis was performed on genomic DNA using HumanOmniExpress DNA Analysis BeadChip (Illumina, San Diego, CA) and GenomeStudio software (Illumina) as described (Bryan, 2017). PCR of *HPS1* using genomic DNA was performed using Platinum™ Pfx DNA Polymerase according to manufacturer's instructions (Invitrogen, Carlsbad, CA).

Quantitative Real-time PCR and Western Blot Analysis for HPS6

Fibroblasts were cultured from a forearm skin biopsy as described (Stephen, 2017). Dermal fibroblasts from two healthy volunteers served as normal controls; dermal fibroblasts from 3 adults with HPS-1 served as BLOC-3 complex controls. Experiments were performed in triplicate.

Total RNA and protein were isolated (Stephen, 2017). Quantitative real-time PCR (qPCR) was performed using TaqMan primers specific for *HPS6* (Thermo Fisher, Waltham, MA), and cDNA from the patient and controls was amplified using TaqMan universal PCR master mix (Thermo Fisher) as described (Stephen, 2017). Results were normalized with expression of RFLP13a (Thermo Fisher) and analyzed. Western blot analysis was performed as described (Stephen, 2017). Membranes were incubated overnight at 4°C with rabbit monoclonal anti-HPS1 antibody (Abcam, Cambridge, UK), rabbit polyclonal anti-HPS4 antibody (Santa Cruz Biotechnology Inc., Dallas TX), rabbit polyclonal anti-HPS6 antibody (Origene Technologies Inc., Rockville, MD), or mouse monoclonal anti-β-actin antibody (Sigma-Aldrich, St. Louis, MO). Densitometry analysis was performed using the Odyssey® imaging system; results were normalized to mean HPS6 protein expression in fibroblasts from two normal controls.

Statistical Analysis

Data shown are mean ± standard error of the mean. Student's t-test was used to analyze significance of difference between means (GraphPad Prism, San Diego, CA).

Results:

Phenotypic Features

The patient is a 58-year old Caucasian woman with a long history for excessive bleeding and no known oculocutaneous albinism. Her pigmentation darkens with exposure to sunlight. She reported easy bruising and prolonged epistaxis. She was treated with blood product transfusions for severe menorrhagia, hemorrhage following vaginal delivery requiring admission to an intensive care unit, and prolonged gastrointestinal bleeding with hemodynamic instability after gastric polypectomy via esophagogastroduodenoscopy. She

also experienced intermittent episodes of lower gastrointestinal bleeding of unknown etiology. Colonoscopy showed no evidence of inflammatory bowel disease and incidental findings of 2 small polyps. Polypectomies caused prolonged lower gastrointestinal bleeding. Initially considered to have von Willebrand's disease, the patient's von Willebrand factor antigen was normal, and she was subsequently diagnosed with a platelet storage pool defect.

Family history is notable for consanguinity. The patient's parents are second and third cousins (Figure 1A). One brother had easy bruising; her other relatives, including her child, did not have albinism or excessive bleeding.

Physical examination was notable for light-colored hair, eyes, and skin. Best corrected visual acuity measured 20/25 and 20/40 in the right and left eyes, respectively. Although she did not have nystagmus, she had mild iris transillumination defects, minimal pigmentation of the peripheral retina, and a poorly developed fovea (Figures 1B-C). Optical coherence tomography demonstrated loss of the foveal depression, no outer segment lengthening relative to the parafoveal outer nuclear layer, and no extrusion of the plexifom layers, consistent with grade 3 foveal hypoplasia (Figure 1D)(Thomas, 2011). Cardiovascular, pulmonary, abdominal, and neurological findings were normal. There were no detectable petechiae, ecchymoses, or hematomas.

Laboratory testing revealed normal white blood count, hemoglobin, prothrombin time, partial thromboplastin time, factor VIII activity, and von Willebrand factor activity and antigen. Platelet count was 158×10^3/ul [$173\text{-}369 \times 10^3$/uL]. Platelet function assay showed prolonged closure time in response to epinephrine (>300 sec [86-154 sec]), but not to adenosine diphosphate (70 sec [73-129 sec]). Platelet aggregation responses to collagen, arachidonic acid, adenosine diphosphate, and ristocetin were normal; rate of aggregation and final amplitude to epinephrine were decreased. Whole mount platelet electron microscopy testing showed virtually no delta granules (Figure 1E).

Pulmonary function and six-minute walk test were normal. High-resolution computed tomography scan of the chest showed bibasilar juxta-pleural linear and nodular atelectasis without clear evidence of interstitial lung disease (Figure 1F).

Mutation Identification

Given her findings of mild oculocutaneous albinism and history of excessive bleeding with absent platelet delta granules, the patient was diagnosed with HPS. To determine her HPS subtype, SNP analysis and exome sequencing were performed. Consistent with a history of consanguinity, SNP analysis showed regions of homozygosity, one of which included *HPS1* and *HPS6*. PCR showed normal full length *HPS1* transcript (data not shown). A targeted NGS panel of 9 HPS genes using the patient's genomic DNA identified a homozygous mutation in *HPS6* (NM_024747.5:c.383T>C; p.V128A). This variant is not found in published reports of *HPS6* mutations (Table 1), and it is not reported in the large population genetics databases 1000 Genomes, NHLBI GO Exome Sequencing Project (ESP), or Genome Aggregation Database (gnomAD). Furthermore, this *HPS6* mutation is predicted to be probably damaging by PolyPhen-2 (v2.2.2r398) Hum Var (score 0.921), deleterious by

Sorting Intolerant from Tolerant (SIFT, score: 0.01), and disease causing by MutationTaster (prob value = 0.964).

Cellular Expression of HPS6

To determine whether the patient's mutation is associated with altered HPS6 expression, mRNA and protein levels were measured in her cells. We found that *HPS6* mRNA levels in this patient's dermal fibroblasts were 37% of that in normal cells ($p<0.001$) and 36% of that in HPS-1 BLOC-3 complex controls ($p<0.001$)(Figure 1G). Western blot analysis showed that HPS6 protein expression in the patient's fibroblasts were 60% of that of normal controls ($p<0.001$) and 29% of that of HPS-1 BLOC-3 complex controls ($p=0.008$)(Figure 1H). HPS1 and HPS4 proteins were expressed in this HPS-6 patient's cells; these results are consistent with this patient's defect in BLOC-2, and not BLOC-3.

Discussion

Hermansky-Pudlak syndrome type 6 was diagnosed in a 58-year old woman with a history of severe bleeding and without overt oculocutaneous albinism. Patients with HPS-6 generally have mild hypopigmentation and bleeding compared to patients with other HPS subtypes, and pulmonary fibrosis has not been reported in patients with HPS-6 (Huizing, 2009; O'Brien, 2016). However, this patient's oculocutaneous albinism was atypical, because it was asymptomatic. Indeed, her findings of albinism were only identified by comprehensive ophthalmologic examination. In contrast to her subclinical oculocutaneous albinism, this patient had severe bleeding, including some instances of hemorrhage requiring blood product transfusions and an episode of prolonged gastrointestinal bleeding with hemodynamic instability. HPS-6 was reported in a 32-year old male with hemophilia B who also had excessive bleeding, but the patient's oculocutaneous albinism facilitated a diagnosis of HPS in that case (O'Brien, 2016).

The diagnosis of HPS-6 in our patient is based upon findings of absent platelet delta granules, identification of a homozygous missense variant in *HPS6* predicted to be deleterious, and molecular studies showing reduced *HPS6* expression in the patient's cells. NGS analysis showed a single missense variant in *HPS6* in a highly conserved region of *HPS6*. Consistent with predictive algorithms, *HPS6* mRNA and protein levels are significantly reduced in this patient's cells. It is possible that this patient's subclinical oculocutaneous albinism is a consequence of sufficient, albeit low, amounts of HPS6 protein in pigment-producing cells in her skin, hair and eyes.

Identifying a patient's HPS subtype has clinical relevance. For example, some manifestations of HPS are subtype-specific, including progressive pulmonary fibrosis. Although fibrotic lung disease is a leading cause of death in patients with HPS-1, HPS-2, or HPS-4, patients with HPS-6 have not been reported to develop pulmonary fibrosis (Huizing, 2009; Huizing, 2017; Gochuico, 2012; O'Brien, 2016). This patient's imaging studies revealed no clear evidence of interstitial lung disease, which is consistent with a diagnosis of HPS-6. In addition, establishing a diagnosis of HPS in this patient will also facilitate management of her bleeding diathesis. In general, treatment of bleeding in patients with HPS includes thrombin-soaked gelfoam for skin wounds, intravenous desmopressin for

invasive procedures, and judicious transfusion of platelets to prevent or treat surgical bleeding (Huizing, 2017).

In conclusion, we report a novel homozygous c.383T>C missense variant in *HPS6* associated with low cellular levels of *HPS6* mRNA and protein in an individual with subclinical oculocutaneous albinism and a history of severe bleeding. Genetic testing and platelet electron microscopy studies combined with molecular analysis in some cases are useful modalities to evaluate and diagnose HPS in patients with atypical clinical features.

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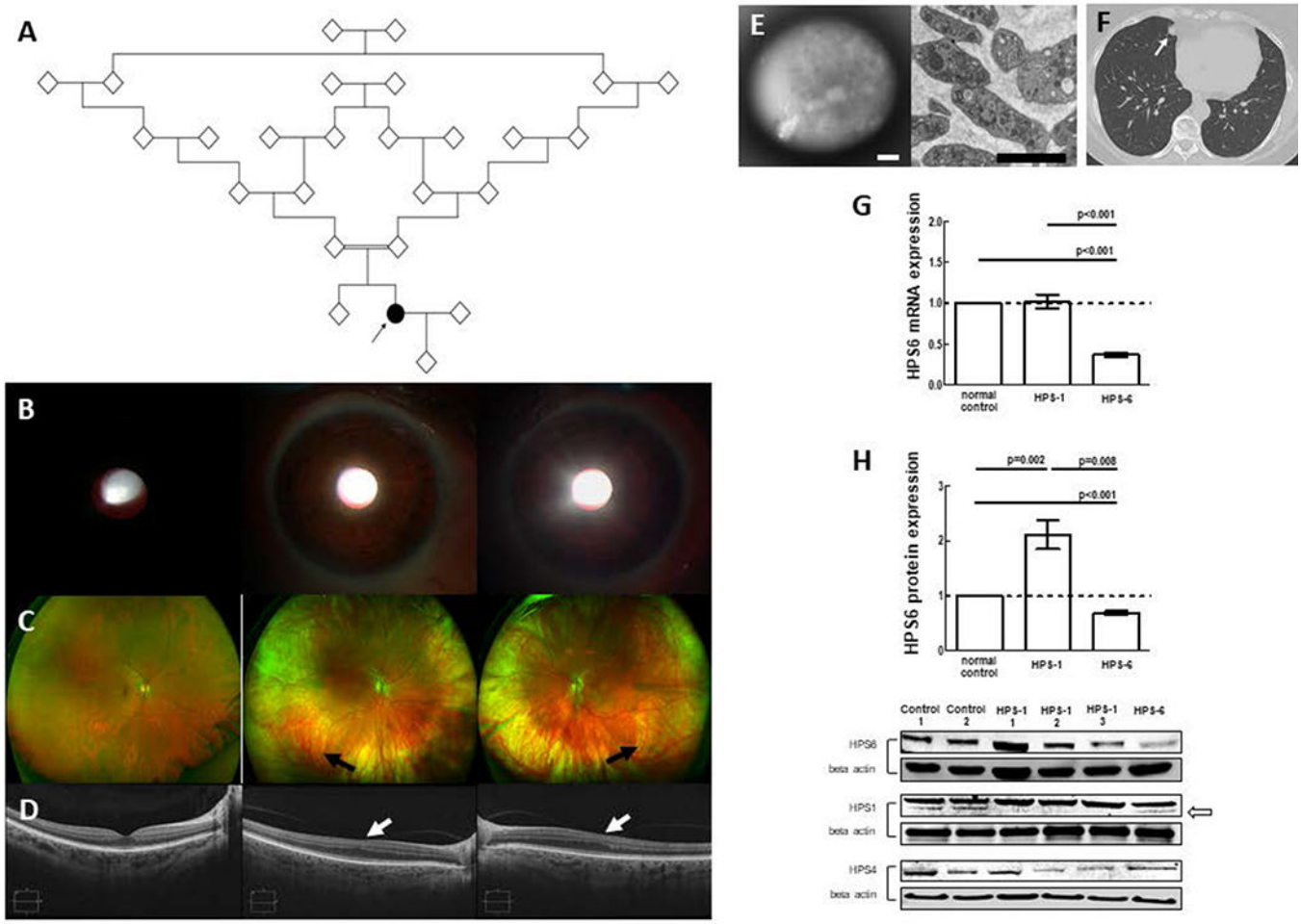

Figure 1.

Clinical and molecular features of patient with Hermansky-Pudlak syndrome type 6. (A) Pedigree shows proband (arrow) with Hermansky-Pudlak syndrome-6 (HPS-6) and consanguinity. (B) Anterior segment photos show absent iris transillumination defects in a normal volunteer (left panel). Mild transillumination defects, seen as dark red scattered across the iris in both the right (middle panel) and left (right panel) eyes were present in this patient with HPS-6. (C) Wide field images of the retina demonstrate normal pigmentation in a healthy volunteer (left panel) in contrast to the minimally pigmented peripheral retina with visible choroidal vasculature (black arrows) due to lack of pigmentation in the patient's right and left eyes (middle and right panels, respectively). (D) Optical coherence tomography shows a normal fovea in the healthy volunteer (left panel), while the patient's fovea shows grade 3 foveal hypoplasia with loss of the foveal depression (white arrow), no outer segment lengthening relative to the parafoveal outer nuclear layer, and no extrusion of the plexifom layers (middle and right panels). (E) Representative platelets from this patient with absent dense granules are shown by whole mount electron microscopy (left panel; size bar = 800 nm) and normal alpha granules by thin-section transmission electron microscopy (right panel; size bar = 2 um). (F) Representative high-resolution computed tomography scan

image of the chest reveals right juxtapleural linear and nodular atelectasis (solid white arrow) without evidence of interstitial lung disease. (G, H) Expression of *HPS6* mRNA and HPS6 protein in this patient's dermal fibroblasts is significantly reduced compared to that in cells from two normal controls or three patients with HPS-1. Western blots for HPS6, HPS1, HPS 4 and beta actin are shown. Open arrow indicates band corresponding to HPS1 protein.

Table 1.

Reported Variants in *HPS6*

Variants	Age, Gender†	Ethnicity/Nationality	Consan‡	Reference(s)
c.383T>C	58, F	Caucasian	Yes	This report
c.1066_1067insG	varied	Israeli Bedouin	Yes	Huizing, 2017; Schreyer-Shafir, 2006
c.1114 C>T	32 y, M	Caucasian	No	O'Brien, 2016
c.238dupG; c.815C>T	13 y, F	German/Dutch	NA	Huizing, 2009
c.223C>T; c.1234C>T	52 y, M	Italian	NA	Huizing, 2009
c.913C>t; del 9,972-bp	22 y, M	Scottish/English/German	NA	Huizing, 2009
c.1865_1866delTG	36 y, F	Irish/German	NA	Huizing, 2009
c.1713_1716delTCTG	39 y, F	Belgian	No	Zhang, 2003
c.87_108ins22	1 y, F	Caucasian	No	Radke, 2013
c.779G>A	1 y, F	Punjabi Afghan	Yes	Hull, 2016
c.902dupT; c.1083dupC	5 mo, M	Punjabi Afghan	Yes	Hull, 2016
c.64_65insGCGGC; c.155del	1 y, M	Chinese	NA	Wei, 2016
c.64_65insGCGGC; c.1513C>T	6 y, M	Chinese	NA	Wei, 2016
c.895C>T; c.1372delG	5 y, M	Chinese	NA	Wei, 2016
c.1898delC	3 y, F	Japanese	No	Miyamichi, 2016
c.2038C>T	11 mo, F	Japanese	No	Miyamichi, 2016
c. 60_64dupGCGGC; c.2038C>T	9 y, F	Japanese	NA	Okamura, 2018

† F, female; M, male; mo, months; y, years

‡ consanguinity; NA, not available