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Hermansky-Pudlak Syndrome: Mutation Update

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Abstract

Hermansky–Pudlak syndrome (HPS) is a group of ten autosomal recessive multisystem disorders, each defined by deficiency of a specific gene. HPS-associated genes encode components of four ubiquitously expressed protein complexes: Adaptor Protein (AP)-3 and Biogenesis of Lysosome-related Organelles Complex (BLOC)-1 through −3. All individuals with HPS exhibit albinism and a bleeding diathesis; additional features occur depending on the defective protein complex. Pulmonary fibrosis is associated with AP-3 and BLOC-3 deficiency, immunodeficiency with AP-3 defects, and gastrointestinal symptoms are more prevalent and severe in BLOC-3 deficiency. Therefore, identification of the HPS subtype is valuable for prognosis, clinical management and treatment options. The prevalence of HPS is estimated at 1–9 per 1,000,000. Here we summarize 264 reported and novel variants in ten HPS genes and estimate that ~333 Puerto Rican HPS subjects and ~385 with other ethnicities are reported to date. We provide pathogenicity predictions for missense and splice site variants and list variants with high minor allele frequencies (MAF). Current cellular and clinical aspects of HPS are also summarized. This review can serve as a manifest for molecular diagnostic and genetic counseling aspects of Hermansky-Pudlak syndrome.

Keywords

albinism; biogenesis of lysosome-related organelles; bleeding diathesis; granulomatous colitis; hypopigmentation; pulmonary fibrosis

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INTRODUCTION

In 1959, two Czechoslovakian clinicians, Frantisek Hermansky and Paulus Pudlak, described what is now called Hermansky-Pudlak syndrome (HPS) in two unrelated individuals with a bleeding disorder associated with oculocutaneous albinism (Hermansky & Pudlak, 1959). Over the last six decades, the syndrome has expanded to a disorder with 10 distinct genetic causes, with over 715 cases reported worldwide and a vastly improved understanding of clinical symptoms, pathomechanism and therapeutic approaches (Bowman, Bi-Karchin, Le, & Marks, 2019; Gahl et al., 1998; Huizing, Helip-Wooley, Westbroek, Gunay-Aygun, & Gahl, 2008; Huizing, Malicdan, Gochuico, & Gahl, 2017 Oct 26 [Updated 2000 July 24]).

HPS (MIM# 203300) is a genetically heterogeneous autosomal recessive multisystem disorder characterized by oculocutaneous albinism, a bleeding diathesis, and, in some cases, granulomatous colitis, neutropenia, or a fatal pulmonary fibrosis (Gahl et al., 1998; Huizing et al., 2008; Huizing et al, 2017 Oct 26 [Updated 2000 July 24]). These features result from defects in lysosome-related organelles (LROs), such as melanosomes in melanocytes and delta granules in platelets (Bowman et al., 2019; Dell'Angelica, 2004; Marks, Heijnen, & Raposo, 2013; Raposo, Marks, & Cutler, 2007). The ten described human HPS subtypes (HPS-1 through HPS-10), are each associated with a specific gene defect (Table 1). Orthologs of these ten genes also cause HPS in mice and other animal models (Table 1) (Huizing et al., 2008; Li et al., 2004).

HPS is a rare disorder with an estimated worldwide prevalence of 1–9 per 1,000,000 individuals (Christensen, Wagner, Coleman, & Appell, 2017; Huizing et al, 2017 Oct 26 [Updated 2000 July 24]). However, the prevalence per subtype can differ due to founder mutations. HPS-1 is more common in Puerto Rico, particularly in the northwestern part of the island where about 1 in 1,800 people are affected and carry the same homozygous mutation (Witkop, Almadovar, Pineiro, & Nunez Babcock, 1990). HPS-1 has also been reported in a small isolate in a Swiss village (Oh et al., 1998; Schallreuter, Frenk, Wolfe, Witkop, & Wood, 1993) and one in Japan (S. Ito et al., 2005). HPS-3 is common in central Puerto Rico, where about 1 in 4,000 individuals are affected (Anikster et al., 2001; Santiago Borrero et al., 2006). Individuals with HPS have been described in many other regions, including China, India, South America and Western Europe (Arcot Sadagopan et al., 2017; Carmona-Rivera et al., 2011; Hermos, Huizing, Kaiser-Kupfer, & Gahl, 2002; Wei et al., 2016).

The protein products of the HPS genes assemble in four multi-subunit complexes, each involved in distinct steps of membrane trafficking and/or component sorting required for LRO biogenesis (Table 1) (Bowman et al., 2019; Dell'Angelica, 2004; Huizing et al., 2008). The adaptor protein-3 (AP-3) complex consist of 4 subunits and includes the protein products of *AP3B1*, which is mutated in HPS-2 (Dell'Angelica, Shotelersuk, Aguilar, Gahl, & Bonifacino, 1999), and *AP3D1*, mutated in HPS-10 (Ammann et al., 2016). Biogenesis of Lysosome-related Organelles Complex (BLOC)-3 consists of the HPS1 and HPS4 proteins (Martina, Moriyama, & Bonifacino, 2003), defective in disease subtypes HPS-1 and HPS-4, respectively (Oh et al., 1998; Suzuki et al., 2002). BLOC-2 consists of HPS3, HPS5 and

HPS6 (Di Pietro, Falcon-Perez, & Dell'Angelica, 2004), whose defects cause subtypes HPS-3, HPS-5 and HPS-6 (Anikster et al., 2001; Huizing et al., 2001; Q. Zhang et al., 2003). BLOC-1 consists of 8 subunits (Falcon-Perez, Starcevic, Gautam, & Dell'Angelica, 2002; Starcevic & Dell'Angelica, 2004), including DTNBP1, BLOC1S3, and PLDN, defective in HPS-7, HPS-8 and HPS-9, respectively (Badolato et al., 2012; Li et al., 2003; Morgan et al., 2006). No defects in humans are reported in the other five BLOC-1 or two AP-3 subunits, but some are defective in HPS-like animal models (Table 1) (Bowman et al., 2019); suggesting that these subunits are candidates for additional human HPS subtypes. Of note, BLOC-1 shares 3 subunits (BLOC1S1, BLOC1S2 and SNAPIN) with a BLOC-1 related complex (BORC) (Table 1), which has a distinct function and is likely necessary for life (Pu et al., 2015). Defects in either one of these 3 subunits are lethal or very deleterious in mice and are unlikely to be identified in individuals with HPS.

The HPS clinical spectrum is similar in subjects with defects in genes encoding different subunits of the same AP-3 or BLOC complex. Therefore, HPS clinical features and cell biology are best understood in the context of BLOC-1, BLOC-2, BLOC-3 or AP-3 disease rather than in the context of each individual gene product (Bowman et al., 2019; Huizing et al., 2008).

Identification of the HPS subtype in each subject is important for several reasons. First, it is clinically valuable for prognosis, clinical management, and consideration of eventual treatment options (Table 2). For example, the fatal pulmonary fibrosis occurs in BLOC-3 and AP-3 deficiency, immunodeficiency is associated with AP-3 defects, while BLOC-2 deficiency results in a relatively milder phenotype without life-threatening features. Second, cell biologists can utilize the association of specific HPS defects in cells and tissues from HPS patients, mice and other animal models to study and understand LRO biology. Third, understanding LRO biology provides insights into the pathomechanism of each HPS subtype that may lead to prospects for development of novel therapies not only for HPS, but also for other LRO disorders.

In this report, we provide an overview of the HPS-related genes, their functions and clinical consequences when deficient. We summarize reported human variants in each HPS-associated gene and list unreported variants identified in an HPS patient cohort evaluated at the National Institutes of Health (NIH). This review can serve as a reference for molecular diagnostic aspects of Hermansky-Pudlak syndrome.

HPS SUBTYPE-SPECIFIC MUTATION UPDATE

We searched online literature databases for reported pathogenic variants in 10 HPS-related human genes (as of November 2019). We also list unreported pathogenic gene variants identified in our NIH HPS patient cohort, enrolled in a protocol entitled, "Clinical and Basic Investigations into Hermansky-Pudlak Syndrome" (ClinicalTrials.gov Identifier NTC00001456). Table 1 provides an overview of the HPS subtypes, features of each gene and protein, numbers of reported pathogenic variants, an estimate of reported subjects and reported vertebrate models per subtype. Table 2 lists subtype-specific features, LRO defects, and therapeutic options. Tables 3–8 and Figures 1–7 provide HPS gene-specific pathogenic

mRNA and protein variants. Footnotes under each Table describe additional variant-specific information. Pathogenicity predictions of missense and splice site variants are listed in Supp. Tables S1 and S2. Supp. Table S3 lists frequently occurring (mostly missense) variants with a high minor allele frequency (MAF > 0.001) that should be considered as possible polymorphisms when encountered in HPS genetic analyses. Supp. Table S4 lists reported variants in human HPS genes associated with traits other than HPS, which should be considered when these variants are found in future HPS cases.

The variant nomenclature in all Tables conforms to human genome variation society (HGVS) recommendations (den Dunnen et al., 2016). The longest mRNA splice variant of each gene is used for variant nomenclature and the GenBank accession number is indicated in each Table. Some previously reported variants are re-named to conform to the current nomenclature convention. Pathogenicity predictions of missense variants (Supp. Table S1) follow the American College of Medical Genetics (ACMG) Standards and Guidelines for interpretation of sequence variants (Richards et al., 2015).

We deposited all unreported variants in the Leiden Open Variation Database 3.0 (http://www.lovd.nl/) (Fokkema et al., 2011) and in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) (Landrum et al., 2018). Other databases with variable HPS-related information exist, including the Albinism Database (http://www.ifpcs.org/albinism/), AP3B1base (http://structure.bmc.lu.se/idbase/AP3B1base/), Retina International Mutation Database (http://www.retina-international.org/sci-news/databases/mutation-database) and Oculocutaneous albinism Database (https://ghr.nlm.nih.gov/condition/oculocutaneous-albinism).

HPS-1 *(Table 3)*

HPS1, also called *BLOC3S1*, is the first identified HPS-associated gene (Oh et al., 1996), causing HPS Type 1 (HPS-1; MIM# 203300) when defective. *HPS1* is located on chromosome 10q24.2; its longest mRNA transcript contains 20 exons and codes for a 700-amino acids protein (~79.3-kD). At least 18 *HPS1* protein-coding mRNA transcript variants are predicted; expression patterns and function of these variants remain unknown. The HPS1 protein interacts with HPS4 in the BLOC-3 complex (Carmona-Rivera, Simeonov, Cardillo, Gahl, & Cadilla, 2013; Martina et al., 2003). *Pale ear* is the murine orthologue of human HPS-1 (Li et al., 2004).

Identification of the *HPS1* gene was aided by linkage analysis in northwest Puerto Rican individuals with HPS, who have a homozygous 16-bp duplication (c.1472_1487dup16-bp, p. p.His497Glnfs*90) in *HPS1* (Fukai, Oh, Frenk, Almodovar, & Spritz, 1995; Oh et al., 1996). There are currently ~261 Puerto Rican subjects with the *HPS1* 16-bp duplication founder variant reported in the literature (including the NIH cohort); it is estimated that ~400 such cases exist (Santiago Borrero et al., 2006; Witkop et al., 1990). HPS-1 has also been reported in a small isolate in a Swiss village (c.972dupC, p.Met325Hisfs*128) (Oh et al., 1998; Schallreuter et al., 1993) and one in Japan (c.398+5G>A) (Ito et al., 2005). Apart from the Puerto Rican founder population, there are an additional ~137 HPS-1 cases reported, plus 11 unreported cases from our NIH cohort (Table 1).

We report a total of 76 *HPS1* variants associated with the HPS-1 phenotype (Table 3), including 5 novel variants identified in our NIH HPS cohort. The variants are located throughout the entire gene and include 1 (1%) start-loss, 20 (26%) frameshift, 15 (20%) missense, 11 (14.5%) nonsense, 18 (24%) insertions and/or deletions, and 11 (14.5%) splice site variants (Figure 1). All reported *HPS1* splice site variants are predicted and/or reported to cause aberrant splicing (Supp. Table S2). Of the 15 reported *HPS1* missense variants, 5 occur at an intron/exon boundary and 3 are predicted and/or reported to affect splicing (Supp. Table S2). Of note, one nonsynonymous (silent) variant, p.Glu169Glu (c.507G>A), was reported to result in a splicing defect in two African-American brothers (Merideth et al., 2009). The start-loss variant p.Met1Lys (c.2T>A) likely leads to a loss of protein translation at the start codon of the longest splice variant of HPS1 (NM_000195.5), it is also predicted to affect splicing, as it is located at the exon 2–3 splice site (Supp. Table S2). The MAFs of all *HPS1* pathogenic missense variants are very low or not reported, supporting possible pathogenicity (Supp. Table S1). Pathogenicity of some *HPS1* missense variants was experimentally assessed (Supp. Table S1). Of the 15 reported *HPS1* missense variants, 7 were predicted to be pathogenic (P) or likely pathogenic (LP) by ACMG standards and guidelines (Richards et al., 2015) (Supp. Table S1), while 8 others were classified as variants of uncertain significance (VUS), which should be taken into account when these variants are found in future HPS cases.

Four *HPS1* variants (c.1286G>A, p.Arg429His; c.1395G>A, p.Trp465*; c.1888G>A, p.Val630Ile; c.1915G>A, p.Gly639Ser) listed in Supp. Table S4 were found heterozygous in nextgen sequencing studies of probands with other traits than HPS (Stearman et al., 2019; Abouelhoda et al., 2016). Although none of these variants were reported in HPS subjects, they should be taken into account when these variants are found in future HPS cases.

The dbSNP/gnomAd/ClinVar databases list 10 frequently occurring (MAF > 0.001) *HPS1* missense variants, with predicted benign or unknown pathogenicity, which should be considered as likely non-pathogenic polymorphisms when encountered in *HPS1* genetic analyses (Supp. Table S3).

There are 3 *HPS1* frameshift variants that occur with high prevalence in HPS-1 subjects of various ethnic backgrounds and have relatively high MAFs; they are c.972dupC, p.Met325Hisfs*128 (ClinVar MAF 0.000317; frequent in Europeans) and c.972delC, p.Met325Trpfs*6 (ClinVar MAF 0.00002; frequent in Europeans and South Asians) in exon 11 and c.1189delC, p.Gln397Serfs*2 (ClinVar MAF 0.000067; frequent in Europeans) in exon 13. In fact, in our NIH cohort of non-Puerto Rican HPS-1 cases, 19 (39%) of 49 cases carry at least one of these two variants. Hence, analyses of exon 11 and exon 13 of *HPS1* could be considered before proceeding to more laborious and costly sequencing techniques in non-Puerto Rican individuals suspected of having HPS-1 disease.

HPS-1 is identified worldwide in individuals with a large spectrum of ethnic backgrounds and is the HPS subtype with the most described cases, even excluding Puerto Rican cases (Table 1). HPS-1 (together with HPS-4) displays the most severe phenotype. In individuals with HPS-1, cutaneous albinism is more profound (higher degree of hypopigmentation of skin and hair) and the ocular findings are more severe than in other subtypes (Huizing et al,

2017 Oct 26 [Updated 2000 July 24]). Of note, Hps1 (and Hps4) variants in mice appear to only have a mild effect on pigmentation and bleeding (Novak, Hui, & Swank, 1984), for unknown reasons. In mice, Hps1 variants appear to impact pigmentation tissue-specific; melanosomes in hair follicles are less affected (i.e. pigmented hair) than in interfollicular melanocytes (i.e. less pigmented skin), perhaps partially explaining the more severe skin pigmentation phenotype in human patients (Nguyen & Wei, 2007). Virtually all HPS-1 subjects develop pulmonary fibrosis by middle age, some develop granulomatous colitis and a majority of female subjects have menorrhagia (Table 2).

HPS-2 *(Table 4)*

HPS-2 (MIM# 608233) is caused by biallelic pathogenic variants in *AP3B1*, located on chromosome 5q14.1, and encoding the β3A subunit of AP3 (Dell'Angelica et al., 1999). The longest *AP3B1* mRNA transcript contains 27 exons and is translated into the 1094-amino acid protein AP3B1 (AP-3 β3A; ~121-kD). Two *AP3B1* protein-coding mRNA transcripts are predicted, varying at the N-terminus, with unexplored expression and functional significance. Vertebrate models of HPS-2 include the *pearl* and $Ap3b1^{LN}$ mice (Yang et al., 2000; Li et al., 2004). With the recognition that HPS-2 is caused by deficiency of AP-3, HPS became an informative disorder for intracellular vesicle/membrane formation and trafficking (Dell'Angelica et al., 1999). HPS cells and models have since been used extensively for LRO-related cell biology (Huizing et al., 2008).

There are currently ~35 reported HPS-2 cases of various ethnic backgrounds, including Caucasian, Chinese, Lebanese and Mexican. A total of 29 *AP3B1* pathogenic variants associated with HPS-2 have been described (Table 4); they are located throughout the gene, including 1 (3%) start-loss, 7 (24%) frameshift, 3 (10.5%) missense, 6 (21%) nonsense, 9 (31%) insertions and/or deletions (including a chromosomal inversion), and 3 (10.5%) splice site variants (Figure 2). There are no known frequently occurring pathogenic variants in *AP3B1*, nor any apparent founder mutations. All 3 reported *AP3B1* splice site variants are predicted and/or reported to cause aberrant splicing (Supp. Table S2). Of the 3 reported pathogenic missense variants, two are likely pathogenic (p.Leu580Arg, p.Ser901Cys), and one is a VUS (p.Leu102Pro).

Next generation sequencing of different cohorts of subjects with primary immunodeficiency or hemophagocytic lymphohistiocytosis (HLH) reported least 8 *AP3B1* variants (Supp. Table S4) in a heterozygous state with or without a variant in another (synergistic) gene. These findings suggest that heterozygous *AP3B1* variants may contribute to an immunologic phenotype (Chi et al., 2018; Gallo et al., 2016; Gao, Zhu, Huang, & Zhou, 2015; Miao et al., 2019; Mukda et al., 2017; Tesi et al., 2015; Xu et al., 2017). These variants have not been reported in HPS subjects but were included in this report because they may cause HPS when occurring in a homozygous or compound heterozygous state.

The dbSNP/gnomAd/ClinVar databases list 7 frequently occurring (MAF > 0.001) *AP3B1* missense variants and two in-frame 3-bp deletions, with predicted benign or unknown pathogenicity, which should be considered as likely non-pathogenic polymorphisms when encountered in *AP3B1* genetic analyses (Supp. Table S3).

Apart from the hypopigmentation and bleeding diathesis of HPS-2, affected individuals are also at risk for developing interstitial lung disease and pulmonary fibrosis in childhood (Gochuico et al., 2012; Hengst et al., 2018); in addition, immunodeficiency associated with neutropenia is the most prevalent clinical feature (Fontana et al., 2006). The immunodeficiency, an impairment of cytotoxic activity, results from T-lymphocyte and/or natural killer cell dysfunction and can present with variable features, from mild recurrent bacterial and viral infections to severe hemophagocytic lymphohistiocytosis (HLH) (Gil-Krzewska et al., 2017; Jessen et al., 2013). These features led to discovery of involvement of AP-3 in different trafficking processes. AP-3 is involved in neutrophil formation (Badolato & Parolini, 2007; Massullo et al., 2005); AP-3 deficient cells mislocalize the neutrophil granule proteins myeloperoxidase and elastase and the lysosomal membrane protein CD63 (de Boer et al., 2017; Di Pietro et al., 2006; Jung et al., 2006; Meng et al., 2010). The AP-3 immunodeficiency also involves defective AP-3 mediated lytic granule exocytosis in natural killer (NK)-cells and cytotoxic T-cells (Clark et al., 2003; Fontana et al., 2006; Gil-Krzewska et al., 2017; Jung et al., 2006). AP-3 deficient dendritic cells showed impaired toll-like receptor recruitment (Mantegazza et al., 2012; Sasai, Linehan, & Iwasaki, 2010), leading to defects in interferon production and antigen presentation in these cells from HPS-2 subjects (Prandini et al., 2016). AP-3-dependent inflammasome positioning and activation was shown in dendritic cells from HPS-2 mice (Mantegazza et al., 2017).

Remarkably, genetic testing in all reported HPS-2 subjects was performed by *AP3B1* gene-specific Sanger sequencing. Individuals with HPS-2 that present to an immunologist with (severe) immunodeficiency may escape diagnosis due to emphasis on their immunodeficiency, other mild manifestations (e.g., hypopigmentation, ocular findings, bleeding diathesis) may be overlooked, there may be unfamiliarity with HPS-2, and costs and lack of availability of *AP3B1* genetic testing may provide obstacles to diagnosis. However, the recent significant number of heterozygous *AP3B1* variants identified by next-generation sequencing in cohorts with immunodeficiency disorders (Chi et al., 2018; Gallo et al., 2016; Gao et al., 2015; Miao et al., 2019; Mukda et al., 2017; Tesi et al., 2015; Xu et al., 2017) emphasizes the importance of including *AP3B1* in immunodeficiency-related gene panels and may result in the diagnosis of additional HPS-2 cases.

HPS-3 *(Table 5)*

HPS-3 (MIM# 614072) is caused by biallelic pathogenic variants in *HPS3*, also called *BLOC2S1*, located on chromosome 3q24. The longest *HPS3* mRNA transcript contains 17 exons, encoding a 1004-amino acid protein (~113.7-kD). Two *HPS3* protein-coding mRNA variants are predicted, but their expression and functional significance remain unexplored. The HPS3 protein interacts with the HPS5 and HPS6 proteins in BLOC-2 (Di Pietro et al., 2004). The mouse model *cocoa* is the murine orthologue of human HPS-3 (Suzuki et al., 2001).

The *HPS3* gene was identified through homozygosity mapping in a genetic isolate of HPS originating in central Puerto Rico. These individuals are homozygous for a 3.9-kb deletion in *HPS3* (NM_032383.5:c.−2993_217+692del or NG_009847.1:g.2131_6049del), detectable with a multiplex PCR amplification assay (Anikster et al., 2001). There are ~63

reported cases homozygous for this deletion (Anikster et al., 2001; Santiago Borrero et al., 2006), and there are an additional 9 such unreported subjects in our NIH cohort. One in 14,000 individuals of central Puerto Rican descent are estimated to be homozygous for this deletion. The carrier frequency in central Puerto-Rico is ~1:32 (Santiago Borrero et al., 2006) and 1:85 in all of Puerto Rico (Torres-Serrant, Ramirez, Cadilla, Ramos-Valencia, & Santiago-Borrero, 2010).

We report 42 non-Puerto Rican HPS-3 subjects, including those described with an Ashkenazi-Jewish founder variant (c.1691+2T>G; 7 cases) (Huizing et al., 2001) and including 9 novel cases from our NIH cohort (Table 5). Apart from central Puerto Rican and Ashkenazi-Jewish cases, HPS-3 subjects with a variety of other ethnic backgrounds are reported, including Arabic, Chinese, northern and southern European, and Pakistani.

We report 37 *HPS3* pathogenic variants, including 11 novel variants from our NIH cohort (Table 5). These pathogenic variants are found throughout the gene and include 7 (19%) frameshift, 3 (8 %) missense, 8 (22%) nonsense, 10 (27 %) insertions and/or deletions, and 9 (24%) splice site variants (Figure 3). All *HPS3* splice site variants are predicted and/or experimentally demonstrated to cause aberrant splicing (Supp. Table S2). One intronic variant, c.2888–1612G>A (originally reported as c.2887+2500G>A) introduces a new consensus splice site, resulting in cryptic exon activation and insertion of a 89-bp pseudo-exon in the cDNA, leading to a frameshift and premature protein termination (p.Glu963Alafs*24) (Huizing et al., 2001; Vorechovsky, 2010). All 3 reported *HPS3* missense variants have a low MAF, one (c.1189C>T, p.Arg397Trp) is predicted likely pathogenic and the other two are predicted VUS (Supp. Table S1).

Next generation sequencing of a cohort of individuals with schizophrenia identified a *de novo HPS3* missense variant c.796G>A (p.Glu266Lys) in one proband, suggesting an association of this variant with the schizophrenia phenotype (Fromer et al., 2014) (Supp. Table S4).

This rare and benign variant has not been reported in HPS subjects. In fact, no other variants in any BLOC-2 subunit (HPS3, HPS5, HPS6) have been reported to be associated with a neuronal phenotype in individuals with or without HPS or in animal models. The dbSNP/gnomAd/ClinVar databases list 5 frequently occurring (MAF > 0.001) *HPS3* missense variants (Supp. Table S3), with predicted benign or unknown pathogenicity, that should be considered as likely non-pathogenic polymorphisms when encountered in *HPS3* genetic analysis.

Subjects with HPS-3 have relatively mild clinical features, including minor hypopigmentation of the hair, skin, and retina. Visual acuity is often only slightly affected, and bleeding tendency is also mild, although some female subjects have significant menorrhagia. Some subjects only appear hypopigmented when compared to their siblings or other family members. Of note, pigmentation and bleeding are also only mildly affected in BLOC-2 (HPS3, HPS5, HPS6) mouse models (Novak et al., 1984). In addition, the bleeding diathesis in BLOC-2-deficient individuals might be exacerbated by disruption not only of

platelet dense granules but also of altered maturation of Weibel-Palade bodies in endothelial cells, which are involved in release of von Willebrand factor (Ma et al., 2016).

Pulmonary fibrosis or immunodeficiency has not been reported in HPS-3 (nor in any other BLOC-2 deficient) subjects, and some BLOC-2 deficient individuals develop granulomatous colitis. The diagnosis of HPS-3 may be elusive in some patients due to the mildness of their symptoms.

HPS-4 *(Table 6)*

HPS-4 (MIM# 614073) is caused by biallelic pathogenic variants in *HPS4,* also called *BLOC3S2*, located on chromosome 22q12.1. The longest *HPS4* mRNA transcript contains 14 exons, encoding a 708-amino acid protein (~76.9-kD). This major transcript variant is expressed in all tissues tested. A second major mRNA variant contains 12 exons, is alternatively spliced in the 5' region and is expressed in limited tissues; its function remains unexplored (Anderson, Huizing, Claassen, White, & Gahl, 2003). There are at least 9 additional predicted *HPS4* protein-coding mRNA transcripts. The HPS4 protein interacts with the HPS1 protein in BLOC-3 (Carmona-Rivera et al., 2013; Martina et al., 2003).

Identification of the human *HPS4* gene was initiated based upon *Hps4* mutations in the *light ear* HPS mouse model (Suzuki et al., 2002). Subsequent genetic screening of the human orthologue gene, *HPS4,* in unclassified HPS subjects identified 7 cases with pathogenic variants (Suzuki et al., 2002). There are currently 37 HPS-4 subjects reported and there are 4 unreported subjects in our NIH cohort. HPS-4 is identified in various populations, including Ashkenazi-Jewish, Chinese, European, Indian, Japanese, Pakistani, Sri Lankan, and Uruguayan (Table 6). We report 34 *HPS4* pathogenic variants, including 4 novel variants from our NIH cohort (Table 6). These variants are located throughout the *HPS4* gene, with c.2089_2093dupAAGCA (p.Lys699Serfs*5) occurring frequently in individuals of European descent (Anderson et al., 2003; Suzuki et al., 2002). The *HPS4* variants include 5 (12 %) frameshift, 5 (14.5%) missense, 16 (47%) nonsense, 4 (12 %) insertions and/or deletions, and 5 (14.5%) splice site variants (Figure 4). The 4 reported *HPS4* splice site variants are all predicted to cause aberrant splicing (Supp. Table S2). Of the 5 reported missense variants, one is likely pathogenic (p.His154Arg) and the other 3 are classified as VUS; one of these occurs at a splice site junction and is predicted (but not demonstrated) to cause aberrant splicing (c.803G>A; p.Arg268Lys) (Supp. Table S1). No additional experimental evidence for pathogenicity is available for these missense variants.

Next generation sequencing of cohorts with non-HPS pulmonary fibrosis identified a heterozygous *HPS4* frameshift variant (c.1102dupG, p.Asp368Glyfs*4) in a subject with sporadic pulmonary fibrosis (Deng et al., 2018) and a heterozygous *HPS4* indel variant (c.1966_1967dupAC, p.Ala657Argfs*46) and a missense variant (c.1396C>T, p.Arg466Cys) in subjects with familial pulmonary fibrosis (Stearman et al., 2019). None of these variants has been reported in HPS subjects but are included in Supp. Table S4 since they may cause HPS when occurring in the homozygous or compound heterozygous state.

The dbSNP/gnomAd/ClinVar databases list 12 frequently occurring (MAF > 0.001) *HPS4* missense variants, with predicted benign or unknown pathogenicity (Supp. Table S3); these

should be considered as likely non-pathogenic polymorphisms when encountered in *HPS4* genetic analysis.

Individuals with HPS-4 have a phenotype similar to that of HPS-1 subjects, including more profound cutaneous and ocular hypopigmentation than in other HPS subtypes, development of pulmonary fibrosis (at middle age) in virtually all subjects, menorrhagia in most female subjects, and occurrence of granulomatous colitis in some subjects (Anderson et al., 2003; Huizing et al., 2008). HPS-4 should be considered in individuals where HPS-1 was suspected based on clinical symptoms (without genetic confirmation). Of note, the HPS4 missense variant p.His154Arg (c.461A>G) was found homozygous in two Japanese siblings with HPS and mental disorder (schizophrenia and major depression). It was suggested that *HPS4* gene single nucleotide polymorphisms variants may be associated with susceptibility to schizophrenia (A. Saito et al., 2013) and/or cognitive function (Kuratomi et al., 2013). However, there are no reports of other HPS-related BLOC-3 (HPS1 and HPS4) variants in individuals with HPS to be associated with neurological phenotypes.

HPS-5 *(Table 7)*

HPS-5 (MIM# 614074) is caused by biallelic pathogenic variants in *HPS5,* also called *BLOC2S2*, located on chromosome 11p15.1. The longest *HPS5* mRNA transcript contains 23 exons, encoding a 1129-amino acid protein (~127.4-kD). There are 3 *HPS5* protein-coding mRNA variants described, each with alternatively spliced 5' exons (Huizing et al., 2004). The HPS5 protein interacts with HPS3 and HPS6 proteins in BLOC-2 (Di Pietro et al., 2004). Vertebrate models of HPS-5 include the *ruby-eye-2* mouse (Zhang et al., 2003), the *snow white* zebrafish (Daly, Willer, Gregg, & Gross, 2013), and the *casper* stickleback (Hart & Miller, 2017) (Table 1).

The *HPS5* gene was discovered after *Hps5* deficiency was identified in the *ruby-eye-2* HPS murine model; subsequent sequencing of the human orthologue in unclassified HPS individuals identified one subject with a homozygous 4 base-pair deletion in *HPS5* (Zhang et al., 2003). There are now ~29 HPS-5 subjects described worldwide of variable ethnic origins, including Arabic, Chinese, European, Mexican, South-American, and Turkish.

We report 31 *HPS5* pathogenic variants (Table 7), including 6 (19%) frameshift, 6 (19%) missense, 4 (13%) nonsense, 11 (36%) insertions and/or deletions, and 4 (13%) splice site variants (Figure 5). The variants are located throughout the *HPS5* gene, without an apparent frequently occurring variant. One *HPS5* splice variant (c.1634+1G>A) results in skipping of exon 13 (Carmona-Rivera, et al., 2011), another (c.285–10A>G) activates a cryptic splice site leading to an in-frame insertion of 9-bp and reduced HPS5 protein expression (Stephen et al., 2017), and a third variant (c.3058+3A>G) is predicted to cause a splicing defect (Supp. Table S2). A silent *HPS5* variant (c.219G>A, p.Arg73Arg; not listed in dbSNP/gnomAd/ClinVar) occurs at the exon 3/intron 3 splice junction and is predicted to weaken the consensus splice site significantly, causing a splice defect (Supp. Tables S1, S2) (Michaud et al., 2017). An additional 6 *HPS5* missense variants are reported, three of which are predicted as likely pathogenic (p.Gly145Glu, p.Arg240Pro, p.Leu624Arg) and three as VUS (p.Leu740Ser, p.Leu745Ser, p.Met1116Val) (Supp. Table S1). Of note, two siblings of Swiss origin were reported homozygous for 2 missense *HPS5* variants, p.Leu624Arg (c.

c.1871T>G) and p.Thr1098Ile (c.3293C>T), and hemizygosity was excluded (Huizing et al., 2004); no pathogenicity predictions were reported at that time. The p.Thr1098Ile variant is a SNP (rs61884288) with a high MAF (0.02362) and low pathogenicity prediction (Supp.l Tables S1, S2, S3). Therefore, this variant should be considered a benign SNP. In contrast, p.Leu624Arg (rs281865102) has no reported allele frequency and is predicted likely pathogenic (Supp. Tables S1); this variant was recently identified in trans with a pathogenic variant in other HPS-5 individuals (Michaud et al., 2017). Therefore, p.Leu624Arg should be considered a pathogenic variant that likely caused the phenotype in the two reported Swiss siblings (Huizing et al., 2004).

There are 10 nonsynonymous *HPS5* variants listed in dbSNP with a high ClinVar MAF (>0.001) and low pathogenicity scores (Supp. Table S3). These variants are likely benign SNPs with a small effect on protein function.

Like other BLOC-2 deficient individuals, HPS-5 subjects exhibit a relatively mild phenotype of hypopigmentation and bleeding diathesis. Pulmonary fibrosis or immunodeficiency has not been reported in HPS-5 subjects, and granulomatous colitis occurs some BLOC-2 deficient subjects. The fact that individuals with BLOC-2 deficiency can escape diagnosis or go undiagnosed for decades was illustrated by new diagnoses of HPS-5 in a 92-year-old man, the oldest reported individual with HPS, who had light skin and hair, nystagmus, decreasing visual acuity with age, and a life-long bleeding history (Ringeisen, Schimmenti, White, Schoonveld, & Summers, 2013), and in a 65 year-old man with oculocutaneous albinism and a mild bleeding diathesis (Botero et al., 2018).

HPS-6 *(Table 8)*

HPS-6 (MIM# 614075) is caused by biallelic pathogenic variants in *HPS6,* also called *BLOC2S3*, on chromosome 10q24.32. *HPS6* is a one-exon gene, with one mRNA transcript, encoding a 775-amino acid protein (~83.0-kD). HPS6 protein interacts with the HPS3 and HPS5 proteins in BLOC-2 (Di Pietro et al., 2004). Vertebrate models of HPS-6 include the *ruby-eye* mouse (Zhang et al., 2003) and the *no privacy* frog (Nakayama et al., 2016).

The *HPS6* gene was discovered by finding *Hps6* mutated in the *ruby-eye* HPS mouse model, and subsequent sequencing of unclassified HPS cases identified one individual with a homozygous 4-bp deletion in *HPS6* (Zhang et al., 2003). An extended Israeli Muslim Bedouin family had ~ 20 affected individuals homozygous for c.1065insG in *HPS6* was reported (Schreyer-Shafir et al., 2006). Another ~45 subjects with *HPS6* variants are reported, and there is one unreported case in our NIH cohort; they are from various ethnic backgrounds, including Arabic, Afghan, Caucasian, Chinese, Japanese and Pakistani (Table 8). The *HPS6* variant c.2038C>T (p.Gln680*), is reported in ClinVar/gnomAD/dbSNP (rs1131692333) with a very low MAF (0.00001), occurs in 5 Japanese subjects (including 2 sisters) and appears to be a frequent Japanese variant. We report 45 pathogenic *HPS6* variants associated with the HPS-6 phenotype (Table 8), including 2 novel variants identified in our NIH HPS cohort. The variants are located throughout the entire coding exon and include 9 (20%) frameshift, 11 (24.5%) missense, 11 (24.5%) nonsense, 14 (31%) insertions and/or deletions, and no splice site variants (Figure 6). Three of 11 reported *HPS6* missense variants are predicted to be likely pathogenic; all others are classified as VUS and require

experimental pathogenicity evidence and/or familial genetic testing to increase pathogenicity predictions (Supp. Table S1).

Next generation sequencing of a cohort of *BRCA1* and *BRCA2*-negative subjects with breast cancer identified a heterozygous *HPS6* stop-loss variant (c.2326T>C, p.*776Arg) in one subject, who also carried heterozygous protein damaging variants in two other genes (Shahi et al., 2019). This variant has not been reported in HPS subjects but is included in Supp. Table S4 because it may cause HPS when occurring in a homozygous or compound heterozygous state.

The dbSNP/gnomAd/ClinVar databases list 4 frequently occurring (MAF > 0.001) *HPS6* missense variants, with predicted benign or unknown pathogenicity (Supp. Table S3); these should be considered when encountered in *HPS6* genetic analysis.

Like the other two BLOC-2 HPS disorders (HPS-3 and HPS-5 subtypes), HPS-6 subjects exhibit a mild phenotype of hypopigmentation and bleeding diathesis. Pulmonary fibrosis and immunodeficiency have not been reported in HPS-6 and granulomatous colitis occurs in some BLOC-2 deficient subjects. As in other BLOC-2 subtypes, mildness of symptoms may prevent or delay diagnosis.

HPS-7 *(Table 9)*

HPS-7 (MIM# 614076) is caused by biallelic pathogenic variants in *DTNBP1*, also called *BLOC1S8* or *HPS7*, located on chromosome 6p22.3. The longest *DTNBP1* mRNA transcript contains 10 exons, encoding a 351-amino acid protein (~39.5-kD) called Dysbindin or HPS7. There are 5 *DTNBP1* protein-coding mRNA variants predicted; their expression and functional significance are unknown. Dysbindin is a subunit of BLOC-1 (Li et al., 2003). The *sandy* mouse is the murine orthologue of human HPS-7 (Li et al., 2003).The *DTNBP1* gene was discovered by finding *Dtnbp1* mutated in the *sandy* mouse, and subsequent sequencing of unclassified HPS subjects identified a 48-year old Portuguese female with a homozygous nonsense variant c.307C>T (p.Gln103*) in *DTNBP1* (Li et al., 2003). We list 4 *DTNBP1* pathogenic variants that cause the HPS-7 phenotype (Figure 7). There are currently seven HPS-7 cases reported, all homozygous for a nonsense or a frameshift *DTNBP1* variant, including a Caucasian female diagnosed at age 77 (Lowe et al., 2013) and 4 cases (including 2 siblings) of Portuguese ethnicity homozygous for c.307C>T (p.Gln103*) (Bastida et al., 2019; Bryan et al., 2017; Li et al., 2003) (Table 9). One unreported Argentinian boy in our NIH cohort (referred by Dr. Rosenzweig, NIH Clinical Center, Bethesda, MD), was compound heterozygous for c.307C>T (p.Gln103*) and the novel indel variant c.1017_1020delAGAG (p.Glu340Profs*44).

Next generation has identified heterozygous *DTNBP1* variants suggested to contribute to different conditions (Supp. Table S4). Specifically, c.286G>T (p.Glu96*) was reported in a subject with idiopathic pulmonary fibrosis that had no other HPS clinical findings (Deng et al., 2018). The missense variant p.Pro272Ser (c.814C>T) was reported as a low penetrance risk for colorectal cancer (Webb et al., 2006). Several association studies have identified *DTNBP1* as a risk allele for schizophrenia, including in European-Americans (Donohoe et al., 2008; Straub et al., 2002; Wang, Xu, Lazarovici, & Zheng, 2017; Zuo et al., 2009).

Schizophrenic subjects have reduced hippocampus *DTNBP1* mRNA expression (Weickert, Straub, Kleinman, Hyde, & Rothmond, 2006) and *DTNBP1* variants are associated with a cognitive response to antipsychotic drug treatment (Scheggia et al., 2018), however, the association of *DTNBP1* with schizophrenia has also been challenged (Ghiana & Dell'Angelica, 2011). Notably, no psychiatric illness in HPS-7 subjects has been reported but it is reasonable to consider such features in HPS-7 and BLOC-1 cases.

The dbSNP/gnomAd/ClinVar databases list 4 frequently occurring (MAF > 0.001) *DTNBP1* missense variants of predicted benign or unknown pathogenicity (Supp. Table S3), which should be considered as likely non-pathogenic polymorphisms when encountered in *DTNBP1* genetic analyses.

Due to the limited number of identified HPS-7 cases, it is difficult to determine whether these individuals are prone to complications other than albinism and a bleeding diathesis. All affected individuals, including two of advanced age, had normal pulmonary function and no signs of immunodeficiency/neutropenia. The 77-year old Caucasian woman had signs of colitis, which was not reported in the other affected subjects.

HPS-8 *(Table 9)*

HPS-8 (MIM# 614077) is caused by biallelic pathogenic variants in *BLOC1S3,* also called *HPS8, RP or BLOS3,* located on chromosome 19q13.32. The longest *BLOC1S3* mRNA transcript contains 2 exons, encoding a 202-amino acid protein (~21.3-kD). There exists only one predicted *BLOC1S3* mRNA transcript. BLOC1S3/HPS8 is a subunit of BLOC-1 (Starcevic & Dell'Angelica, 2004). *Reduced pigmentation* is the murine orthologue of human HPS-8 (Gwynn et al., 2004).

HPS-8 was first reported in an extended consanguineous Pakistani family with 6 affected individuals; autozygosity mapping assisted in identifying a homozygous frameshift variant, c.448delC (p.Gly150Argfs*75), in *BLOC1S3* in all affected individuals (Morgan et al., 2006). Three additional HPS-8 cases with homozygous pathogenic *BLOC1S3* variants have since been reported (Cullinane et al., 2012; Lasseaux et al., 2018) (Table 9, Figure 7).

The dbSNP/gnomAd/ClinVar databases list 3 frequently occurring (MAF > 0.001) *BLOC1S3* missense variants, with predicted benign or unknown pathogenicity (Supp. Table S3); these should be considered as likely non-pathogenic polymorphisms when encountered in genetic analyses.

The few reported HPS-8 cases show typical HPS features including hypopigmentation and a bleeding diathesis. None has been reported to exhibit pulmonary fibrosis, granulomatous colitis, immunodeficiency or other complications. Identification of additional HPS-8 cases may confirm or broaden this phenotype.

HPS-9 *(Table 9)*

HPS-9 (MIM# 614171) is caused by biallelic pathogenic variants in *BLOC1S6,* also called *HPS9, PLDN or BLOS6,* located on chromosome 15q21.1. The longest *BLOC1S6* mRNA transcript contains 5 exons encoding a 177-amino acid protein (~20.3-kD), called

BLOC1S6, HPS9 or Pallidin. There are 3 predicted *BLOC1S6* mRNA transcripts with unknown expression patterns and function. The longest variant 1 (NM_001311255.1) only recently appeared in databases, causing all previously described pathogenic variants to be attributed to mRNA splice variant 2 (NM_012388.3). Variant 1 (open reading frame 534-bp) and Variant 2 (open reading frame 519-bp) both have 5 exons and vary in their 5' UTR and 5' coding region in exon 1, and each initiate translation at a different start codon; exons 2–5 are identical in both variants. BLOC1S6/HPS9 is a subunit of BLOC-1 (Falcon-Perez et al., 2002; Moriyama & Bonifacino, 2002). *Pallid* is the murine orthologue of human HPS-9 (Moriyama & Bonifacino, 2002).

All 3 reported HPS-9 cases were identified through exome sequencing. A 17-year-old Italian female (Badolato et al., 2012) and a 4-year-old Pakistani female (Yousaf et al., 2016) were both homozygous for the same HPS9 nonsense variant: c.232C>T, p.Gln78* (NM_012388.3, transcript variant 2). A 52-year-old Japanese female was reported homozygous for c.285_286dupTC, p.H96Lfs*22 (NM_012388.3) (Okamura et al., 2018) (Table 9, Figure 7).

The dbSNP/gnomAd/ClinVar databases list one frequently occurring (MAF > 0.001) *BLOC1S6* missense variant (p.Ala12Thr; MAF 0.0030), with predicted benign or unknown pathogenicity (Supp. Table S3); it should be considered as likely non-pathogenic polymorphism when encountered in genetic analyses.

All three HPS-9 subjects exhibited hypopigmentation, visual impairment and a bleeding diathesis. No pulmonary fibrosis or granulomatous colitis was reported in HPS-9 subjects. However, the Italian (17-year-old female) and Japanese (52-year-old female) subjects both had mild thrombocytopenia and recurrent leukopenia, causing immunodeficiency (Badolato et al., 2012; Okamura et al., 2018). In addition, the Japanese subject developed schizophrenia in her late forties, a phenotype previously associated with *DTNBP1* haplotypes (Donohoe et al., 2008; Straub et al., 2002; Wang et al., 2017), however, this association appears controversial and needs further consideration(Ghiani & Dell'Angelica, 2011). Both immunodeficiency and schizophrenia should be considered in future evaluations of HPS-9 subjects.

HPS-10 *(Table 9)*

HPS-10 (MIM# 617050) is caused by biallelic pathogenic variants in *AP3D1*, also called *HPS10* or *ADTD*, located on chromosome 19p13.3. The longest *AP3D1* mRNA transcript contains 32 exons, encoding the 1215-amino acid protein AP3D1 (δ subunit of AP-3; ~136.7-kD). There are 2 predicted protein-coding *AP3D1* mRNA transcripts without reported expression or functional data. The AP3D1 protein is a subunit of AP-3 (Ammann et al., 2016; Dell'Angelica et al., 1999). *Ap3d1*-deficient animal models include the *mocha* mouse (Kantheti et al., 1998).

There are only 2 *AP3D1* pathogenic variants reported to cause the HPS-10 phenotype (Table 9, Figure 7). A homozygous *AP3D1* pathogenic indel variant c.3565_3566delGT (p.Val1189Leufs*8) was reported in a Turkish boy, who died at age 3.5 years as result of septic pneumonia (Ammann et al., 2016). The boy had albinism, neutropenia,

immunodeficiency, neurodevelopmental delay, generalized seizures, interstitial lung disease and impaired hearing. T cells from the *AP3D1*-deficient boy showed significantly decreased AP3D1 protein expression compared to healthy control T cells; protein expression levels of other AP-3 subunits (β3A, σ, and μ) were also reduced, consistent with an unstable AP-3 heterotetramer (Ammann et al., 2016). Cytotoxic lymphocytes from the subject exhibited an impaired degranulation response, similar to individuals with pathogenic variants in *AP3B1*. Immunologic investigations excluded HLH in the subject (Ammann et al., 2016; Enders et al., 2006; Jessen et al., 2013). A homozygous *AP3D1* pathogenic frameshift variant, c.1978delG (p.Ala660Argfs*54), was identified in 3 siblings with seizures, developmental delay, albinism and immunodeficiency; twin girls died before 6 days of age and their brother died at age 2 years of pneumonia and sepsis (Mohammed et al., 2018).

Next generation sequencing of cohorts with autism spectrum disorder identified a *de novo* heterozygous *AP3D1* splicing variant (c.273+1G>T) (Takata et al., 2018) and a *de novo* *AP3D1* heterozygous missense variant (p.Gln406Arg) (Iossifov et al., 2014). Next generation sequencing of a schizophrenia cohort identified a *de novo* heterozygous *AP3D1* missense variant (p.Asn605Lys) (Fromer et al., 2014). None of these variants has been reported in HPS subjects but they are included in Supp. Table S4 because they may cause HPS when occurring in a homozygous or compound heterozygous state.

The dbSNP/gnomAd/ClinVar databases list 2 frequently occurring (MAF > 0.001) *AP3D*1 missense variants, with predicted benign or unknown pathogenicity (Supp. Table S3); these should be considered as likely non-pathogenic polymorphisms when encountered in genetic analyses.

The *AP3D1*-deficient boys manifested features of albinism and immunodeficiency from birth. These are features characteristic of *AP3B1* deficiency (HPS-2) and can likely be attributed to AP-3 deficiency. They did not have an overt tendency for bleeding. They also exhibited neurological findings not previously reported in other HPS subtypes, including microcephaly, severe neurodevelopmental delay, generalized seizures. Hearing impairment occurred in the Turkish boy. The *mocha* mouse shows a similar HPS-like phenotype with seizures and hearing loss, indicating that these features are likely due to *AP3D1* deficiency. A diagnosis of HPS-10 should be considered in individuals with hypopigmentation, immunodeficiency, seizures, hearing loss and possibly other neurologic involvement.

DIAGNOSIS OF HPS

Individuals with HPS can present to different clinical specialties, including dermatology, ophthalmology, pulmonology, hematology, gastroenterology, immunology and neurology. The presence of a combination of hypopigmentation (light hair and skin color), ocular symptoms (nystagmus and decreased visual acuity) (Summers, Knobloch, Witkop, & King, 1988), and a bleeding diathesis (bruising, epistaxis, gingival bleeding, colonic bleeding, prolonged bleeding after minor surgeries) (Gunay-Aygun, Huizing, & Gahl, 2004) leads most physicians to suspect a diagnosis of HPS. The diagnosis of HPS is primarily established by clinical features and platelet phenotyping that show an absence or severe reduction of platelet dense granules, which can be demonstrated by whole mount electron

microscopy (EM) (Witkop, Krumwiede, Sedano, & White, 1987). This semi-specialized method is not routinely offered by hematology services. Alternatively, demonstrating an absence of a secondary aggregation response of platelets to exogenous stimuli through platelet aggregation testing also supports the HPS diagnosis (White & Witkop, 1972). Quantification of mepacrine uptake (Billio et al., 2001), and super-resolution immunofluorescence microscopy analyses (Westmoreland et al., 2016) have also been presented as potential alternatives to whole mount EM analysis for diagnosis of dense granule deficiency.

Identification of biallelic variants in one of the 10 HPS-related genes ultimately confirms the HPS diagnosis and the HPS subtype. However, since HPS is a heterogenous genetic disorder, a molecular diagnosis of a particular subtype can be difficult to reach. There is no direct genotype-phenotype association among HPS genes or variants within a gene. When using a single gene testing strategy, we recommend sequence analysis of *HPS1* and *HPS4* in subjects with more severe clinical manifestations (hypopigmentation, ocular symptoms, bleeding diathesis, pulmonary symptoms) and analysis of *HPS3*, *HPS5* and *HPS6* (BLOC-2 subunits), followed by *DTNBP1*, *BLOC1S3* and *BLOC1S6* (BLOC-1 subunits) in mildly affected subjects. Subjects with immunological symptoms should be tested for *AP3B1* and *AP3D1* defects. In this era of next generation sequencing, the genetic diagnosis of HPS is increasingly established by testing all HPS genes simultaneously. This approach can also identify new HPS associated genes, since some subjects with HPS-related symptoms have no apparent pathologic variants in any of the 10 HPS genes. Candidate genes for new HPS subtypes may include genes affected in mouse models of HPS that do not yet have a human counterpart (Table 1), as well as proteins that interact with the BLOC and AP-3 complexes.

The inclusion of HPS-related genes in genetic screening panels of cohorts with clinical features of HPS has resulted in the recent identification of groups of undiagnosed HPS subjects, especially those with milder clinical phenotypes. Targeted sequencing of 990 cases with albinism identified 46 HPS subjects (Lasseaux et al., 2018). A similar study of 21 Arabian individuals with ocular hypopigmentation identified 10 HPS subjects (Khan, Tamimi, Lenzner, & Bolz, 2016), a study of 46 Japanese cases with (OCA-1 and HPS-1 negative) albinism identified 9 HPS subjects (Okamura et al., 2019), and a study of Chinese hypopigmentation cases identified 10 HPS subjects (Wei et al., 2019). Similarly, targeted sequencing of a cohort of 159 cases with bleeding, thrombotic, and platelet disorders identified 6 HPS individuals (Simeoni et al., 2016). These studies suggest that HPS is underdiagnosed, especially when clinical features are mild.

Other recent next generation sequencing approaches identified heterozygous variants in HPS genes that are considered risk alleles for certain conditions (Tables 3–9) these are not classified as HPS-causing pathogenic variants. Heterozygous *HPS1*, *HPS4* and *DTNBP1* variants were reported in familial (Stearman et al., 2019) or sporadic (Deng et al., 2018) pulmonary fibrosis cases (Tables 3, 6 and 9). Heterozygous *AP3B1* variants have been reported in cases with primary immunodeficiency (Chi et al., 2018; Gallo et al., 2016) or HLH (Gao et al., 2015; Miao et al., 2019; Mukda et al., 2017; Tesi et al., 2015; Xu et al., 2017) (Table 4), and heterozygous variants in *AP3D1*, *HPS3* and *HPS4* were reported in

cases with autism spectrum disorder or schizophrenia (Fromer et al., 2014; Iossifov et al., 2014; Takata et al., 2018).

Apart from direct sequencing of the exonic regions of HPS genes, alternative molecular methods to establish the HPS type have been used. When a subject's mRNA has been isolated from whole blood or cultured cells, mRNA expression (i.e., by northern blot or quantitative PCR) and/or cDNA sequencing of each gene can be performed. Another advantage of mRNA availability is that the effects of splicing variants and variants suspected of causing nonsense mediated mRNA decay can be investigated (Anderson et al., 2003; Huizing et al., 2001; Huizing et al., 2004). Immunoblotting of cultured skin fibroblast or platelet rich plasma extracts has also proven helpful to determine or validate the HPS subtype. HPS mouse and human studies have shown that a defect in one HPS protein leads to destabilization of the entire protein complex, i.e., AP-3, BLOC-1, −2, −3 (Ammann et al., 2016; Dell'Angelica et al., 1999; Huizing et al., 2002; Li et al., 2003; Wei et al., 2019). Therefore, the use of immunoblotting with an antibody against one subunit of the complex (AP-3, BLOC-1,−2,−3) allows determination of which complex is defective in unclassified HPS subjects, reducing subsequent sequencing of genes encoding the corresponding subunits (Carmona-Rivera, et al., 2011; Nazarian et al., 2008; Wei et al., 2019).

EPIDEMIOLOGY OF HPS

The worldwide prevalence of HPS is estimated to be 1–9/1,000,000 (Christensen et al., 2017; Huizing et al, 2017 Oct 26 [Updated 2000 July 24]). A few ethnic founder variants occur in HPS genes, in particular in northwest region of Puerto Rico, an estimated 400 individuals are affected (~1/1,800 affected; carrier frequency 1:21) and carry a homozygous 16-bp duplication in *HPS1* (c.1472_1487dup16-bp; Table 3) (Santiago Borrero et al., 2006; Witkop et al., 1990), and in Central Puerto Rico a 3.9-kb deletion in *HPS3* (NM_032383.5(HPS3):c.−2993_217+692del; Table 5) has an estimated population prevalence of ~1/4000 (carrier frequency 1:32) in (Anikster et al., 2001; Santiago Borrero et al., 2006; Torres-Serrant et al., 2010). Other founder variants without frequency estimates have been reported and are discussed elsewhere in this report for each HPS subtype (Oh et al., 1998; Schallreuter et al., 1993; Ito et al., 2005; Schreyer-Shafir et al., 2006).

Compared to the ~189 reported BLOC-3 deficient individuals (not including ~261 cases with the Puerto Rican *HPS1* 16-bp duplication variant), there are remarkably fewer reported AP-3 deficient individuals (~35 cases), BLOC-1 deficient individuals (~24 cases) and BLOC-2 deficient individuals (~117 cases; not including ~72 cases with the Puerto Rican *HPS3* 3.9-kb deletion and ~20 cases with the Israeli Bedouin *HPS6* c.1065insG variants) (Table 1).

BLOC-2 deficient cases may escape diagnosis because of their much milder hypopigmentation compared to BLOC-3 deficiency. This is in line with BLOC-2 deficient mice, which inhibit brownish-black eumelanin, but not reddish-yellow pheomelanin production (Hirobe, Ito, & Wakamatsu, 2013), and individuals with HPS have reduced levels of total melanin, but increased pheomelanin production compared to unaffected family

members (Okamura et al., 2018), indicating that hypopigmentation might not be detected in HPS cases from fair-skinned families, particularly those with red-blonde hair.

BLOC-2 deficient individuals may get medical attention only for a bleeding diathesis and may be classified as storage pool deficiency, as illustrated by new diagnoses of HPS-5 in 92- and 65-year-old individuals with histories of excessive bleeding (Botero et al., 2018; Ringeisen et al., 2013).

Similarly, AP-3 deficient individuals may avoid an HPS diagnosis or have it delayed because a severe immune disorder dominates medical attention. It is puzzling why so few BLOC-1 deficient individuals are reported. Perhaps BLOC-1 defects are extremely rare or embryonically lethal (although mouse models of BLOC-1 deficiency are viable), or the human phenotypes may have features that are not considered compatible with the HPS phenotype. For example, the absence of platelet delta granules is currently essential for the HPS diagnosis, but a subset of subjects with BLOC-1 may have normal/decreased platelet delta granules and may therefore not be considered for a HPS diagnosis. In addition, reported brain-associated functions of BLOC-1 (A. Ito et al., 2018; Newell-Litwa et al., 2010; Spiegel, Chiu, James, Jentsch, & Karlsgodt, 2015) may underlay a neurologic phenotype of BLOC-1 deficiency. Recognition of these features may facilitate the diagnosis of affected individuals with HPS subtypes associated with BLOC-1 defects. Several association studies have identified *DTNBP1* variants as risk alleles for schizophrenia (Donohoe et al., 2008; Straub et al., 2002; Wang et al., 2017; Zuo et al., 2009) and one HPS-9 subject was diagnosed with oculocutaneous albinism and developed schizophrenia in her forties; she was only diagnosed with HPS-9 at age 52 through a whole exome screen (Okamura et al., 2018). However, some reports have challenged brain-associated functions of BLOC-1 and/or a BLOC-1 association with schizophrenia (Ghiani & Dell'Angelica, 2011), suggesting that this issue needs further consideration. With the increased availability of exome/genome sequencing, more HPS subjects with mild or atypical HPS phenotypes will likely be identified and will expand the clinical spectrum of HPS.

CLINICAL MANAGEMENT AND THERAPEUTIC ASPECTS

The myriad of symptoms associated with HPS, some subtype or age specific and some life threatening, require multidisciplinary clinical care (Table 2) (Christensen et al., 2017; Seward & Gahl, 2013).

All individuals with HPS exhibit some degree of albinism, involving hypopigmentation of skin, hair or eyes. The skin is often light- and sun-sensitive and may develop solar keratoses and melanocytic nevi. Subjects are at increased risk for squamous cell carcinoma, basal cell carcinoma, and possibly melanoma. Protection or avoidance from ultraviolet radiation is critical (Toro, Turner, & Gahl, 1999). The hair varies from silvery-white to light brown and hypopigmentation may be evident when affected and unaffected family members are compared. The eyes appear light blue, light green or hazel, but iris color may be darker in mild HPS cases. Iris transillumination is found in most HPS subjects. Due to their albinism, HPS subjects have abnormal crossing of optic nerve fibers (Hoffmann, Lorenz, Morland, & Schmidtborn, 2005) and horizontal nystagmus, the retinal fundus appears pale and visual

acuity ranges from 20/60 to 20/400 and can be mildly improved with refractive lenses (Summers et al., 1988). Many subjects are legally blind, i.e., have visual acuity worse than 20/200. BLOC-3 deficient subjects show more severe hypopigmentation than subjects with AP-3 or BLOC-2 defects. The albinism of BLOC-1 individuals has not been well characterized.

The bleeding diathesis of HPS varies in severity in all subtypes, and may include spontaneous bruising, prolonged epistaxis, menorrhagia, pronounced oozing after dental extractions, and excessive surgical blood loss. Topical thrombin, administration of pro-coagulant drugs, or intravenous 1-desamino-8D-arginine vasopressin may ameliorate or prevent bleeding. Platelet transfusion may also be used as prophylaxis or as treatment for bleeding in individuals with HPS (Han et al., 2018; Minkin, Bertetti, Lindsey, & Bovino, 2015; Ozgur & Yilmaz, 2015; Van Avermaete, Muys, & Jacquemyn, 2016). Avoidance of aspirin products and non-steroidal anti-inflammatory drugs is recommended.

A granulomatous colitis involving intestinal granulomas, erosions and inflammatory cells, which resembles Crohn's disease, occurs in ~10–20% of all BLOC-2 and BLOC-3 subjects (Hussain et al., 2006). One BLOC-1 deficient individual (HPS-7) was diagnosed with Crohn's colitis in adulthood (Lowe et al., 2013). It is unknown if colitis occurs in AP-3 deficiency. The colitis may respond to corticosteroids or anti-TNF-α drugs; surgical bowel resection is performed in refractory cases (Demirtas, Alahdab, Kani, Atug, & Imeryuz, 2019; Kouklakis et al., 2007; Mora & Wolfsohn, 2011). Abnormal endosomal membrane formation was suggested as an underlying cause for HPS colitis leading to ceroid lipofuscin formation, abnormal autophagy and phagocytosis, and inflammation (Felipez, Gokhale, & Guandalini, 2010; Sofia, Sakuraba, & Rubin, 2017). It was suggested that the presence of risk alleles in Crohn's disease-associated genes, like *NOD2* or *ATG16L1*, in HPS subjects may contribute to developing colitis (Lozynska et al., 2018). Low vitamin D levels, which may be a factor in HPS subjects avoiding sun exposure, could also contribute to developing colitis (Lozynska et al., 2018).

Ceroid lipofuscin, an amorphous, granular, electron-dense, autofluorescent lipid-protein material, was identified in LROs in HPS cell types, including alveolar macrophages, cells of the gastrointestinal tract, renal tubular cells, bone marrow, lymph nodes, liver, spleen, and heart (Gahl et al., 1998; Harada et al., 2014; Hermansky & Pudlak, 1959; Sparrow et al., 2010; Takahashi & Yokoyama, 1984). Ceroid lipofuscin may accumulate because cells cannot rapidly degrade mistargeted vesicular membranes. Accumulation of ceroid lipofuscin was suggested to underlie the colitis and pulmonary fibrosis in HPS, but this has not been confirmed and other pathogenic mechanisms have been proposed. End stage renal disease attributed to deposition of ceroid lipofuscin has occurred in a few HPS subjects, for which renal transplant is a treatment option (Abdullah, Davis, Quinn, & Mohan, 2018; Gordillo, Del Rio, Thomas, Flynn, & Woroniecki, 2011; Tagboto et al., 2001).

Immunodeficiency and/or neutropenia occurs in AP-3-deficient HPS, resulting in susceptibility to infections (subtypes HPS-2 and HPS-10) (Ammann et al., 2016; de Boer et al., 2017; Fontana et al., 2006; Huizing et al., 2002; Mohammed et al., 2018). No BLOC-2 or BLOC-3 deficient subjects are described with immunodeficiency, but it was reported in

two unrelated individuals with HPS-9 (Badolato et al., 2012; Okamura et al., 2018) and therefore needs consideration in future BLOC-1 deficient individuals.

Manifestations of the AP-3 immunodeficiency can vary from mild recurrent viral and bacterial infections to severe hemophagocytic lymphohistiocytosis (HLH) (Dell'Acqua et al., 2019; Enders et al., 2006; Jessen et al., 2013). The neutropenia associated with *AP3B1* (HPS-2) deficiency is granulocyte colony-stimulating factor (G-CSF) responsive, but G-CSF therapy has not been used in *AP3D1*-deficienct subjects, all of whom died before age 3.5 of pneumonia and/or sepsis without signs of HLH. Of note, G-CSF therapy restores the neutrophil numbers, but not the recurrent infections in HPS-2 subjects (Fontana et al., 2006), suggesting defects in innate immunity and bacterial antigen presentation, supported by several studies in AP3-deficient dendritic, natural killer and lymphoblastoid cells from mice and humans (Briken, Jackman, Dasgupta, Hoenig, & Porcelli, 2002; Fontana et al., 2006; Meantegazza et al., 2012; Mantegazza et al., 2017; Sugita et al., 2002; Sasai et al., 2010).

A few *AP3B1*-deficient subjects developed HLH, which was lethal in 2 subjects (Dell'Acqua et al., 2019; Enders et al., 2006; Fontana et al., 2006). Although the risk of HLH should be considered in AP-3 deficient subjects, preemptive hematopoietic stem cell transplantation (HSCT, therapeutic for HLH but challenging for the subject) has been deemed to not be justified. HSCT could certainly be considered after a severe HLH episode (Dell'Acqua et al., 2019).

Pulmonary fibrosis, a progressive interstitial lung disease with a variable time course, occurs in BLOC-3 (HPS-1 and HPS-4) and AP-3 (HPS-2 and HPS-10) subjects. There are no reports of pulmonary fibrosis in BLOC-1 and BLOC-2 cases. Most BLOC-3 deficient subjects develop pulmonary fibrosis in middle age (30–50 years) and progress to death within a decade (Brantly et al., 2000; Gahl et al., 1998). AP-3 deficiency-related pulmonary fibrosis is reported in a few HPS-2 cases and one HPS-10 case, and symptoms can start as early as childhood (Ammann et al., 2016; Gochuico et al., 2012; Hengst et al., 2018). While the natural history of BLOC-3-related pulmonary fibrosis has been well-documented, that of AP-3 related lung disease needs further elucidation with longitudinal data from more subjects (Gochuico et al., 2012). The exact cause of lung disease in HPS remains unknown; it was suggested that altered LRO formation within alveolar epithelial type II cells may lead to defective formation of lamellar bodies and/or intracellular processing of surfactant proteins, leading to endoplasmic reticulum-stress, apoptosis, and a fibrotic lung phenotype (Guttentag et al., 2005; Mahavadi et al., 2010; Kook et al., 2018). The fibrotic lung phenotype in BLOC-3- or AP-3-deficient mice was shown to be due to a non-hematopoietic cell type and could be averted in Ap3b1-deficient mice by re-expression of Ab3b1 specifically in lung epithelial type 2 cells (Young et al., 2012), strongly supporting the lamellar body defect as causative for lung disease, at least in mice. Abnormal alveolar macrophage or mast cell function was also suggested to underlie HPS-related pulmonary fibrosis (Kirshenbaum et al., 2016; Mahavadi et al., 2010; Nakatani et al., 2000; Rouhani et al., 2009).

No approved medical therapy for or prophylaxis against HPS-related pulmonary fibrosis exists. Maximizing pulmonary function before onset of pulmonary fibrosis by avoidance of

cigarette smoke and other lung toxins, treatment of pulmonary infections, influenza and pneumococcal immunization, and regular moderate exercise are recommended. Steroids have no apparent beneficial effect. The anti-fibrotic drug pirfenidone may slow the progression of HPS-related pulmonary fibrosis in some cases (Gahl et al., 2002; O'Brien et al., 2011; O'Brien, Introne, et al., 2018), but it is not an approved therapy for HPS-related pulmonary fibrosis (O'Brien, Gahl, & Gochuico, 2018). Lung transplant is the only known treatment for pulmonary fibrosis, and several individuals with *HPS1*-related pulmonary fibrosis successfully underwent bilateral or single-lung transplantation (El-Chemaly et al., 2018; Gahl et al., 2002; Lederer et al., 2005).

HPS pathogenesis and therapeutic options continue to be investigated, including through the use of organoids (Korogi et al., 2019; Strikoudis et al., 2019) and explorations of gene therapy (Ikawa et al., 2015; Iyer et al., 2019; Shen et al., 2018).

CONCLUSION

HPS is a rare autosomal recessive disorder characterized by genetic and phenotypic heterogeneity. With the recent rapid evolution of affordable next generation sequencing methods, there is an increased recognition of HPS subjects and new HPS genetic subtypes (Arcot Sadagopan et al., 2017; A. Wei et al., 2016; Yousaf et al., 2016). This is also evidenced by the increased diagnosis of subjects with non-classic HPS phenotypes (i.e. HPS-2, HPS-7, HPS-8, HPS-9, HPS-10) (Ammann et al., 2016; Bryan et al., 2017; Cetica et al., 2015; Iwata et al., 2017; Okamura et al., 2018), as well as diagnosis of 'unexpected' HPS in cohorts with albinism (Ito et al., 2005; Khan et al., 2016), immunodeficiency (Badolato et al., 2012), ocular disease (Hull et al., 2016; Miyamichi et al., 2016), or platelet disorders (Jones et al., 2012).

These recent developments have created the need for a current overview of molecular diagnostic and genetic counseling aspects of HPS. We intend this report to serve as a reference for interpretation of molecular data for HPS. The extensive HPS mutational spectrum provides pathogenicity interpretation for future HPS-related variants (such as missense variants currently classified as VUS), phenotype-genotype relationships (in particular atypical symptoms such as autism, schizophrenia and immune deficiency), assistance in genetic counseling for affected individuals (surveillance, management of anticipated symptoms), and tools for cell biologists to elucidate pathways, investigate interactions of HPS-related proteins, and initiate therapeutic efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the the Leiden Open Variation Database (http://www.lovd.nl/) and in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). The data that support the findings of this study are also available from the corresponding author upon reasonable request.

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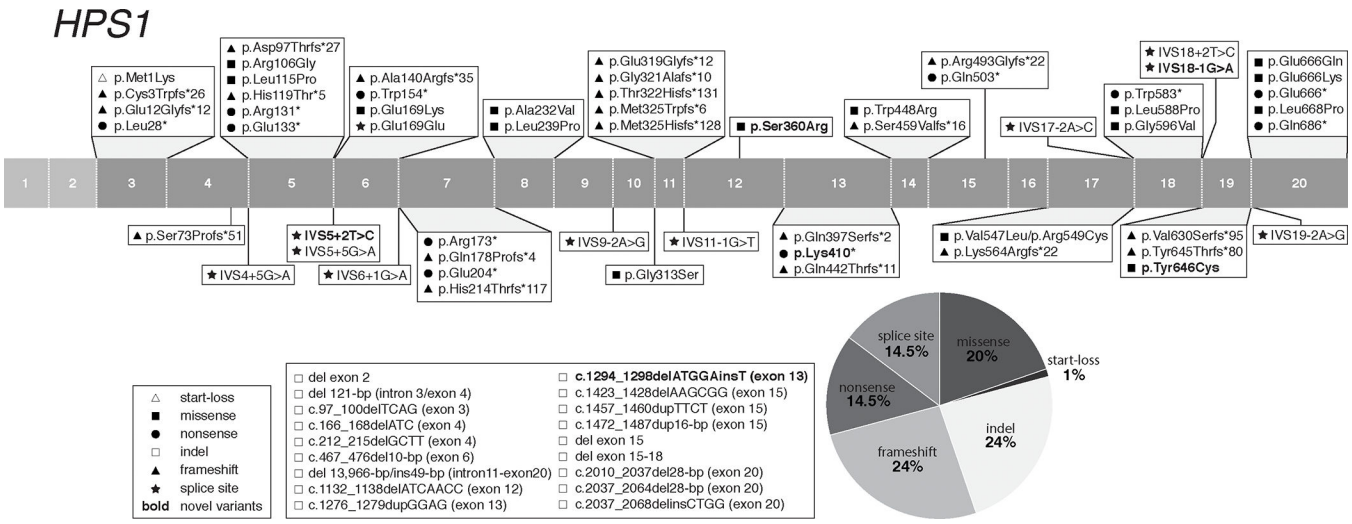

Figure 1:
Distribution of *HPS1* Gene Variants

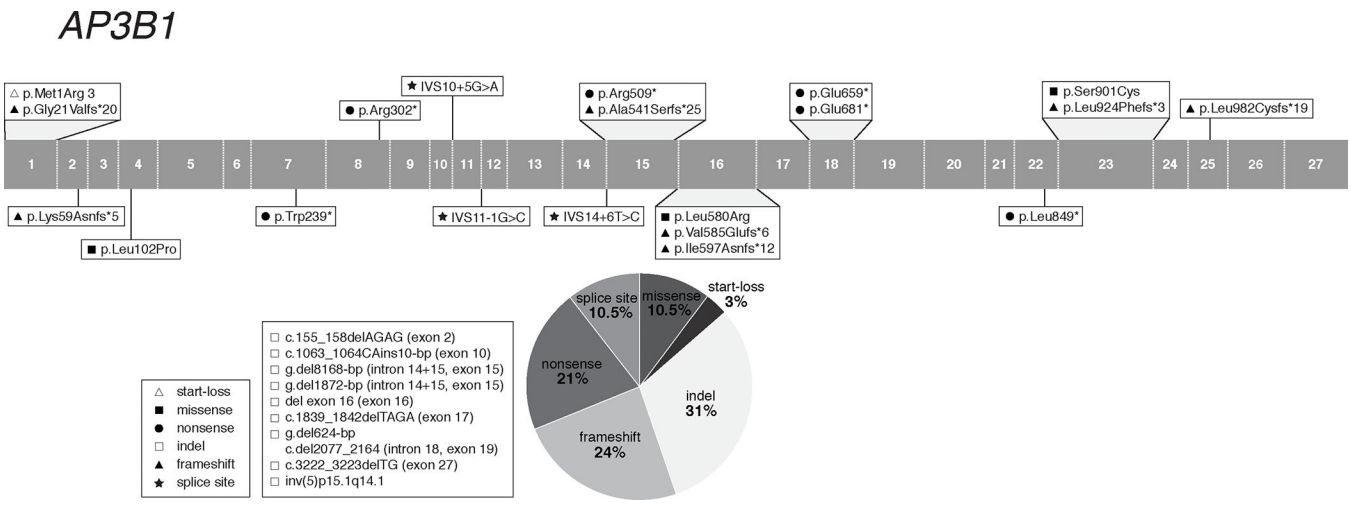

Figure 2:
Distribution of *AP3B1* Gene Variants

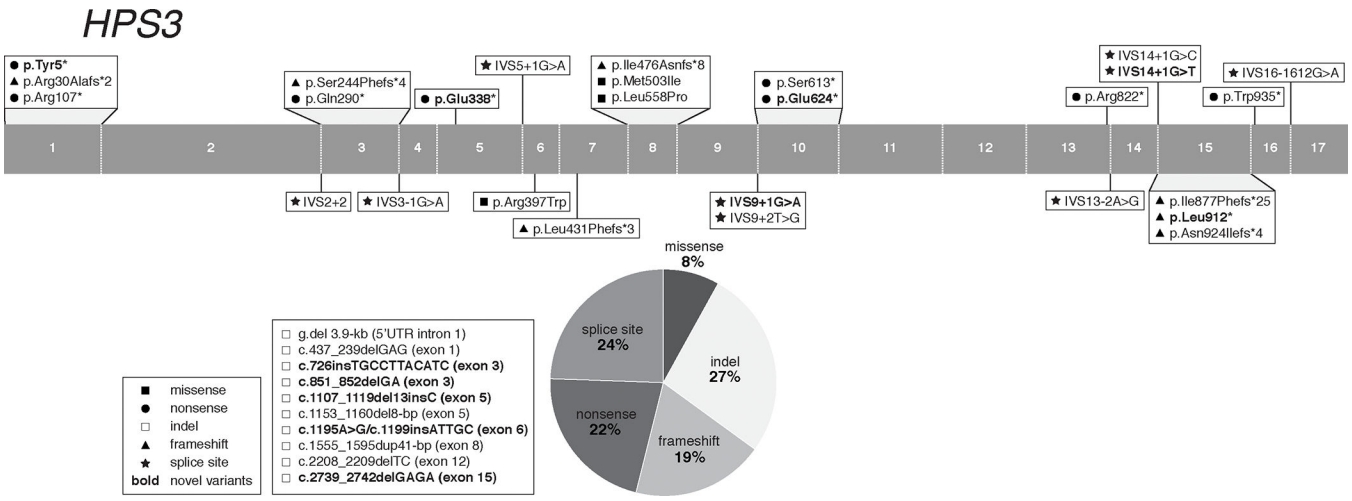

Figure 3:
Distribution of *HPS3* Gene Variants

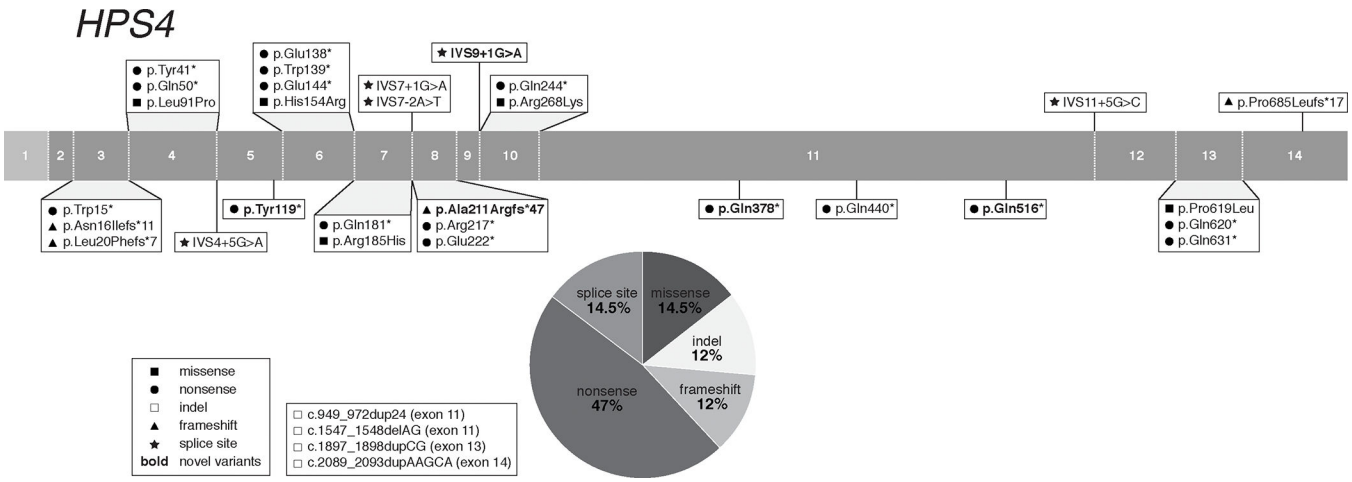

Figure 4:
Distribution of *HPS4* Gene Variants

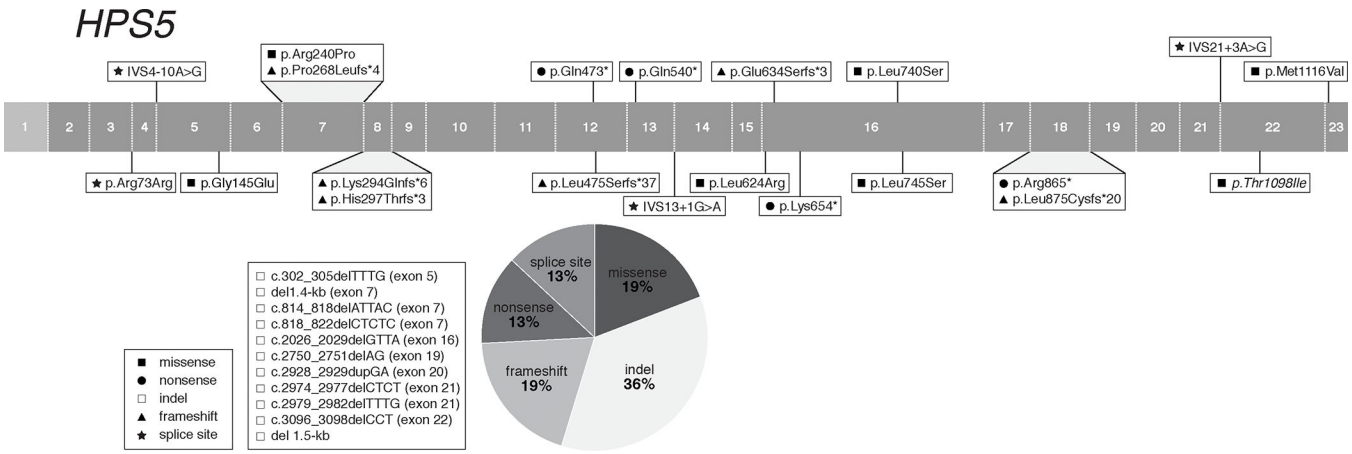

Figure 5:
Distribution of *HPS5* Gene Variants

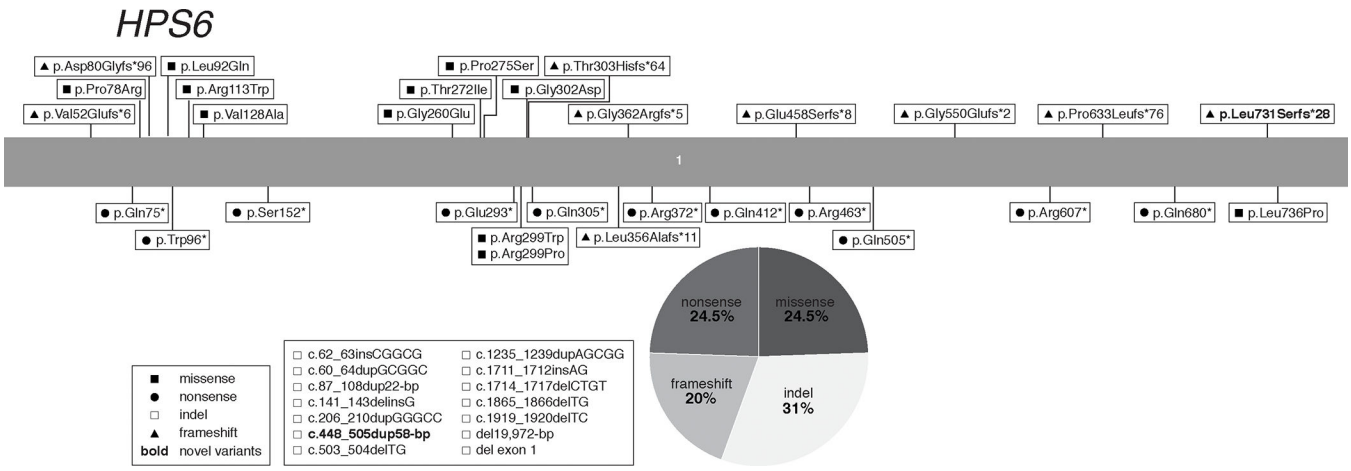

Figure 6:
Distribution of *HPS6* Gene Variants

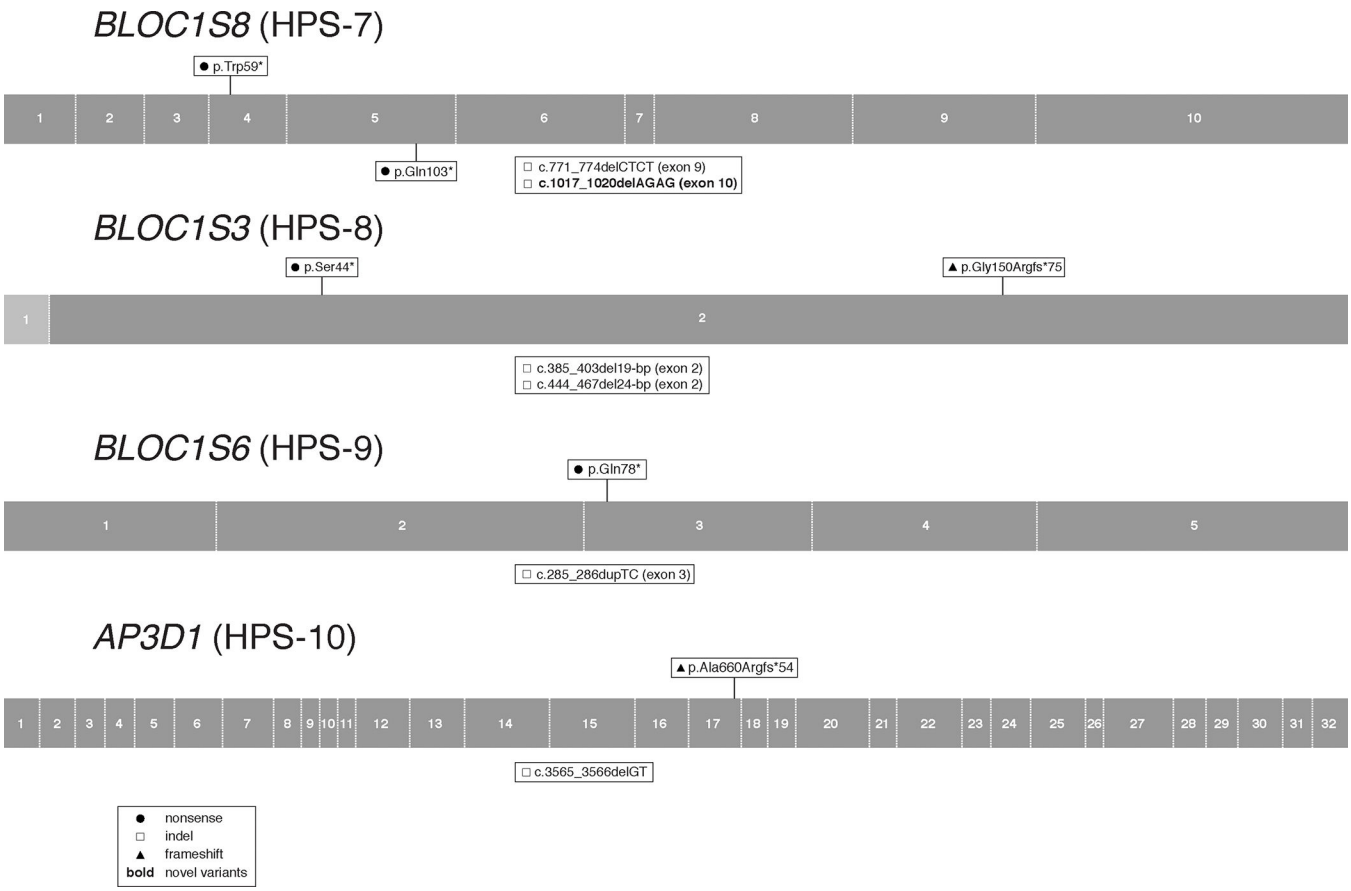

Figure 7:

Distribution of *BLOC1S8* (HPS-7), *BLOC1S3* (HPS-8), *BLOC1S6* (HPS-9), *and AP3D1* (HPS-10) Gene Variants

Table 1:

Overview of Hermansky-Pudlak Syndrome Subtypes, (Candidate) Genes and Protein Complexes

HPS Subtype	Gene Name [1] (*alternative names*)	Protein Complex	Human Locus	mRNA; GeneID [2] (# exons # splice variants)	Protein ID (# amino acids; molecular weight)	Reported Cases	Human Pathogenic Variants	Animal Model [3]
HPS-1	*HPS1 (BLOC3S1)*	BLOC-3	10q24.2	NM_000195; ID: 3257 (20 exons; 18 variants)	NP_000186 (700 aa; 79.3 kD)	~148 [4] ~261 (dup16-bp) [5]	76 [4]	*pale ear (m)*
HPS-2	*AP3B1 (ADTB3)*	AP-3	5q14.1	NM_003664; ID: 8546 (27 exons; 2 variants)	NP_003655 (1094 aa; 121.3 kD)	~35	29	*pearl (m), $Ap3b1^{LN}$ (m)*
HPS-3	*HPS3 (BLOC2S1)*	BLOC-2	3q24	NM_032383; ID: 84343 (17 exons; 2 variants)	NP_115759 (1004 aa; 113.7 kD)	~42 [6] ~72 (del 3.9-kb) [7]	37 [6]	*cocoa (m)*
HPS-4	*HPS4 (BLOC3S2)*	BLOC-3	22q12.1	NM_022081; ID: 89781 (14 exons; 11 variants)	NP_071364 (708 aa; 76.9 kD)	~41 [8]	34 [8]	*light ear (m)*
HPS-5	*HPS5 (BLOC2S2)*	BLOC-2	11p15.1	NM_181507; ID: 11234 (23 exons; 3 variants)	NP_852608 (1129 aa; 127.4 kD)	~29	31	*ruby-eye-2 (m), snow white (z), casper (sb)*
HPS-6	*HPS6 (BLOC2S3)*	BLOC-2	10q24.32	NM_024747; ID: 79803 (1 exon; 1 variant)	NP_079023 (775 aa; 83.0 kD)	~46 [9] ~20 (1065insG) [10]	45 [9]	*ruby-eye (m) no privacy (x)*
HPS-7	*DTNBP1 (BLOC1S8, HPS7)*	BLOC-1	6p22.3	NM_032122; ID: 84062 (10 exons; 5 variants)	NP_115498 (351 aa; 39.5 kD)	8	4	*sandy (m)*
HPS-8	*BLOC1S3 (HPS8, RP, BLOS3)*	BLOC-1	19q13.32	NM_212550; ID: 388552 (2 exons; 1 variant)	NP_997715 (202 aa; 21.3 kD)	3 6 (448delC) [11]	4	*reduced pigmentation (m)*
HPS-9	*BLOC1S6 (HPS9, PLDN, BLOS6)*	BLOC-1	15q21.1	NM_001311255; ID: 26258 (5 exons; 3 variants)	NP_001298184 (177 aa; 20.3 kD)	3	2	*pallid (m)*
HPS-10	*AP3D1 (HPS10, ADTD)*	AP-3	19p13.3	NM_001261826; ID: 8943 (32 exons; 2 variants)	NP_001248755 (1215 aa; 136.7 kD)	4	2	*mocha (m)*
-	*BLOC1S4 (CNO, BLOS4)*	BLOC-1	4p16.1	NM_018366; ID: 55330 (1 exon; 1 variant)	NP_060836 (217 aa; 23.3 kD)	-	-	*cappuccino (m)*
-	*BLOC1S5, MUTED, BLOS5*	BLOC-1	6p24.3	NM_201280; ID: 63915 (5 exons; 3 variants)	NP_958437 (187 aa; 21.6 kD)	-	-	*muted (m)*
-	*BLOC1S1, BLOS1*	BLOC-1 (BORC) [12]	12q13.2	NM_001487; ID: 2647 (4 exons; 1 variant)	NP_001478 (153 aa; 17.2 kD)	-	-	*$Blos1^{Ell\text{-}Cre/loxp}$ (m) $Blos1^{nestin\text{-}Cre/loxp}$ (m)*

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HPS Subtype	Gene Name [1] (*alternative names*)	Protein Complex	Human Locus	mRNA; GeneID [2] (# exons # splice variants)	Protein ID (# amino acids; molecular weight)	Reported Cases	Human Pathogenic Variants	Animal Model [3]
								bloc1s1^{ihb815} *(z)*
-	*BLOC1S2, BLOS2*	BLOC-1 (BORC)	10q24.31	NM_173809; ID: 282991 (5 exons; 6 variants)	NP_776170 (142 aa; 16.0 kD)	-	-	*Bloc1s2*$^{-/-}$ *(m)* *bloc1s2*^{ihb818} *(z)*
-	*BLOC1S7, BLOS7 SNAPIN, SNAPAP*	BLOC-1 (BORC) *12*	1q21.3	NM_012437; ID: 23557 (4 exons; 1 variant)	NP_36569 (136 aa; 14.9 kD)	-	-	*snapin*$^{-/-}$ *(m)*
-	*AP3M1, Mu3A*	AP-3	10q22.2	NM_207012; ID: 26985 (10 exons; 5 variants)	NP_996895 (418 aa; 46.9 kD)	-	-	-
-	*AP3S1, Sigma3A*	AP-3	5q22.3-q23.1	NM_001284; ID: 1176 (6 exons; 6 variants)	NP_001275 (193 aa; 21.7 kD)	-	-	-
Total:						**385 non-PR** *13* **333 PR**	**264 variants**	

*1*The commonly used HPS-subtype-related gene name is grey highlighted, alternative names are listed in brackets.

*2*Genbank accession numbers of the mRNA encoding the longest isoform (often transcript variant 1), its number of exons, GeneID, and the number of predicted protein-encoding splice variants of each HPS gene. As of November 2019.

*3*Reported vertebrate HPS animal models: *m*, mouse; sb, stickleback (*gasterosteus aculeatus*); *x*, *xenopus tropicalis* (frog); *z*, zebrafish (*danio rerio*), see (Bowman et al., 2019; Huizing et al., 2008) for details and references. See (Bowman et al., 2019) for invertebrate HPS models.

*4*The ~148 reported non-Puerto Rican HPS-1 cases include 11 novel NIH cohort cases. The 76 reported *HPS1* variants include 5 novel variants from the NIH HPS cohort.

*5*The ~261 reported HPS-1 cases with the northwest Puerto Rican founder variant c.1472_1487dup16-bp is an estimate and includes 166 cases from the NIH cohort and ~ 95 cases from the literature (Oh et al., 1996; Oh et al., 1998; Santiago Borrero et al., 2006). The number of worldwide cases homozygous for the *HPS1* c.1472_1487dup16-bp variant is estimated to be ~ 400 (Santiago Borrero et al., 2006).

*6*The ~42 reported HPS-3 cases include those reported with the Ashkenazi-Jewish founder variants (7 cases) as well as those novel from the NIH cohort (9 cases). The 37 reported *HPS3* variants include 11 novel variants from the NIH cohort.

*7*The ~72 HPS-3 cases with the central Puerto Rican founder 3.9-kb del variant (NM_032383.5:c.-2993_217+692del) include 63 cases from the literature (Anikster et al., 2001; Santiago Borrero et al., 2006) and 9 additional cases from the NIH cohort.

*8*The ~41 reported HPS-4 cases include 4 novel cases from the NIH cohort. The 34 reported *HPS4* variants include 4 novel NIH cohort variants.

*9*The ~46 reported HPS-6 cases include one novel case from the NIH cohort. The 45 reported *HPS6* variants include 2 novel variants from the NIH cohort.

*10*The ~20 reported HPS-6 cases with the c.1065insG variant are part of an extended Israeli Muslim Bedouin family (Schreyer-Shafir et al., 2006).

[11] One Pakistani family with 6 affected HPS-8 cases homozygous for c.448delC was reported (Morgan et al., 2006).

[12] BORC = BLOC-one-related complex (Pu et al., 2015).

[13] PR = Puerto Rican.

Table 2:

Hermansky-Pudlak Syndrome Main Clinical Features

Clinical Feature	Manifestations	LRO Defect (Cell Type)	Deficiency of HPS Complex	Prevention/Therapy
Cutaneous Albinism	white/light hair, hypopigmented and sun-sensitive skin [1]	melanosome (skin melanocytes)	AP-3, BLOC-1, -2, -3	*Preventive care*: sun avoidance, sun protection (sunscreen, hat, clothing), periodic skin cancer screening
Ocular Albinism	horizontal nystagmus, decreased visual acuity, pale fundus, foveal hypoplasia, iris transillumination [2]	melanosome (retinal pigment epithelial cells)	AP-3, BLOC-1, -2, -3	*Preventive care*: sun avoidance, eye protection (sunglasses, hat) *Symptomatic care*: vision corrective glasses, ophthalmologic care
Bleeding Diathesis	easy bruising, epistaxis, menorrhagia, gingival bleeding, colonic bleeding, prolonged bleeding after trauma or surgery or postpartum [3]	delta granule [3] (platelets)	AP-3, BLOC-1, -2, -3	*Symptomatic care*: local pressure on wounds, topical thrombin, 1-desamino-8D-arginine vasopressin (DDAVP) and other pro-coagulant drugs *Therapeutic*: platelet transfusion
Pulmonary Fibrosis (PF)	nonproductive cough, exertional dyspnea, diffuse rales, hypoxia	lamellar body [4] (type II alveolar epithelial cells)	BLOC-3, AP-3 [4]	*Preventive care*: avoidance of tobacco products *Symptomatic care*: supplemental oxygen for hypoxemia, pulmonary rehabilitation *Therapeutic*: lung transplantation
Enterocolitis	abdominal pain, cramps, fever, weight loss, malabsorption, frequent watery and bloody diarrhea.	unknown LRO-membrane formation [5]	BLOC-3, BLOC-2, (BLOC-1) [5]	*Therapeutic*: corticosteroids, non-steroidal immunomodulator drugs, anti-tumor necrosis factor-alpha drugs (effective for only some subjects)
Neutropenia	immunodeficiency	lytic and azurophil granules (neutrophils)	AP-3 (BLOC-1) [6]	*Therapeutic*: granulocyte colony-stimulating factor (G-CSF) [7]
Recurrent Infections	frequent viral and bacterial infections	LRO-related granules (dendritic cells, natural killer cells)	AP-3	*Therapeutic*: Not prevented by G-CSF therapy [7]

[1] Sunburn, photo-aging of the skin, solar keratosis and melanocyte nevi are common in HPS and patients are at risk of developing squamous cell carcinoma, basal cell carcinoma, and melanoma (Toro et al., 1999).

[2] HPS visual acuity is generally stable at 20/200 (legally blind in the United States) or worse. Most HPS patients exhibit nystagmus resulting from abnormal crossing of the optic nerve fibers. Iris transillumination is when a light is shone into the pupil is transmitted back through the iris because of a lack of iris pigmentation (Schneier & Fulton, 2013; Summers et al., 1988).

[3] Absent platelet delta granules (determined by whole mount electron microscopy) is a diagnostic hallmark of HPS. Bleeding tendency varies widely between HPS patients. Due to absent delta granules, a secondary platelet aggregation response cannot occur (Huizing et al, 2017 Oct 26 [Updated 2000 July 24]).

[4] Apart from type II epithelial cell defect, aberrant alveolar macrophage or mast cell function has been suggested to underlie HPS-PF (Kirshenbaum et al., 2016; Mahavadi et al., 2010; Nakatani et al., 2000; Rouhani et al., 2009). Onset of PF is in childhood in AP-3 deficiency (Gochuico et al., 2012) and middle age (30–50 years) in BLOC-3 deficiency (Huizing et al, 2017 Oct 26 [Updated 2000 July 24]). AP-3 related PF has not been described in HPS-10 patients (Ammann et al., 2016; Mohammed et al., 2018). There is no approved medical therapy for HPS PF. Lung transplantation may be considered (El-Chemaly et al., 2018; Gahl et al., 2002; Huizing et al, 2017 Oct 26 [Updated 2000 July 24]; Lederer et al., 2005).

[5] HPS colitis involves intestinal granulomas, erosions and inflammatory cells, and resembles Crohn's disease. The underlying cause remains unknown. Abnormal endosomal (LRO-related) membrane formation was suggested, leading to ceroid lipofuscin formation, abnormal autophagy and phagocytosis, inflammation (Felipez et al., 2010; Sofia et al., 2017). Some BLOC-2 or BLOC-3 deficient cases

develop colitis (Huizing et al, 2017 Oct 26 [Updated 2000 July 24]; Hussain et al., 2006). One BLOC-1 deficient case (HPS-7) developed Crohn's colitis in adulthood (Lowe et al., 2013). It is unknown if colitis occurs in AP-3 deficiency.

[6] Immunodeficiency was reported in two unrelated individuals with HPS-9 (BLOC-1 deficiency) (Badolato et al., 2012; Okamura et al., 2018) and needs consideration in future BLOC-1 deficient individuals.

[7] G-CSF therapy was only used in HPS-2 patients (AP3B1 deficiency) (Ammann et al., 2016; Fontana et al., 2006). While G-CSF restores neutrophil numbers, it does not prevent recurrent infections caused by defects in innate immunity in HPS-2 (Fontana et al., 2006).

Table 3:

HPS1 Pathogenic Gene Variants Associated with Hermansky-Pudlak Syndrome Type 1 (HPS-1)

#	mRNA *NM_000195.5*	Amino Acid *NP_000186.2*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
1	del exon 2 [3]	-	Exon 2	Indel	-	(Lasseaux et al., 2018) [4]
2	c.2T>A	p.Met1Lys [5]	Exon 3	Start-loss	-	(Lasseaux et al., 2018) [4,5]
3	c.9delC	p.Cys3Trpfs*26	Exon 3	Frameshift	*Chinese*	(Power et al., 2019)
4	c.34dupG	p.Glu12Glyfs*12	Exon 3	Frameshift	-	(Lasseaux et al., 2018) [4]
5	c.81delG	p.Leu28*	Exon 3	Nonsense	*Korean*	(Sim et al., 2019)
6	del 121-bp [3,6]	p.Pro41Aspfs*12	Intron 3/Exon 4	Indel	*Pakistani*	(Yousaf et al., 2016) [4,6]
7	c.97_100delTCAG	p.Ser33Argfs*18	Exon 3	Indel	*English, Irish, German, Scottish*	(Sandrock et al., 2010) [7]
8	c.166_168delATC	p.Ile56del	Exon 4	Indel	*Afghan*	(Oh et al., 1998)
9	c.212_215delGCTT	p.Cys71Serfs*52	Exon 4	Indel	-	(Lasseaux et al., 2018) [4]
10	c.217delT	p.Ser73Profs*51	Exon 4	Frameshift	-	(Lasseaux et al., 2018) [4]
11	c.255+5G>A	IVS4+5G>A (p.Tyr81Leufs*38)	Intron4	Splice site	*Iranian*	(Ghafouri-Fard et al., 2016)
12	c.288delT	p.Asp97Thrfs*27	Exon 5	Frameshift	*Japanese*	(Ito et al., 2005; Spritz & Oh, 1999)
13	c.316C>G	p.Arg106Gly [8]	Exon 5	Missense	*Chinese*	(Wei et al., 2016) [4]
14	c.344T>C	p.Leu115Pro	Exon 5	Missense	*Arabic*	(Khan et al., 2016) [4]
15	c.355delC	p.His119Thr*5	Exon 5	Frameshift	*German, Polish, Russian*	(Hermos et al., 2002; Sandrock et al., 2010)
16	c.391C>T	p.Arg131*	Exon 5	Nonsense	*Caucasian, Chinese, Spanish*	(Arcot Sadagopan et al., 2017; Gonzalez-Conejero et al., 2003; Hermos et al., 2002; Wei et al., 2011)
17	c.397G>T	p.Glu133*	Exon 5	Nonsense	*German, Italian, Ukrainian*	(Hermos et al., 2002; Shotelersuk et al., 1998)
18	c.398+2T>C	IVS5+2T>C	Intron 5	Splice site	*Mexican*	*novel* [4,9,10]
19	c.398+5G>A	IVS5+5G>A	Intron 5	Splice site	*Chinese, Indian, Japanese*	(Furuhashi et al., 2014; Horikawa et al., 2000; Ito et al., 2005; Li et al., 2016; Mai et al., 2019; Natsuga et al., 2005; Oh et al., 1998; Suzuki et al., 2004; Tanaka et al., 2015; Vincent et al., 2009; Wei et al., 2016) [4,11]

#	mRNA *NM_000195.5*	Amino Acid *NP_000186.2*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
20	c.418delG	p.Ala140Argfs*35	Exon 6	Frameshift	*European*	(Hermos et al., 2002)
21	c.461G>A	p.Trp154*	Exon 6	Nonsense	*Dutch*	(Thielen et al., 2010)
22	c.467_476del10	p.Tyr156Cysfs*16	Exon 6	Indel	*Honduran, Salvadoran*	(Carmona-Rivera, Golas, et al., 2011)
23	c.505G>A	p.Glu169Lys	Exon 6	Missense- Splice site	*Arabic*	(Khan et al., 2016) [4,12]
24	c.507G>A	p.Glu169Glu [13]	Exon 6	Splice site	*African-American*	(Merideth et al., 2009) [13]
25	c.507+1G>A	IVS6+1G>A	Intron 6	Splice site	*Japanese*	(Lasseaux et al., 2018; Natsuga et al., 2005) [14]
26	c.517C>T	p.Arg173*	Exon 7	Nonsense	*Chinese*	(Wei et al., 2016) [4]
27	c.532dupC	p.Gln178Profs*4	Exon 7	Frameshift	*Japanese*	(Ito et al., 2005; Iwakawa et al., 2005)
28	c.610G>T	p.Glu204*	Exon 7	Nonsense	*Spanish*	(Sanchez-Guiu et al., 2014)
29	c.640delC	p.His214Thrfs*117	Exon 7	Frameshift	*Chinese*	(Wei et al., 2019) [4]
30	c.695C>T	p.Ala232Val	Exon 8	Missense	*Arabic*	(Khan et al., 2016) [4]
31	c.716T>C	p.Leu239Pro	Exon 8	Missense	*Dutch, German, Irish*	(Hermos et al., 2002; Lasseaux et al., 2018; Thielen et al., 2010) [4,15]
32	c.868–2A>G	IVS9–2A>G	Intron 9	Splice site	*Chinese*	(Wei et al., 2019) [4]
33	c.937G>A	p.Gly313Ser	Exon 10	Missense- Splice site	*Puerto Rican*	(Carmona-Rivera, Hess, et al., 2011; Lasseaux et al., 2018) [4,16]
34	c.956delA	p.Glu319Glyfs*12	Exon 11	Frameshift	*Chinese*	(Wei et al., 2019) [4]
35	c.962delG	p.Gly321Alafs*10	Exon 11	Frameshift	*Ukrainian*	(Oh et al., 1998)
36	c.962dupG	p.Thr322Hisfs*131	Exon 11	Frameshift	*Japanese*	(Horikawa et al., 2000)
37	c.972delC	p.Met325Trpfs*6	Exon 11	Frameshift	*African-American, Chinese, Japanese, Mexican, Northern European, Puerto Rican*	(Carmona-Rivera, Golas, et al., 2011; Carmona-Rivera, Hess, et al., 2011; Hermos et al., 2002; Lasseaux et al., 2018; Merideth et al., 2009; Oh et al., 1996; Oh et al., 1998; Shotelersuk et al., 1998; Wei et al., 2016) [4,17]
38	c.972dupC	p.Met325Hisfs*128	Exon 11	Frameshift	*Chinese, Japanese, Northern European, Swiss*	(Hermos et al., 2002; Lasseaux et al., 2018; Oh et al., 1996; Oh et al., 1998; Okamura et al., 2019; Wei et al., 2010; Wei et al., 2011; Wei et al., 2019) [4,,17,18]
39	c.988–1 G>T	IVS11–1G>T	Intron 11	Splice site	*Indian*	(Vincent et al., 2009) [19]
40	del13,966-bp/ins49-bp [3]	p.Gln329fs	Intron 11-Exon 20	Indel	*Northern European*	(Griffin et al., 2005)

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#	mRNA *NM_000195.5*	Amino Acid *NP_000186.2*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
41	c.1080C>G	p.Ser360Arg	Exon 12	Missense	*Canadian, German, Irish, Scottish, Swedish, Ukrainian*	*novel* [4,9,20]
42	c.1132_1138delATCAACC	p.Ile378Trpfs*4	Exon 12	Indel	*Chinese*	(Wei et al., 2019) [4]
43	c.1189delC	p.Gln397Serfs*2	Exon 13	Frameshift	*American, Hispanic, Northern European, Russian, Ukrainian*	(Doubkova et al., 2019; Griffin et al., 2005; Hermos et al., 2002; Lasseaux et al., 2018; Oh et al., 1998; Sandrock et al., 2010; Shotelersuk et al., 1998) [4,17,20-24]
44	c.1228A>T	p.Lys410*	Exon 13	Nonsense	*Ukrainian*	*novel* [9,21]
45	c.1276_1279dupGGAG	p.Asp427Glyfs*27	Exon 13	Indel	*Chinese*	(Wei et al., 2019) [4]
46	c.1294_1298delATGGAinsT	p.Met432Serfs*42	Exon 13	Indel	*Mexican*	*novel* [4,9,10]
47	c.1323dupA	p.Gln442Thrfs* 11	Exon 13	Frameshift	*Japanese*	(Oh et al., 1996)
48	c.1342T>C	p.Trp448Arg	Exon 14	Missense	*Pakistani*	(Yousaf et al., 2016) [4]
49	c.[1375delA; c.1388C>A]	p.Ser459Valfs*16	Exon 14	Frameshift	*Northern European*	(Hermos et al., 2002)
50	c.1423_1428delAAGCGG	p.Lys475_Arg476del	Exon 15	Indel	-	(Lasseaux et al., 2018) [4]
51	c.1457_1460dupTTCT	p.Thr488Serfs*95	Exon 15	Indel	*Chinese*	(Wei et al., 2016) [4]
52	c.1472_1487dup16 [24]	p.His497Glnfs*90	Exon 15	Indel	*NW-Puerto Rican*	(Hermos et al., 2002; Oh et al., 1996; Santiago Borrero et al., 2006) [25]
53	c.1477delA	p.Arg493Glyfs*22	Exon 15	Frameshift	*Chinese*	(Power et al., 2019)
54	c.1507C>T	p.Gln503*	Exon 15	Nonsense	*Caucasian*	(Doubkova et al., 2019) [4]
55	del exon 15	deletion	Exon 15	Indel	*Chinese*	(Wei et al., 2019) [4]
56	del exon 15–18 [3]	deletion	Ex15–18	Indel	*Chinese*	(Wei et al., 2016) [4]
57	c.1639G>T/c.1645C>T	p.Val547Leu/ p.Arg549Cys	Exon 17	Missense	*Assyrian, English, German, Irish*	(Nazarian et al., 2008) [15,26]
58	c.1691delA	p.Lys564Argfs*22	Exon 17	Frameshift	*Japanese*	(Ito et al., 2005)
59	c.1744–2A>C	IVS17–2A>C	Intron17	Splice site	*Caucasian, English, German, Irish*	(Hermos et al., 2002; Lasseaux et al., 2018; McElvaney et al., 2018; Oetting & King, 1999) [4,22,27]
60	c.1749G>A	p.Trp583*	Exon 18	Nonsense	*Japanese, Arabic*	(Ito et al., 2005) [4,28]
61	c.1763T>C	p.Leu588Pro	Exon 18	Missense	*Japanese*	(Okamura et al., 2019) [4]

#	mRNA *NM_000195.5*	Amino Acid *NP_000186.2*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
62	c.1787G>T	p.Gly596Val	Exon 18	Missense	*Japanese*	(Okamura et al., 2019; Takeuchi et al., 2014) [4]
63	c.1857+2T>C	IVS18+2T>C	Intron 18	Splice site	*Irish*	(McElvaney et al., 2018) [27]
64	c.1858–1G>A	IVS18–1G>A	Intron18	Splice site	*Dutch, French, German, Irish, Native American*	*novel* [9,29]
65	c.1887delC	p.Val630Serfs*95	Exon 19	Frameshift	*Chinese*	(Wei et al., 2011)
66	c.1932delC	p.Tyr645Thrfs*80	Exon 19	Frameshift	*Chinese*	(Wei, Lian, Wang, & Li, 2009; Wei, Zang, Zhang, Yang, & Li, 2015; Wei et al., 2019) [4]
67	c.1937A>G	p.Tyr646Cys	Exon 19	Missense	*English, Irish, Scottish*	*novel* [9,15,24]
68	c.1941–2A>G	IVS19–2A>G	Intron 19	Splice site	*Japanese*	(Okamura et al., 2019) [4]
69	c.1996G>A	p.Glu666Lys	Exon 20	Missense	*Korean*	(Sim et al., 2019)
70	c.1996G>C	p.Glu666Gln	Exon 20	Missense	-	(Lasseaux et al., 2018) [4]
71	c.1996G>T	p.Glu666*	Exon 20	Nonsense	*Scottish*	(Oh et al., 1998)
72	c.2003T>C	p.Leu668Pro	Exon 20	Missense	*Chinese, Japanese*	(Ito et al., 2005; Iwata et al., 2017; Kanazu et al., 2014; Mai et al., 2019; Okamura et al., 2019; Wei et al., 2016) [4]
73	c.2010_2037del28	p.His671Trpfs*45 [29]	Exon 20	Indel	-	(Lasseaux et al., 2018) [4,30]
74	c.2037_2064del28	p.Leu680Glyfs*36 [29]	Exon 20	Indel	-	(Girot et al., 2019) [30]
75	c.2037_2068delinsCTGG	p.Leu680Trpfs*36 [29]	Exon 20	Indel	-	(Lasseaux et al., 2018) [4,30]
76	c.2056C>T	p.Gln686*	Exon 20	Nonsense	*Pakistani*	(Yousaf et al., 2016) [4]

[1] When deletion/insertion is 1 nucleotide it is named *Frame shift*, when larger it is named *Indel.*

[2] Extracted from literature reference. '-' = unreported.

[3] The nomenclature of these *HPS1* variants are included in this Table as reported, see reference for each specific variant for more details.

[4] At least one of the reported cases with this variant was identified by next generation sequencing.

[5] This variant likely leads to a loss of protein translation at the start codon of the longest splice variant of HPS1 (NM_000195.5). It is also predicted to affect splicing, as it is located at the exon 2–3 splice junction (Supplemental Table S2).

[6] NC_000010.11:g.10:98435762–98435882 (GRCh38): Genomic 121-bp deletion, including a part of intron 3 and exon 4 (Yousaf et al., 2016).

[7] Two unreported siblings from the NIH HPS cohort with this c.97_100delTCAG variant were of *English-Irish-Scottish* descent.

[8] Gray highlight: missense variant. See Supplemental Table S1 for pathogenicity predictions.

[9] *novel* = previously unreported variant detected in the NIH HPS cohort.

[10] This novel *HPS1* variant was found heterozygous by next generation sequencing in 2 unreported siblings of *Mexican* descent from the HPS cohort. They were compound heterozygous for c.398+2T>C and c.1294_1298delATGGAinsT. This splice site variant is predicted to delete the splice junction of exon 18/intron 18 (Supplemental Table S2).

[11] This variant was reported to result in skipping of exon 5 (Suzuki et al., 2004), and is a frequent variant in Japanese HPS patients (Ito et al., 2005).

[12] This variant occurs 3-bp from a splice junction and is predicted to affect the splice site (Supplemental Table S2). No experimental evidence is available (Khan et al., 2016). An alternative intronic splice site, inserting 43-bp of intron 6 sequence may be used as reported for variant c.507G>A occurring in the same codon (Merideth et al., 2009).

[13] This (silent) *HPS1* variant p.Glu169Glu results in a splice defect (Merideth et al., 2009).

[14] This variant is reported to result in use of an alternative intronic splice donor site, 44-bp into intron 6, resulting in a frameshift of the coding region (Natsuga et al., 2005).

[15] In vitro studies showed that the HPS1 protein with this missense variant was unstable (Carmona-Rivera et al., 2013).

[16] This (missense) *HPS1* variant occurs at the 3' splice junction of exon 10, resulting in a cryptic intronic splice site and an aberrantly spliced mRNA that includes 144-bp intronic sequence, producing 11 novel amino acids followed by a stop codon (Carmona-Rivera, Hess, et al., 2011).

[17] This *HPS1* frameshift variant occurs with a high prevalence in HPS-1 subjects of various ethnic backgrounds.

[18] This variant c.972dupC was reported as an ethnic founder variant in a small isolate in a Swiss village (Oh et al., 1998; Schallreuter et al., 1993)

[19] This variant was reported to result in in-frame skipping of exon 12 and removing 56 amino acids from the protein (Vincent et al., 2009).

[20] This *HPS1* variant was identified in one unreported subject of *Canadian-German-Irish-Scottish-Swedish-Ukrainian* descent from the NIH HPS cohort. This subject is compound heterozygous for c.1080C>G and c.1189delC.

[21] This *HPS1* variant was identified in one unreported subject of *Ukrainian* descent from the NIH HPS cohort. This subject is compound heterozygous for c.1189delC and c.1228A>T.

[22] This *HPS1* variant was identified homozygous in one unreported subject of *German* descent from the NIH HPS cohort.

[23] This *HPS1* variant was identified in one unreported subject of *German-English-Irish* descent in the NIH HPS cohort. This subject is compound heterozygous for c.1189delC and c.1744–2A>C.

[24] This *HPS1* variant was found heterozygous in one unreported subject of *English-Irish-Scottish* in the NIH HPS cohort. This subject is compound heterozygous for c.1189delC and c.1937A>G.

[25] This *HPS1* 16-bp duplication (c.1472_1487dup16-bp) is originates from a genetic isolate in northwest Puerto Rico (Oh et al., 1996; Santiago Borrero et al., 2006).

[26] These 2 missense variants occur heterozygous on the same allele in two HPS siblings of our NIH cohort, their cells showed aberrant BLOC-3 assembly (Nazarian et al., 2008). Both missense variants are predicted to be deleterious to protein function (Supplemental Table S3). In vitro studies showed that the HPS1 protein with the p.Val547Leu variant was unstable and prevents proper BLOC-3 formation (Carmona-Rivera et al., 2013). No *HPS1* coding/splice site variant was detected on the other allele, but this allele appeared to be subject to non-sense mediated mRNA decay (on cDNA analysis), indicating a likely (intronic) gene-truncation variant on this allele.

[27] This *HPS1* variant was identified in a subject with of *Irish* descent with HPS clinical features and accelerated pulmonary fibrosis. He was compound heterozygous for c.1744–2A>C (predicted to cause exon skipping (Oetting & King, 1999)) and c.1857+2T>C (predicted to result in use of alternative intronic splice site 4 base-pairs into intron 18, resulting in a frameshift of the coding region) (Supplemental Table S2) (McElvaney et al., 2018).

[28] This *HPS1* variant was identified homozygous by next generation sequencing in one unreported subject of *Arabic* descent in the NIH HPS cohort.

[29] This *HPS1* variant was found homozygous in one unreported subject of *Dutch-French-German-Irish-Native American* descent in the NIH HPS cohort. This novel splice site variant c.1858–1G>A, is predicted to create an alternative splice site 1-bp into exon 18, resulting in a frameshift of the coding region (Supplemental Table S2).

[30] These Indels occur in the same region and result in a loss of the HPS1 termination codon (codon #701) and extension of the translated HPS1 protein.

Table 4:

AP3B1 Pathogenic Gene Variants Associated with Hermansky-Pudlak Syndrome Type 2 (HPS-2)

#	mRNA *NM_003664.4*	Amino Acid *NP_003655.3*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
1	c.2T>G	p.Met1Arg [3]	Exon 1	Start-loss	*Australian*	(Cetica et al., 2015)
2	c.62delG	p.Gly21Valfs*20	Exon 1	Frameshift	-	(Jessen et al., 2013)
3	c.155_158delAGAG	p.Glu52Alafs*11	Exon 2	Indel	*Caucasian, English*	(Wenham et al., 2010)
4	c.177delA	p.Lys59Asnfs*5	Exon 2	Frameshift	-	(de Boer et al., 2017)
5	c.305T>C	p.Leu102Pro [4]	Exon 4	Missense	-	(Jessen et al., 2013)
6	c.716G>A	p.Trp239*	Exon 7	Nonsense	*Moroccan*	(de Boer et al., 2017)
7	c.904A>T	p.Arg302*	Exon 8	Nonsense	-	(Enders et al., 2006)
8	c.1063_1064delCAinsTATCAATATC	p.Gln355Tyrfs*6	Exon 10	Indel	*Italian*	(Fontana et al., 2006)
9	c.1095+5G>A	IVS10+5G>A	Intron10	Splice site	*Mexican*	(Chiang et al., 2010)
10	c.1168–1G>C [6]	IVS11–1G>C	Intron11	Splice site	*Dutch*	(Dell'Angelica et al., 1999; Gochuico et al., 2012) [5,6]
11	c.1473+6T>C	IVS14+6T>C	Intron14	Splice site	-	(Clark et al., 2003)
12	c.1525C>T	p.Arg509*	Exon 15	Nonsense	*Cajun, Houma Indian*	(Huizing et al., 2002)
13	c.1619dupG	p.Ala541Serfs*25	Exon 15	Frameshift	-	(Clark et al., 2003)
14	g.del8168-bp [7]	del exon 15	Introns14+15, Exon 15	Indel	*Turkish*	(Jung et al., 2006) [7]
15	g.del1872-bp [7]	del exon 15	Introns14+15, Exon 15	Indel	-	(Hengst et al., 2018) [7]
16	del exon 16	-	Exon 16	Indel	-	(Jessen et al., 2013)
17	c.1739T>G	p.Leu580Arg	Exon 16	Missense	*Dutch*	(Dell'Angelica et al., 1999)
18	c.1754delT	p.Val585Glufs*6	Exon 16	Frameshift	*Caucasian*	(de Boer et al., 2017)
19	c.1789dupA	p.Ile597Asnfs*12	Exon 16	Frameshift	*Italian*	(Fontana et al., 2006)
20	c.1839_1842delTAGA	p.Asp613Glufs*38	Exon 17	Indel	-	(de Boer et al., 2017; Hengst et al., 2018; Jung et al., 2006)
21	c.1975G>T	p.Glu659*	Exon 18	Nonsense	*Cajun, Houma Indian*	(Huizing et al., 2002)
22	c.2041G>T	p.Glu681*	Exon 18	Nonsense	-	(Ammann et al., 2017; Jessen et al., 2013)

#	mRNA *NM_003664.4*	Amino Acid *NP_003655.3*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
23	g.del624-bp [8] c.del2077_2164	p.Glu693Valfs*13	Intron18, Exon 19	Indel	*Maltese*	(Wenham et al., 2010)
24	c.2546T>G	p.Leu849*	Exon 22	Nonsense	-	(Hengst et al., 2018)
25	c.2702C>G [9]	p.Ser901Cys	Exon 23	Missense Splice site	*Caucasian*	(de Boer et al., 2017) [9]
26	c.2770delC	p.Leu924Phefs*3	Exon 23	Frameshift	-	(Jessen et al., 2013)
27	c.2944delC	p.Leu982Cysfs*19	Exon 25	Frameshift	-	(Hengst et al., 2018)
28	c.3222_3223delTG [10]	p.Lys1076Asnfs*60	Exon 27	Indel-Stop-loss	*United Arabic Emirates*	(Hengst et al., 2018; Jessen et al., 2013; Kurnik et al., 2013) [10]
29	inv(5)p15.1-q14.1 [11]	-	-	Indel-chrom. inversion	*Lebanese*	(Jones et al., 2013) [11]

[1] When deletion/insertion is 1 nucleotide it is named *Frame shift*, when larger it is named *Indel.*

[2] Extracted from literature reference. '-' = unreported.

[3] This variant likely leads to a loss of protein translation in the start codon of the longest splice variant of *AP3B1* (NM_003664.4).

[4] Gray highlight: missense variant. See Supplemental Table S1 for pathogenicity predictions.

[5] At least one of the reported cases with this variant was identified by next generation sequencing.

[6] This variant was originally described as del63-bp in the patients' cDNA (Dell'Angelica et al., 1999), but later found to be due to a gDNA splice site variant, skipping the 63-bp exon 12 (Gochuico et al., 2012).

[7] Described as g.151312_159483del8172-bp (NG_007268) (Hengst et al., 2018). It is possible that del8168-bp reported by (Jung et al., 2006) is the same deletion.

[8] This deletion was reported as: NC_00005.8:g.180242–180866del.

[9] This nucleotide change activates a cryptic donor splice and causes a deletion of 112bp within exon 23 on the mRNA level, resulting in a frame shift and a premature termination codon p.Val900Thrfs*63 (de Boer et al., 2017).

[10] This frameshift in the *AP3B1* C-terminal coding region results in a prolonged altered protein, beyond the termination codon, with 42 additional C-terminal amino acids compared to the wild type protein (Kurnik et al., 2013).

[11] Chromosomal inversion breakpoints occur within the *AP3B1* gene (Jones et al., 2013).

Table 5:

HPS3 Gene Variants Associated with Hermansky-Pudlak Syndrome Type 3 (HPS-3)

No	mRNA *NM_032383.5*	Amino Acid *NP_115759.2*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
1	c.-2993_217+692del [3]	-	5'UTR Intron 1	Indel	*Central Puerto Rican*	(Anikster et al., 2001; Torres-Serrant et al., 2010) [3,4]
2	c.15C>G	p.Tyr5*	Exon 1	Nonsense	*Dutch, German*	*novel* [5,6]
3	c.87dupG	p.Arg30Alafs*2	Exon 1	Frameshift	*Japanese*	(Saito et al., 2019)
4	c.319C>T	p.Arg107*	Exon 1	Nonsense	*Japanese*	(Okamura et al., 2019) [7]
5	c.437_439delGAG	p.Gly146del	Exon 1	Indel	*Japanese*	(Okamura et al., 2019) [7,8]
6	c.712+2T>C	IVS2+2	Intron 2	Splice site	*Chinese*	(A. Wei et al., 2016) [7]
7	c.726_727insTGCCTTACATC	p.Ile243Cysfs*41	Exon 3	Indel	*Puerto Rican*	*novel* [4,5]
8	c.728_729insA	p.Ser244Phefs*4	Exon 3	Frameshift	*Italian, Sicilian*	(Boissy et al., 2005) [9]
9	c.851_852delGA	p.Arg284Lysfs*11	Exon 3	Indel	*Portuguese*	*novel* [5,11]
10	c.868C>T	p.Gln290*	Exon 3	Nonsense	*Arabic*	(Khan et al., 2016) [7]
11	c.885–1G>A	IVS3–1G>A	Intron 3	Splice site	*Libyan*	(Thielen et al., 2010)
12	c.1012G>T	p.Glu338*	Exon 5	Nonsense	*Caucasian*	*novel* [5,12]
13	c.1107_1119del13insC	p.Pro370_Ser373del	Exon 5	Indel	*French-Canadian*	*novel* [5,13,14]
14	c.1153_1160del8	p.Val385Lysfs*2	Exon 5	Indel	*Middle-Eastern*	(Trujillano et al., 2017) [7]
15	c.1163+1G>A	IVS5+1G>A	Intron 5	Splice site	*Ashkenazi Jewish*	(Huizing et al., 2001)
16	c.1189C>T	p.Arg397Trp	Exon 6	Missense	*Canadian, Caucasian, Chinese, German, Japanese, Polish, Russian, Swiss*	(Huizing et al., 2001; Nazarian et al., 2008; Okamura et al., 2019; Wei et al., 2016) [7,12,15]
17	c.1195A>G/ c.1199_1200insATTGC	p.Ser399Gly/ p.Ala401Leufs*16	Exon 6	Indel	*English, German, Irish, Scottish, Cherokee*	*novel* [5,16]
18	c.1291delC	p.Leu431Phefs*3	Exon 7	Frameshift	*Japanese*	(Okamura et al., 2019) [7,8]
19	c.1426dupA	p.Ile476Asnfs*8	Exon 8	Frameshift	*Japanese*	(Saito et al., 2019)
20	c.1509G>A	p.Met503Ile	Exon 8	Missense-Splice site	*Pakistani*	(Yousaf et al., 2016) [7,17]

No	mRNA *NM_032383.5*	Amino Acid *NP_115759.2*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
21	c.1555_1595dup41	p.Leu533Phefs*10	Exon 8	Indel	*Chinese*	(Power et al., 2019)
22	c.1673T>C	p.Leu558Pro	Exon 8	Missense	-	(Lasseaux et al., 2018) [7]
23	c.1691+1G>A	IVS9+1G>A	Intron 9	Splice site	*French-Canadian*	*novel* [5,13]
24	c.1691+2T>G	IVS9+2T>G	Intron 9	Splice site	*Ashkenazi Jewish*	(Huizing et al., 2001)
25	c.1838C>G	p.Ser613*	Exon 10	Nonsense	*Chinese*	(Wei et al., 2019) [7]
26	c.1870G>T	p.Glu624*	Exon 10	Nonsense	*German, Irish*	*novel* [5,18]
27	c.2208_2209delTC	p.Gln737Alafs*20	Exon 12	Indel	*Chinese*	(Wei et al., 2016) [7]
28	c.2464C>T	p.Arg822*	Exon 13	Nonsense	*Dutch, German, Portuguese, Spanish*	(Bastida et al., 2019) [6,7,11]
29	c.2482–2A>G	IVS13–2A>G	Intron 13	Splice site	*Irish/German*	(Huizing et al., 2001)
30	c.2589+1G>C	IVS14+1G>C	Intron14	Splice site	*German/Swiss*	(Huizing et al., 2001)
31	c.2589+1G>T	IVS14+1G>T	Intron14	Splice site	*German, Irish*	*novel* [5,18]
32	c.2628delT	p.Ile877Phefs*25	Exon 15	Frameshift	-	(Lasseaux et al., 2018) [7]
33	c.2733delG	p.Leu912*	Exon 15	Frameshift	*English, German, Irish, Scottish, Cherokee*	*novel* [5,16,19]
34	c.2739_2742delGAGA	p.Glu913Aspfs*14	Exon 15	Indel	-	*novel* [5,14]
35	c.2771delA	p.Asn924Ilefs*4	Exon 15	Frameshift	*Turkish*	(Sandrock-Lang et al., 2017)
36	c.2805G>A	p.Trp935*	Exon 16	Nonsense	*Chinese*	(Wei et al., 2016) [7]
37	c.2888–1612G>A[21]	IVS16–1612G>A p.Glu963Alafs*24	Intron16	Splice site	*English, Irish*	(Huizing et al., 2001) [20]

[1] When deletion/insertion is 1 nucleotide it is named *Frame shift*, when larger it is named *Indel.*

[2] Extracted from literature reference. '-' = unreported.

[3] This *HPS3* 3.9-kb deletion occurs within two *Alu* repeats, encompassing exon 1 and originates from a genetic isolate of central Puerto Rico (Anikster et al., 2001). Current nomenclature (as annotated in ClinVar) for this deletion is NM_032383.5(HPS3):c.-2993_217+692del or NC_000003.12:g.149126714_149130632del (GRCh38) or NG_009847.1:g.2131_6049del.

[4] This *HPS3* variant was identified in one unreported female subject of *Puerto Rican* descent in the NIH cohort. This subject was compound heterozygous for c.726delinsTGCCTTACATC and the *Central Puerto Rican* founder variant g.del3.9-kb.

[5] *novel* = previously unreported variant detected in the NIH HPS cohort.

[6] This *HPS3* variant was identified in one unreported male subject of *Dutch-German* descent in the NIH HPS cohort. This subject was compound heterozygous for c.15C>G and c.2464C>T.

[7] At least one of the reported cases with this variant was identified by next generation sequencing.

[8] The HPS3 variant c.437_439delGAG occurred compound heterozygous with c.1291delC in a subject of Japanese descent who also had non-segmental vitiligo (Okamura et al., 2019).

[9] This *HPS3* variant c.728insA was identified homozygous in one unreported female subject of *Sicilian* decent in the NIH HPS cohort.

[10] Gray highlight: missense variant. See Supplemental Table S1 for pathogenicity description.

[11] This *HPS3* variant was identified in one unreported male subject of *Portuguese* decent in the NIH HPS cohort. This subject was compound heterozygous for c.851_852delGA and c.2464C>T.

[12] This *HPS3* variant was identified in one unreported female subject of *Caucasian* descent in the NIH HPS cohort. This subject was compound heterozygous for c.1012G>T and c.1189C>T.

[13] This *HPS3* variant was identified in one unreported female subject of *French-Canadian* descent in the NIH HPS cohort. This subject was compound heterozygous for c.1107_1119del13insC and c.1691+1G>A.

[14] This *HPS3* variant was identified in one unreported female subject of in the NIH cohort (referred by Dr. Doherty, Carilion Clinic, Roanoke, VA). This subject was compound heterozygous for c.1107_1119del13insC and c.2739_2742delGAGA.

[15] This *HPS3* variant c.1189C>T was identified homozygous in one unreported female subject of *Canadian-Polish-Russian* decent in the NIH cohort. Cells of this patient showed destabilized BLOC-2 assembly, likely due to pathogenicity of this variant (Nazarian et al., 2008).

[16] This *HPS3* variant was identified in one unreported female subject of *English-German-Irish-Scottish-Cherokee* descent in the NIH HPS cohort. This subject was compound heterozygous for c.1195A>G/1199insATTGC and c.2733delG.

[17] This (missense) *HPS3* variant c.1509G>A; p.Met503Ile occurs at the exon8/intron 8 splice site junction and may affect splicing. This variant occurs homozygous in 4 subjects of a consanguineous Pakistani family (Yousaf et al., 2016).

[18] This *HPS3* variant was identified in one unreported male subject of *German-Irish* descent. This subject was compound heterozygous for c.1870G>T and c.2589+1G>T.

[19] Subject HPS34 of *English-Irish* descent in (Huizing et al., 2001) was reported heterozygous for c.2887+2500G>A. We found c.2733delG to be the second *HPS3* variant in this subject.

[20] This *HPS3* variant was reported in an alternative nomenclature as c.2887+2500G>A. This intronic variant introduces a new consensus splice site that results in insertion of 89-bp (a ‘pseudoexon’) in the patient’s cDNA (Huizing et al., 2001; Vorechovsky, 2010).

Table 6:

HPS4 Pathogenic Gene Variants Associated with Hermansky-Pudlak Syndrome Type 4 (HPS-4)

No	mRNA *NM_022081.5*	Amino Acid *NP_071364.4*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
1	c.45G>A	p.Trp15*	Exon 3	Nonsense	*Uruguayan, Japanese*	(Carmona-Rivera, Golas, et al., 2011; Okamura et al., 2018) [3]
2	c.47delA	p.Asn16Ilefs*11	Exon 3	Frameshift	*Uruguayan*	(Carmona-Rivera, Golas, et al., 2011)
3	c.57delT	p.Leu20Phefs*7	Exon 3	Frameshift	*French, German, Irish, Northern European*	(Suzuki et al., 2002) [4]
4	c.123T>A	p.Tyr41*	Exon 4	Nonsense	*Japanese*	(Okamura et al., 2018) [3]
5	c.148C>T	p.Gln50*	Exon 4	Nonsense	*Chinese*	(Wei et al., 2019) [3]
6	c.272T>C	p.Leu91Pro [5]	Exon 4	Missense	*Turkish*	(Bastida et al., 2019) [3]
7	c.276+5G>A	IVS4+5G>A	Intron 4	Splice site	*Pakistani*	(Yousaf et al., 2016) [3]
8	c.357C>G	p.Tyr119*	Exon 5	Nonsense	*Dutch, English, Irish, Polish, Slovak*	*novel* [6,7]
9	c.412G>T	p.Glu138*	Exon 6	Nonsense	*Indian*	(Anderson et al., 2003)
10	c.416G>A	p.Trp139*	Exon 6	Nonsense	*Chinese*	(Power et al., 2019)
11	c.430G>T	p.Glu144*	Exon 6	Nonsense	*Indian*	(Arcot Sadagopan et al., 2017) [3]
12	c.461A>G	p.His154Arg	Exon 6	Missense	*Caucasian, Japanese*	(Anderson et al., 2003; Saito et al., 2013) [8,9]
13	c.541C>T	p.Gln181*	Exon 7	Nonsense	*Southern Italian*	(Suzuki et al., 2002)
14	c.554G>A	p.Arg185His	Exon 7	Missense	*Indian*	(Arcot Sadagopan et al., 2017) [3]
15	c.596+1G>A	IVS7+1G>A	Intron 7	Splice site	*Japanese*	(Okamura et al., 2019) [3]
16	c.597–2A>T	IVS7–2A>T	Intron 7	Splice site	-	(Jones et al., 2012) [3]
17	c.630dupC	p.Ala211Argfs*47	Exon 8	Frameshift	*Chinese*	(Wu et al., 2019)
18	c.649C>T	p.Arg217*	Exon 8	Nonsense	*Ashkenazi Jewish, English, Polish*	(Anderson et al., 2003; Lozynska et al., 2018)
19	c.664G>T	p.Glu222*	Exon 8	Nonsense	*Indian*	(Anderson et al., 2003)
20	c.706+1G>A	IVS9+1G>A	Intron 9	Splice site	*Dutch, English, Irish, Polish, Slovak*	*novel* [6,7]
21	c.730C>T	p.Gln244*	Exon 10	Nonsense	*Japanese*	(Araki et al., 2014)

No	mRNA *NM_022081.5*	Amino Acid *NP_071364.4*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
22	c.803G>A [10]	p.Arg268Lys	Exon 10	Missense-Splice Site	-	(Lasseaux et al., 2018) [3,10]
23	c.949_972dup24	p.Ala317_Glu324dup	Exon 11	Indel	*Dutch*	(Suzuki et al., 2002)
24	c.1132C>T	p.Gln378*	Exon 11	Nonsense	-	*novel* [11]
25	c.1318C>T	p.Gln440*	Exon 11	Nonsense	*Turkish*	(Sandrock-Lang et al., 2018)
26	c.1546C>T	p.Gln516*	Exon 11	Nonsense	*Caucasian*	*novel* [6,8]
27	c.1547_1548delAG	p.Gln516Argfs*42	Exon 11	Indel	*Indian*	(Arcot Sadagopan et al., 2017) [3]
28	c.1713+5G>C	IVS11+5G>C	Intron 11	Splicing	*Chinese*	(Wei et al., 2019) [3]
29	c.1856C>T	p.Pro619Leu	Exon 13	Missense	-	(Lasseaux et al., 2018) [3]
30	c.1858C>T	p.Gln620*	Exon 13	Nonsense	-	(Sakata et al., 2013)
31	c.1891C>T	p.Gln631*	Exon 13	Nonsense	*German South Tirol*	(Suzuki et al., 2002)
32	c.1897_1898dupCG	p.Ser634Alafs*3	Exon 13	Indel	*Japanese*	(Okamura et al., 2019) [3]
33	c.2054delC	p.Pro685Leufs*17	Exon 14	Frameshift	*Sri Lankan, Spanish*	(Bachli et al., 2004; Bastida et al., 2019) [3]
34	c.2089_2093dupAAGCA	p.Lys699Serfs*5	Exon 14	Indel	*Austrian, Czech, English, German, Hungaran, Irish, Scandinavian, Swiss*	(Anderson et al., 2003; Suzuki et al., 2002)

[1] When deletion/insertion is 1 nucleotide it is named *Frame shift*, when larger it is named *Indel.*

[2] Extracted from literature reference. '-' = unreported.

[3] At least one of the reported cases with this variant was identified by next generation sequencing.

[4] This *HPS4* variant was identified in heterozygous state in one unreported subject of *French-German-Irish* descent in the NIH HPS cohort.

[5] Gray highlight: missense variant. See Supplemental Table S1 for pathogenicity description.

[6] *novel* = previously unreported variant detected in the NIH HPS cohort.

[7] This *HPS4* variant was identified in one unreported subject of *Dutch-English-Irish-Polish-Slovak* descent in the NIH HPS cohort. This subject is compound heterozygous for c.357C>G and c.706+1G>A.

[8] This *HPS4* variant was identified in one unreported subject of *Caucasian* descent in the NIH HPS cohort. This individual is compound heterozygous for c.461A>G and c.1546C>T.

[9] This variant was found homozygous in two Japanese siblings with HPS and mental disorder (schizophrenia and major depression). It was suggested that *HPS4* gene variants are associated with susceptibility to schizophrenia (Saito et al., 2013) and/or cognitive function (Kuratomi et al., 2013).

[10] This (missense) *HPS4* variant c.803G>A; p.Arg268Lys (Lasseaux et al., 2018) occurs at the exon10/intron 11 splice site junction and is predicted to affect splicing (Supplemental Table S2).

[11] This nonsense variant c.1132C>T (p.Gln378*) was found homozygous in one unreported female subject in the NIH cohort (referred by Dr. Everman, Greenwood Genetics Center, Greenville, SC).

Table 7:

HPS5 Pathogenic Gene Variants Associated with Hermansky-Pudlak Syndrome Type 5 (HPS-5)

No	mRNA *NM_181507.1*	Amino Acid *NP_852608.1*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
1	c.219G>A	p.Arg73Arg [3]	Exon 3	Splice site	*Turkish*	(Lasseaux et al., 2018; Michaud et al., 2017) [3,4]
2	c.285–10A>G	IVS4–10A>G	Intron 4	Splice site	*Turkish*	(Stephen et al., 2017) [4]
3	c.302_305delTTTG	p.Val101Glyfs*3	Exon 5	Indel	*Cuban, Venezuelan*	(Carmona-Rivera, Golas, et al., 2011)
4	c.434G>A	p.Gly145Glu [5]	Exon 5	Missense	*German, Irish, Welsh*	(Nazarian et al., 2008)
5	c.719G>C	p.Arg240Pro	Exon 7	Missense	*African-French*	(Lasseaux et al., 2018; Michaud et al., 2017) [4]
6	c.803delC [6]	p.Pro268Leufs*4	Exon 7	Frameshift	-	(Ringeisen et al., 2013) [6]
7	del 1.4-kb [7,8]	-	Exon 7	Indel	*African-French*	(Michaud et al., 2017) [4,7]
8	c.814_818delATTAC	p.Ile272Serfs*8	Exon 7	Indel	-	(Lasseaux et al., 2018) [4]
9	c.818_822delCTCTC	p.Thr273Lysfs*7	Exon 7	Indel	*French*	(Michaud et al., 2017) [4]
10	c.879dupC	p.Lys294Glnfs*6	Exon 8	Frameshift	*English, Irish*	(Huizing et al., 2004)
11	c.888dupA	p.His297Thrfs*3	Exon 8	Frameshift	*Turkish*	(Korswagen et al., 2008)
12	c.1417C>T	p.Gln473*	Exon12	Nonsense	*Turkish*	(Lasseaux et al., 2018; Michaud et al., 2017) [4]
13	c.1423delC	p.Leu475Serfs*37	Exon 12	Frameshift	*Mexican*	(Carmona-Rivera, Golas, et al., 2011)
14	c.1618C>T	p.Gln540*	Exon 13	Nonsense	*Arabic*	(Khan et al., 2016) [4]
15	c.1634+1G>A	IVS13+1G>A	Intron13	Splice site	*Cuban, Venezuelan*	(Carmona-Rivera, Golas, et al., 2011)
16	c.1871T>G	p.Leu624Arg [9]	Exon 16	Missense	*Swiss*	(Huizing et al., 2004; Lasseaux et al., 2018; Michaud et al., 2017) [4,9]
17	c.1900delG	p.Glu634Serfs*3	Exon 16	Frameshift	-	(Lasseaux et al., 2018; Michaud et al., 2017) [4]
18	c.1960A>T	p.Lys654*	Exon 16	Nonsense	*English, German, Scottish*	(Botero et al., 2018) [4]
19	c.2026_2029delGTTA	p.Val676Metfs*8	Exon 16	Indel	*Turkish*	(Zhang et al., 2003)
20	c.2219T>C	p.Leu740Ser	Exon 16	Missense	-	(Lasseaux et al., 2018; Michaud et al., 2017) [4]
21	c.2234T>C	p.Leu745Ser	Exon 16	Missense	*Chinese*	(Wei et al., 2016) [4,10]

No	mRNA *NM_181507.1*	Amino Acid *NP_852608.1*	Exon/Intron	Variant Type [1]	Ethnic Background [2]	References and Footnotes
22	c.2593C>T	p.Arg865*	Exon 18	Nonsense	*Dutch, English, Irish, Swedish*	(Huizing et al., 2004)
23	c.2624delT	p.Leu875Cysfs*20	Exon 18	Frameshift	*Dutch, English, Irish, Swedish*	(Huizing et al., 2004)
24	c.2750_2751delAG	p.Glu917Valfs*14	Exon19	Indel	*French*	(Lasseaux et al., 2018; Michaud et al., 2017) [4]
25	c.2928_2929dupGA	p.Thr977Argfs*15	Exon 20	Indel	*English, Irish*	(Huizing et al., 2004)
26	c.2974_2977delCTCT	p.Leu992Valfs*17	Exon 21	Indel	-	(Lasseaux et al., 2018) [4]
27	c.2979_2982delTTTG	p.Cys993Trpfs*16	Exon 21	Indel	*French*	(Michaud et al., 2017) [4]
28	c.3058+3A>G	IVS21+3A>G	Intron 21	Splice site	*Turkish*	(Lasseaux et al., 2018; Michaud et al., 2017) [4]
29	c.3096_3098delCCT	p.Leu1033del	Exon 22	Indel	*French*	(Michaud et al., 2017) [4]
- [8]	*c.3293C>T*	*p.Thr1098Ile* [9]	Exon 22	Missense	*Swiss*	(Huizing et al., 2004) [9]
30	c.3346A>G	p.Met1116Val	Exon 23	Missense	*Chinese*	(Wei et al., 2016) [4,10]
31	del 1.5-kb [8]	-	-	Indel	-	(Lasseaux et al., 2018) [4]

[1] When deletion/insertion is 1 nucleotide it is named *Frame shift*, when larger it is named *Indel.*

[2] Extracted from literature reference. '-' = unreported.

[3] This (silent) *HPS5* variant c.219G>A; p.Arg73Arg occurs at the exon3/intron 3 splice site junction and is predicted to affect splicing (Supplemental Table S2).

[4] At least one of the reported cases with this variant was identified by next generation sequencing.

[5] Gray highlight: missense variant. Gray highlight: missense variant. See Supplemental Table S1 for pathogenicity description.

[6] This variant was previously described as c.1081delC (Ringeisen et al., 2013).

[7] Described as Chr11:18327845 to Chr11:18329253 (Michaud et al., 2017).

[8] The nomenclature of these *HPS6* variants are included in this Table as reported, see reference for each specific variant for more details.

[9] Two siblings were homozygous for 2 missense *HPS5* variants (hemizygosity was excluded): p.Leu624Arg and p.Thr1098Ile (Huizing et al., 2004). The high MAF and low pathogenicity prediction (Supplemental Table S1) classifies p.Thr1098Ile as a benign SNP. Variant p.Leu624Arg classifies as a likely pathogenic missense and is also identified in other HPS-5 individuals in trans with a pathogenic variant (Lasseaux et al., 2018; Michaud et al., 2017).

[10] These variants were originally reported as c.1892T>C and c.3004A>G, using NM_007216 (HPS5 mRNA Variant 2) nomenclature. For this report, the nomenclature of these variants was converted to NM_181507.1 (*HPS5* mRNA Variant 1).

Table 8:

HPS6 Pathogenic Gene Variants Associated with Hermansky-Pudlak Syndrome Type 6 (HPS-6)

No	mRNA *NM_024747.5*	Amino Acid *NP_079023.2*	Exon/Intron [1]	Variant Type [2]	Ethnic Background [3]	References and Footnotes
1	c.62_63insCGGCG	p.Leu22Glyfs*33	Exon 1	Indel	-	(Lasseaux et al., 2018) [4]
2	c.60_64dupGCGGC	p.Leu22Argfs*33	Exon 1	Indel	*Chinese, Japanese, Portuguese*	(Bastida et al., 2019; Okamura et al., 2018; Wei et al., 2016; Wei et al., 2019) [4]
3	c.87_108dup22	p.Ser37Leufs*146	Exon 1	Indel	*Czech, Eastern/Northern European, German, Polish*	(Radke et al., 2013; Summers & Schimmenti, 2014) [5]
4	c.141_143delinsG	p.Pro49Trpfs*126	Exon 1	Indel	-	(Lasseaux et al., 2018) [4]
5	c.155delT	p.Val52Glufs*6	Exon 1	Frameshift	*Chinese*	(Wei et al., 2016) [4]
6	c.206_210dupGGGCC	p.Trp71Glyfs*158	Exon 1	Indel	*Chinese*	(Wei et al., 2019) [4]
7	c.223C>T	p.Gln75*	Exon 1	Nonsense	*Italian*	(Huizing et al., 2009)
8	c.233C>G	p.Pro78Arg [6]	Exon 1	Missense	*Japanese*	(Okamura et al., 2019) [4]
9	c.238dupG	p.Asp80Glyfs*96	Exon 1	Frameshift	*Dutch, German*	(Huizing et al., 2009)
10	c.275T>A	p.Leu92Gln [7]	Exon 1	Missense	-	(Lasseaux et al., 2018) [4,7]
11	c.288G>A	p.Trp96*	Exon 1	Nonsense	*Arabic*	(Khan et al., 2016) [4]
12	c.337C>T	p.Arg113Trp	Exon 1	Missense	-	(Lasseaux et al., 2018) [4]
13	c.383T>C	p.Val128Ala	Exon 1	Missense	*Caucasian*	(Han et al., 2018) [4]
14	c.448_505dup58	p.Glu169Glyfs*26	Exon 1	Indel	*Caucasian*	*novel* [4,8,9]
15	c.455C>G	p.Ser152*	Exon 1	Nonsense	-	(Lasseaux et al., 2018) [4]
16	c.503_504delTG	p.Leu168Argfs*7	Exon 1	Indel	*Chinese*	(Wei et al., 2019) [4]
17	c.779G>A	p.Gly260Glu	Exon 1	Missense	*Punjabi Afghan*	(Hull et al., 2016) [4]
18	c.815C>T	p.Thr272Ile	Exon 1	Missense	*Dutch, German*	(Huizing et al., 2009)
19	c.823C>T	p.Pro275Ser	Exon 1	Missense	*Pakistani*	(Yousaf et al., 2016) [4]
20	c.877C>T	p.Glu293*	Exon 1	Nonsense	-	(Shamseldin et al., 2017) [4]

No	mRNA *NM_024747.5*	Amino Acid *NP_079023.2*	Exon/Intron [1]	Variant Type [2]	Ethnic Background [3]	References and Footnotes
21	c.895C>T	p.Arg299Trp	Exon 1	Missense	*Chinese*	(Wei et al., 2016) [4]
22	c.896G>C	p.Arg299Pro	Exon 1	Missense	-	(Lasseaux et al., 2018) [4]
23	c.905G>A	p.Gly302Asp	Exon 1	Missense	-	(Lasseaux et al., 2018) [4]
24	c.902dupT	p.Thr303Hisfs*64	Exon 1	Frameshift	*Russian-Palestinian*	(Hull et al., 2016) [4]
25	c.913C>T	p.Gln305*	Exon 1	Nonsense	*English, German, Scottish*	(Huizing et al., 2009)
26	c.1065dupG [10]	p.Leu356Alafs*11	Exon 1	Frameshift	*Israeli Bedouin*	(Schreyer-Shafir et al., 2006) [10]
27	c.1083dupC	p.Gly362Argfs*5	Exon 1	Frameshift	*Russian-Palestinian*	(Hull et al., 2016) [4]
28	c.1114 C>T	p.Arg372*	Exon 1	Nonsense	*Irish, Native American (Cherokee), Scottish*	(O'Brien et al., 2016)
29	c.1234C>T	p.Gln412*	Exon 1	Nonsense	*Italian*	(Huizing et al., 2009)
30	c.1235_1239dupAGCGG	p.Arg414Serfs*15	Exon 1	Indel	*Chinese*	(Wei et al., 2019) [4]
31	c.1372delG	p.Glu458Serfs*8	Exon 1	Frameshift	*Chinese*	(Wei et al., 2016) [4]
32	c.1387C>T	p.Arg463*	Exon 1	Nonsense	-	(Lasseaux et al., 2018) [4]
33	c.1513C>T	p.Gln505*	Exon 1	Nonsense	*Chinese*	(Wei et al., 2016; Wei et al., 2019) [4]
34	c.1644delA	p.Gly550Glufs*2	Exon 1	Frameshift	*Arabic*	(Khan et al., 2016) [4]
35	c.1711_1712insAG	p.Cys571*	Exon 1	Indel	*Czech, Eastern/Northern European, German, Polish*	(Radke et al., 2013; Summers & Schimmenti, 2014) [5]
36	c.1714_1717delCTGT	p.Leu572Alafs*40	Exon 1	Indel	*Belgian*	(Lasseaux et al., 2018; Zhang et al., 2003) [4]
37	c.1819C>T	p.Arg607*	Exon 1	Nonsense	*Chinese*	(Lasseaux et al., 2018; Wei et al., 2019) [4]
38	c.1865_1866delTG	p.Leu622Argfs*12	Exon 1	Indel	*German, Irish*	(Huizing et al., 2009)
39	c.1898delC	p.Pro633Leufs*76	Exon 1	Frameshift	*Japanese*	(Miyamichi et al., 2016) [4]
40	c.1919_1920delTC	p.Val640Glyfs*29	Exon 1	Indel	*German-Caucasian*	(Andres et al., 2017) [4]
41	c.2038C>T	p.Gln680*	Exon 1	Nonsense	*Japanese*	(Miyamichi et al., 2016; Okamura et al., 2018; Okamura et al., 2019) [4, 11]
42	c.2189dupC	p.Leu731Serfs*28	Exon 1	Frameshift	*Caucasian*	*novel* [4,8,9]

No	mRNA *NM_024747.5*	Amino Acid *NP_079023.2*	Exon/Intron [1]	Variant Type [2]	Ethnic Background [3]	References and Footnotes
43	c.2207T>C	p.Leu736Pro	Exon 1	Missense	-	(Lasseaux et al., 2018) [4]
44	del19,972-bp [12]	-	Exon 1	Indel	*English, German, Scottish*	(Huizing et al., 2009)
45	del exon 1 [12]	-	Exon 1	Indel	-	(Lasseaux et al., 2018) [4]

[1]The *HPS6* gene consists of 1 exon.

[2]When deletion/insertion is 1 nucleotide it is named *Frameshift*, when larger it is named *Indel*.

[3]Extracted from literature reference. '-' = unreported.

[4]At least one of the reported individuals with this variant was identified by next generation sequencing.

[5]The subject described in these references was also seen at NIH and is of *Eastern/Northern European* (*Czech, German, Polish*) descent. This subject is compound heterozygous for c.87_108dup22-bp and c.1711_1712insAG.

[6]Gray highlight: missense variant. See text and Supplemental Tables for pathogenicity description.

[7]This variant is listed as a variant of uncertain significance with a high MAF in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/).

[8]*novel* = previously unreported variant and/or ethnicity, detected in the NIH HPS cohort.

[9]This *HPS6* variant was identified by exome sequencing in one unreported subject of *Caucasian* descent in the NIH HPS cohort. This subject is compound heterozygous for c.448_505dup58-bp and c.2189dupC.

[10]This frameshift variant was previously described as c.1066_1067insG (p.Leu356Argfs*11) (Schreyer-Shafir et al., 2006).

[11]This *HPS6* variant c.2038C>T (p.Gln680*) appears to be a Japanese variant, as it occurs in 5 Japanese subjects and is not reported in dbSNP/ExAc databases.

[12]The nomenclature of these *HPS6* variants are included in this Table as reported, see reference for each specific variant for more details.

Table 9:

Pathogenic Gene Variants Associated with Hermansky-Pudlak Syndrome Types 7 through 10 (HPS-7 - HPS-10)

#	mRNA	Amino Acid	Exon/Intron	Variant Type [1]	Reference SNP (dbSNP) [2]	Ethnic Background (age, gender) [3]	References and Footnotes
HPS-7: *DTNBP1* (*BLOC1S8, Dysbindin*)							
	NM_032122.4	*NP_115498.2*					
1	c.177G>A	p.Trp59*	Exon 4	Nonsense	rs727502866	*Caucasian* (77y, F)	(Lowe et al., 2013) [4]
2	c.307C>T	p.Gln103*	Exon 5	Nonsense	rs104893945	*Portuguese* (48y, M), *Paraguayan* (6y, M) *Portuguese* (26y, M;56y, F) *Portuguese* (18y, F) Argentinian (M)	(Li et al., 2003) (Bryan et al., 2017) [5] (Bastida et al., 2019) [5] (Bastida et al., 2019) [5] *unreported* *5,6*
3	c.771_774delCTCT	p.Asn257Lysfs*13	Exon 9	Indel	-	*- (1 case)*	(Lasseaux et al., 2018) [5]
4	c.1017_1020delAGAG	p.Glu340Profs*44	Exon 10	Indel	-	*Argentinian* (M)	*unreported* [5,6]
HPS-8: *BLOC1S3* (*Reduced Pigmentation*)							
	NM_212550.4	*NP_997715.1*					
1	c.131C>A	p.Ser44*	Exon 2	Nonsense	rs281865115	*Iranian* (6y, M)	(Cullinane et al., 2012)
2	c.385_403del19	p.Ser129Glnfs*90	Exon 2	Indel	-	*- (1 case)*	(Lasseaux et al., 2018) [5]
3	c.444_467del24	p.Gln150_Ala157del	Exon 2	Indel	rs754841982	*- (1 case)*	(Lasseaux et al., 2018) [5]
4	c.448delC	p.Gly150Argfs*75	Exon 2	Frameshift	rs281865116	*Pakistani* (6 familial cases)	(Morgan et al., 2006) [7]
HPS-9: *BLOC1S6* (*PLDN*)							
	NM_012388.3 [8]	*NP_036520.1*					
1	c.232C>T	p.Gln78*	Exon 2	Nonsense	rs201348482	*Italian* (17y, F), *Pakistani* (4y, F) Indian (9mo, M)	(Badolato et al., 2012) [5,9] (Yousaf et al., 2016) [5] (Cullinane et al, NIH unpublished)
2	c.285_286dupTC	p.His96Leufs*22	Exon 3	Indel	-	*Japanese* (52y, F)	(Okamura et al., 2018) [5,9]

#	mRNA	Amino Acid	Exon/Intron	Variant Type [1]	Reference SNP (dbSNP) [2]	Ethnic Background (age, gender) [3]	References and Footnotes
HPS-10: *AP3D1*							
	NM_001261826.3	*NP_001248755.1*					
1	c.1978delG	p.Ala660Argfs*54	Exon 17	Frameshift	-	*3 siblings*	(Mohammed et al., 2018) [5,10]
2	c.3565_3566delGT	p.Val1189Leufs*8	Exon 32	Indel	rs879255646	*Turkish* (3.5y, M)	(Ammann et al., 2017; Ammann et al., 2016) [5,11]

[1] When deletion/insertion is 1 nucleotide it is named *Frameshift*, when larger it is named *Indel.*

[2] Reference SNP numbers for each variant as listed in dbSNP (https://www.ncbi.nlm.nih.gov/snp; searched November 2019), none of the listed SNPs in this Table has a reported allele frequency, suggesting they are rare variants.

[3] Extracted from literature reference. Age (y, years at reporting) and gender (M, male; F, female) of each subject is included for future comparison of additional cases. '-' = unreported.

[4] This subject also developed granulomatous colitis (Lowe et al., 2013).

[5] The variant in this report was identified by next generation sequencing.

[6] This *DTNBP1* variant was identified by exome sequencing in one unreported male subject of *Argentinian* descent in the NIH HPS cohort referred by Dr. Rosenzweig, NIH Clinical Center, NIH, Bethesda, MD). This subject is compound heterozygous for c.307C>T and c.1017_1020delAGAG.

[7] One extended Pakistani family with 6 affected HPS-8 cases homozygous for c.448delC was reported (Morgan et al., 2006).

[8] Both *BLOC1S6* pathogenic variants were reported according to transcript variant 2 (NM_012388.3) nomenclature and are listed as such in this Table to avoid confusion. A longer transcript variant (Variant 1, NM_001311255.1), appeared recently in databases, and future reports may adjust variant nomenclature.

[9] Both the Italian and Japanese subjects had a history of recurrent leucopenia and mild thrombocytopenia, causing immunodeficiency (Badolato et al., 2012; Okamura et al., 2018). The Japanese subject developed schizophrenia in her late forties, a phenotype also associated with *DTNBP1* haplotypes.

[10] Next generation sequencing identified this rare *AP3D1* frameshift variant c.1978delG homozygous in 3 siblings with seizures, developmental delay, albinism and immunodeficiency. Twin girls died before 6 days of age and their brother died at age 2 years of pneumonia and sepsis (Mohammed et al., 2018).

[11] Next generation sequencing identified this rare *AP3D1* variant c.3565_3566delGT in a proband with albinism, neutropenia, immunodeficiency, neurodevelopmental delay, generalized seizures, and impaired hearing. Immunologic investigations excluded HLH in this subject. The proband died at age 3.5 years as result of septic pneumonia (Ammann et al., 2016).