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MINIREVIEW

Hermansky-Pudlak Syndrome: Models for Intracellular Vesicle Formation

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Hermansky-Pudlak syndrome (HPS) is an autosomal recessive disorder characterized by pigment dilution, nystagmus, decreased visual acuity, a bleeding diathesis, and lysosomal accumulation of ceroid lipofuscin. Electron microscopic evidence demonstrating lack of platelet-dense bodies provides the *sine qua non* for diagnosing HPS. Ceroid lipofuscinosis is considered to cause several serious complications, including progressive pulmonary fibrosis leading to death in the fourth or fifth decades. Currently, only symptomatic treatment can be offered. Although rare in the general population, HPS occurs in northwest Puerto Rico with a prevalence of 1 in 1800. *HPS1*, the first gene found to be responsible for HPS, was mapped to chromosome 10q23 and subsequently isolated and sequenced. It consists of 20 exons encoding a 700-amino acid, 79.3-kDa peptide with no homology to any known protein. All 10 *HPS1* mutations reported to date, including the 16-bp duplication found in all northwest Puerto Rican patients, result in truncated proteins. The two mutations in the mouse *pale ear* gene (*ep*), which is the murine homology of *HPS1*, cause similarly truncated proteins. The pathologic nature of these truncation mutations may result from unstable mRNA. However, in combination with the absence of any disease-causing missense mutations, it may indicate that the C-terminus of the HPS1 peptide is functionally important. The disorder HPS displays locus heterogeneity, consistent with the existence of 14 mouse strains manifesting both hypopigmentation and a platelet storage pool deficiency. Two mouse models, *pearl* and *mocha*, have mutations in the β3A and δ subunits of the adaptor-3 complex, respectively. This suggests that defective vesicular trafficking, specifically cargo packaging, vesicle formation, vesicle docking, or membrane fusion, may comprise the basic defect in HPS. Studies of the proteins involved in intercompartmental transport for melanosomes, platelet-dense bodies, and lysosomes should lead to a better understanding of the mechanisms of organellogenesis and to more effective therapies for HPS. © 1998 Academic Press

Key Words: **albinism; platelet storage pool deficiency; vesicle trafficking; membrane fusion; ceroid lipofuscin.**

In 1959, two Czechoslovakian physicians described two patients who manifested a constellation of findings including oculocutaneous albinism and a platelet-related bleeding diathesis (1). The syndrome eventually assumed the physicians' names and became recognized as a rare genetic entity defined by the combination of pigment dilution and a platelet storage pool defect (2,3). It was also characterized by presumably lysosomal accumulation of a lipid-protein material known as ceroid lipofuscin. In practical terms, Hermansky-Pudlak syndrome (HPS) came to be diagnosed by the absence of platelet-dense bodies on electron microscopy in a hypopigmented patient with a bleeding diathesis; the

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demonstration of ceroid lipofuscin is not required. Although the basic defect in HPS is not known, it is considered to involve a vesicular membrane shared by the melanosome, dense body, and lysosome, all of which are affected in HPS. The discovery of one HPS-causing gene, i.e., *HPS1* (4), and its homologue, *ep,* in the mouse model *pale ear* (5,6), may lead us to the basic defect, but the function of the *HPS1/ep* protein product has not yet been determined. Mutations in genes other than *HPS1* undoubtedly result in the clinical manifestations of HPS (7–9); the various genes responsible for this disorder may well contribute to different steps in a common pathway of intracellular vesicle formation and trafficking. The present review describes HPS from clinical and molecular perspectives and promotes this heterogeneous disorder as a model for investigations into vesicular trafficking and organellogenesis.

PREVALENCE

HPS is an autosomal recessive disorder that exists in a wide variety of ethnic groups (2,3). Over the past two decades, it has been recognized that HPS occurs very commonly in northwest Puerto Rico (10), where it affects approximately 400 individuals and has a prevalence of 1 in 1800, apparently due to a founder effect. A Swiss isolate has also been described (11,12), and consanguineous patients have been reported in Japan (4). Approximately 100 non-Puerto Rican patients are known in the United States, but this probably represents an underestimate due to a low index of suspicion for this disorder, with consequently poor ascertainment.

CLINICAL MANIFESTATIONS

Albinism

In general, the oculocutaneous albinism of HPS is recognized at birth by the presence of hypopigmentation and horizontal nystagmus. The degree of hypopigmentation of the skin, hair, iris, and retinal fundus varies extensively, even in patients homozygous for the same mutation (12). The skin, when exposed to intense sunlight, as in Puerto Rico, acquires a typical appearance characterized by nevi, actinic keratoses, and sun damage (Fig. 1A). Patients are at risk for basal cell carcinoma and other dermatologic disorders, including ephelids and lentigines (Toro J, Turner M, Gahl WA. Dermatologic manifestations of HPS in patients with and without a 16-bp duplication in the *HPS* gene. Submitted for publication, 1998). The hair color can range from dark (7) to completely white (Fig. 1B), but the typical patient has a tan/blond color which is quite distinctive (Fig. 1C). An occasional patient reports darkening of hair color during childhood. Both Puerto Rican and non-Puerto Rican patients exhibit a wide range of skin and eye pigmentation (13).

The ophthalmic findings of HPS are also variable (13–15). Visual acuity in the better eye varies from 20/50 to 20/250, and does not usually change with age. (Legal blindness in the United States is 20/200 or worse.) Corrective lenses are only occasionally beneficial to patients. Nystagmus, which occasionally has a rotatory component in HPS, accompanies the decreased visual acuity. Foveal hypoplasia reflects decreased retinal pigment and may be the cause of photophobia in affected patients. Iris transillumination documents the absence or paucity of iris pigment. As for other patients with albinism, individuals with HPS generally manifest decreased decussation of optic nerve fibers.

Platelet Storage Pool Deficiency

In HPS, a bleeding diathesis results from a platelet storage pool deficiency. Although there are normal numbers of platelets (2), their dense bodies, which contain ADP, ATP, calcium, and serotonin, are virtually absent in HPS, and this provides the *sine qua non* for diagnosis (16). Dense bodies are intracellular vesicles which disgorge their contents upon platelet stimulation, causing platelet aggregation and clot formation. This secondary aggregation response is impaired in HPS patients (2,3), who usually have a prolonged bleeding time despite normal coagulation factors and a normal or increased platelet count. In general, HPS patients experience mild bleeding events, including bruising, epistaxis, gingival bleeding, prolonged bleeding during menstruation or after tooth extraction or circumcision, postpartum hemorrhage, and bleeding colitis. In one study (13), 20 of 49 HPS patients had major bleeding events, some of which were life-threatening. Childbirth can be dangerous, and a variety of traumatic and surgical events can precipitate exsanguination in severely affected patients. Just as the degree of hypopigmentation is not uniform in all patients, the severity of the bleeding diathesis in HPS varies substantially.