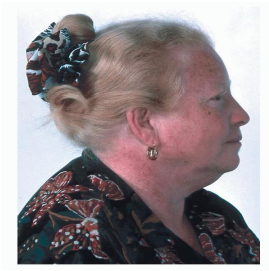

HERMANSKY-PUDLAK

SYNDROME

Mutations in eight different genes to date have been associated with HPS. Currently, our understanding of the function of their gene products varies greatly. However, a common theme is their functional involvement in trafficking cell type-specific products in cells containing lysosome
-related organelles, including
melanosomes
in
melanocytes
.

HPS patients have OCA, with variable hypopigmentation of the skin, hair, and irides, and ocular

abnormalities . In addition, they lack platelet dense bodies and demonstrate prolonged bleeding time, mucous membrane bleeding, a predisposition to
epistaxis
, easy bruising, and metromenorrhagia. Whole-mount electron microscopy is used to provide a definitive determination of the absence of platelet dense bodies.

The greatest clinical experience exists with patients with HPS1 , HPS3 , and HPS4 . Pulmonary fibrosis is a common and severe manifestation of HPS1 and HPS4, generally causing death between the fourth and sixth decades of life. Pulmonary fibrosis appears not to be associated with HPS3, however, which also features less severe pigmentary abnormalities. Among HPS1 and HPS4 patients, a granulo
matous
colitis is seen, occurring in approximately 15 percent.
Ceroid
lipofuscin
, a complex lipid-protein material, has been reported to accumulate in the cells of HPS patients, predominantly those with HPS1.

Mutations in distinct genes, rather than clinical phenotypes, define the various types of HPS. For example, 23 distinct mutations have been found to cause HPS1. The most common, found in over 400 Puerto Rican individuals, is a 16-base-pair frameshift duplication in exon 15. Although the precise function of HPS1 protein is not yet known, HPS1 associates with HPS4 in the 200-kd BLOC-3 (biogenesis of
lysosome
-related organelles complex-3) complex and has also been found in association with HPS4 in a larger, 500-kd complex in melanoma cells and fibroblasts. In
melanocytes
cultured from the skin of HPS1 patients, the
melanogenic
enzymes TYR, TYRP1, and DCT (
dopachrome
tautomerase
)/TYRP2 are found in large vesicular structures in the cell body and dendrites, instead of in the granular pattern typically associated with
melanosomal
localization, which suggests a role in the control of protein trafficking to the
melanosome
. Mutations in HPS4 have been described in 15 patients
,
although its exact cellular role is not yet known. Functionally, the adenosine
triphosphate
-dependent pump MRP4 (

multidrug
resistance protein 4), also known

as ABCC4 (adenosine triphosphate-binding cassette, subfamily C, member 4), normally localized to platelet granules and the plasma membrane, was found to be greatly reduced in HPS4 platelets.

Mutations or deficiencies in the AP3B1 gene, encoding the β_{3A} subunit of adaptor complex 3 (AP-3), one of four known adaptor complexes, cause HPS2 disease.
[78]

AP-3 interacts with
tyrosinase
, which is not targeted properly to
melanosomes
in AP3B1-deficient
melanocytes
. Hence, AP-3 is required for the trafficking of
tyrosinase
, and possibly other
melanosomal
proteins, from an intracellular site to
melanosomes
. Interestingly, the sub-cellular distribution of TYRP1 is unchanged in HPS2
melanocytes
, which suggests that transport of TYRP1, in contrast to
tyrosinase
, is not entirely dependent on the AP-3 mechanism. The respiratory infections associated with HPS2 may be due to the abnormal movement of
lytic
granules in
cytotoxic
T lymphocytes to the immunologic synapse, impairing microbial killing.

The most commonly described mutation in HPS3 is a 3904-base-pair deletion mutation that includes the entire first exon, found in a Puerto Rican population, which is distinct from the HPS1 Puerto Rican mutation. In addition, a splice site mutation has been described in Ashkenazi Jews with HPS3 who are either homozygous for this mutation or compound heterozygous for this mutation and other, non-conserved mutations. The HPS3 protein associates with the HPS5 and HPS6 proteins in the 340-kd BLOC-2 complex.

Melanocytes
from HPS3 patients exhibit defective localization of
tyrosinase
and TYRP1 in later-stage
melanosomes
, whereas proteins normally incorporated into early-stage
melanosomes
, such as silver/Pmel17/gp100 and melan-a/MART1, are unaffected. These
melanocytes
exhibited lower levels of melanin than control
melanocytes
, which suggests that the trafficking defect in
tyrosinase
, and perhaps also TYRP1, is responsible for the
pigmentary
dilution observed in these patients.