From the Departments of Internal Medicine (AJV, ET, MHHK, CAJMG), and Surgery (AJCM), Eemland Hospital, Amersfoort, The Netherlands.

Correspondence should be addressed to Carlo A.J.M. Gaillard, MD, PhD, Department of Internal Medicine, Eemland Hospital, 3818 ES Amersfoort, The Netherlands.

Manuscript submitted March 12, 1999, and accepted in revised form August 31, 1999.

A New Variant of Hermansky-Pudlak Syndrome due to Mutations in a Gene Responsible for Vesicle Formation

Vorasuk Shotelersuk, MD,
Esteban C. Dell'Angelica, PhD, Lisa Hartnell, BS,
Juan S. Bonifacino, PhD, William A. Gahl, MD, PhD

Hermansky-Pudlak syndrome is a recessive type of oculocutaneous albinism that is prevalent in northwest Puerto Rico due to a founder effect (1–3). In this syndrome, bleeding and bruising occur because of the absence of platelet dense bodies, which normally release serotonin, calcium, and adenosine diphosphate to trigger a secondary aggregation response (4). In addition, the accumulation of a lipid-protein complex called ceroid lipofuscin (5,6) is thought to cause the pulmonary fibrosis (7) and granulomatous colitis (8) seen in this disease.

One gene causing Hermansky-Pudlak syndrome, *HPS-1*, encodes a 700 amino acid protein of unknown function (9–11). Northwest Puerto Rican patients are homozygous for a 16 base pair (bp) duplication in *HPS-1*, but most non-Puerto Rican patients have no mutations in this gene (12,13). Consequently, it has become accepted that several different genes, when mutated, can cause Hermansky-Pudlak syndrome (12–14). This phenomenon, called locus heterogeneity, is also found in mice: 14 different mouse strains manifest a type of Hermansky-Pudlak syndrome (pigment dilution and platelet storage pool deficiency), each due to a different gene (15). To date, three of these genes have been cloned. *Pale ear* is the murine analogue of patients with *HPS-1* mutations (16,17), and *pearl* (18) and *mocha* (19) have defects in adaptor complex-3 (AP-3). One protein subunit of adaptor complex-3, called β3A, is mutated in the *pearl* mouse, while another protein subunit, called δ, is mutated in the *mocha* mouse.

Adaptor complex-3 is an aggregate of four different peptides and serves as a "coat" protein that concentrates in a donor membrane and recruits other membrane components to become part of a newly formed vesicle. These vesicles, such as lysosomes and peroxisomes, are functional compartments that provide an optimal environment for specialized biochemical processes. Adaptor complex-3 is thought to be responsible for the formation of pigment-forming vesicles (melanosomes) and platelet storage vesicles (dense bodies) (20,21).

We describe two brothers with Hermansky-Pudlak syndrome with mutations in the β3A subunit of adaptor complex-3 (22,23).

CASE REPORTS

We admitted 49 Hermansky-Pudlak syndrome patients to the NIH Clinical Center under an Institutional Review Board-approved protocol (24). Patient 40, aged 20 years, and patient 42, aged 25 years, were brothers who had normal gestations, deliveries, and birth weights. Bilateral congenital hip dislocations, due to dysplastic acetabulae, required closed reduction in patient 40 and splinting in patient 42. The family was of Dutch origin with no known consanguinity or miscarriages. The brothers' healthy parents had two normal, unaffected sons.

Nystagmus was observed in the newborn period. Skin color was light, and the brothers' white hair gradually turned blond. Bruising occurred in early childhood, with recurrent epistaxis decreasing in frequency by adolescence. In patient 42, extraction of several teeth was performed with minimal bleeding. Neither brother experienced hemoptysis, hematemesis, hematochezia, or melena. Hermansky-Pudlak syndrome was suspected when the patients were 8 and 13 years old, and absence of platelet dense bodies was documented by Dr. James White of the University of Minnesota.

From infancy to adolescence, the brothers had recurrent upper respiratory tract infections and episodes of otitis media that responded to antibiotic treatment. Neutropenia was consistently noted. The patients' unaffected siblings did not have recurrent upper respiratory tract infections.

Developmentally, the brothers achieved major milestones on time, but complained of poor balance causing stumbling and falling. They completed 11th grade and work on a family farm and nearby factory. Patient 42 smoked one half to 1 pack of cigarettes daily since age 13 years; patient 40 never smoked. Patient 40 had a physiologic cardiac murmur noted since age 3 years, with normal echocardiograms.

Patient 40 had a height of 172.3 cm, weight of 86.5 kg, and head circumference of 56.8 cm. Patient 42 had a height of 173.1 cm, weight of 67.9 kg, and head circumference of 56.5 cm. The brothers' hair was dark blond.

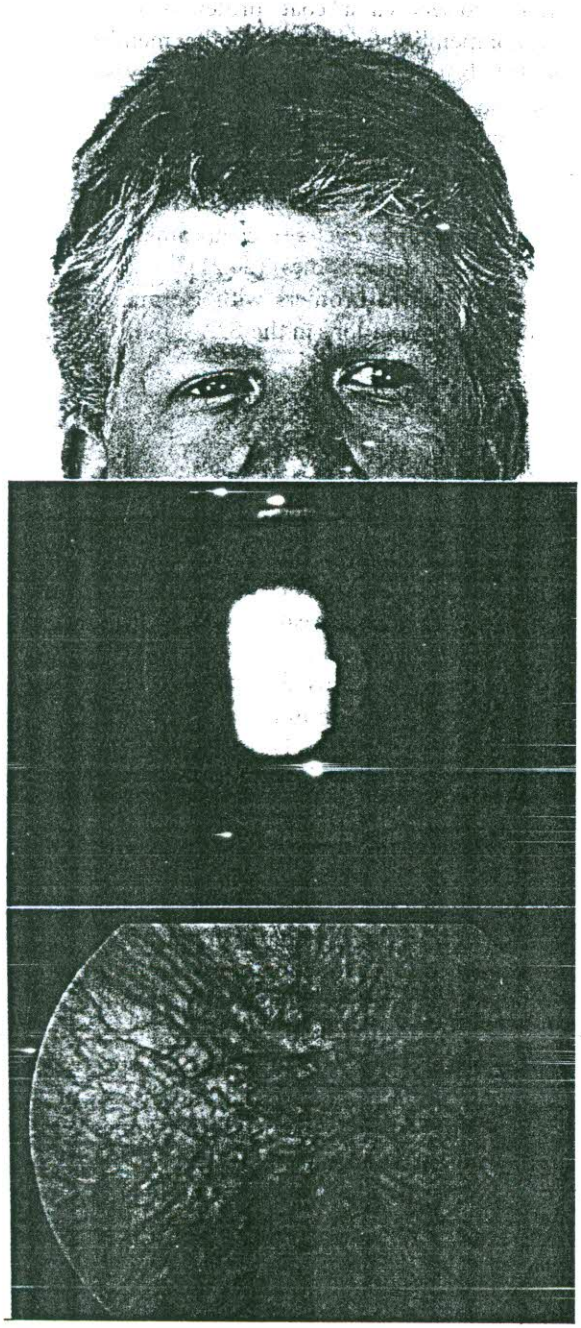

Figure 1. The hair of patient 40 is tan-blond, and the skin is somewhat light (top panel). Marked transillumination of the iris is apparent (middle panel). The fundus has areas of hypopigmentation peripherally (bottom). Similar findings were seen in patient 42 (see Figure 2B of reference 24).

Dark adaptation was normal, but iris transillumination and fundal hypopigmentation were marked (Figure 1). Both brothers had horizontal nystagmus, radial opacities of both lenses, and decreased visual acuity (Table 1). Visual evoked potentials showed an asymmetric pattern typical for albinism. The skin was hypopigmented, with acanthosis nigricans, actinic keratoses, hypertrichosis, darkly pigmented irregular nevi, and brown-pink macules. The tympanic membranes and oropharynx were clear. No cervical lymphadenopathy was observed. Neurologic examination revealed dysmetria and poor tandem gait, worse in patient 42, who also had a postural and intention tremor and decreased vibratory sense in his feet. The neurological examinations were otherwise normal. Magnetic resonance imaging studies of the head revealed no cerebellar abnormalities; patient 40 had incidental mastoid air cell opacification.

Laboratory results, compared with other Hermansky-Pudlak syndrome patients, are shown in Table 1. Absolute neutrophil counts of patient 40 from 7 months to 20 years of age were 275, 310, 570, 720, and 832 cells per μL; those of patient 42 from 11 to 25 years of age were 320, 480, 550, 725, 750, 790, and 1160 cells per μL. The neutrophils had normal morphology. On electron microscopy, dense bodies were absent from the platelets of the affected brothers, but present in all other family members (Figure 2). Bleeding times exceeded 20 minutes but the prothrombin time, partial thromboplastin time, and von Willebrand factor levels were normal. Platelet aggregation tests were abnormal upon adenosine diphosphate and collagen stimulation, but normal with epinephrine and ristocetin. Bone marrow aspiration showed mild granulocytic hypoplasia. Pulmonary function tests were slightly reduced (Table 1). High-resolution thin-section tomography of the chest revealed bilateral scarring in the anterior upper lobes in patient 40 and mild interstitial fibrosis in patient 42. Immunologic studies performed at ages 6 months (patient 40) and 5 years (patient 42) revealed normal T cell rosettes, nitroblue tetrazolium tests, neutrophil functions, and neutrophil morphology on electron microscopy. Karyotypes were normal.

DNA sequencing showed no mutations in the *HPS-1* gene in either brother. Sequencing of the β3A subunit of adaptor complex-3 (22) revealed that the brothers had different mutations in each of their two alleles. Specifically, a 63-bp deletion, 1166-1228del (Δ390-410), was inherited from the patients' father, and a 1739T->G substitution (L580R) was inherited from their mother (22). The two unaffected brothers are carriers for 1166-1228del.

DISCUSSION

We describe two brothers with oculocutaneous albinism, a bleeding tendency, mild pulmonary fibrosis, recurrent upper respiratory tract infections in childhood with persistent neutropenia, congenital hip dislocations, a mild balance defect and radial opacities of the ocular lens. Absence of platelet dense bodies supports the diagnosis of Hermansky-Pudlak syndrome (4), and the dermatologic,