Dermatologic Manifestations of Hermansky-Pudlak Syndrome in Patients With and Without a 16–Base Pair Duplication in the HPS1 Gene

Jorge Toro, MD; Maria Turner, MD; William A. Gahl, MD, PhD

Background: Hermansky-Pudlak syndrome (HPS) consists of oculocutaneous albinism, a platelet storage pool deficiency, and lysosomal accumulation of ceroid lipofuscin. Patients with HPS from northwest Puerto Rico are homozygous for a 16–base pair (bp) duplication in exon 15 of HPS1, a gene on chromosome 10q23 known to cause the disorder.

Objective: To determine the dermatologic findings of patients with HPS.

Design: Survey of inpatients with HPS by physical examination.

Setting: National Institutes of Health Clinical Center, Bethesda, Md (a tertiary referral hospital).

Patients: Sixty-five patients aged 3 to 54 years were diagnosed on the basis of the absence of platelet dense bodies in individuals with albinism and a bleeding diathesis. The presence of a 16-bp duplication in HPS1 was determined by polymerase chain reaction amplification; 40 patients were homozygous for the duplication and 25 lacked the duplication. All patients with the duplication were from northwest Puerto Rico; all patients without the duplication were non–Puerto Rican except 4 from central Puerto Rico.

Results: Both patients homozygous for the 16-bp duplication and patients without the duplication displayed skin color ranging from white to light brown. Patients with the duplication, as well as those lacking the duplication, had hair color ranging from white to brown and eye color ranging from blue to brown. New findings in both groups of patients with HPS were melanocytic nevi with dysplastic features, acanthosis nigricans–like lesions in the axilla and neck, and trichomegaly. Eighty percent of patients with the duplication exhibited features of solar damage, including multiple freckles, stellate lentigines, actinic keratoses, and, occasionally, basal cell or squamous cell carcinomas. Only 8% of patients lacking the 16-bp duplication displayed these findings. As a group, the patients with the duplication lived closer to the equator than those without the duplication.

Conclusion: Patients with HPS exhibit wide variation in pigmentation and dermatologic findings. Arch Dermatol. 1999;135:774-780

Hermansky-Pudlak syndrome (HPS), an autosomal recessive disorder, consists of oculocutaneous albinism, a platelet storage pool deficiency, and lysosomal accumulation of ceroid lipofuscin.1-3 The oculocutaneous albinism results in variable pigmentation, congenital nystagmus, a visual acuity approximating 20/200, and marked iris transillumination in the majority of patients. The storage pool deficiency and lack of a secondary platelet aggregation response arise from the absence of platelet dense bodies, diagnosable on wet-mount electron microscopy.4 Patients with HPS generally exhibit easy bruising and epistaxis in childhood, excessive menstrual and postpartum bleeding, and prolonged bleeding during dental extraction and surgical procedures. The accumulation of ceroid lipofuscin is associated with primary pulmonary fibrosis in a large number of patients and with granulomatous colitis in 10% to 20% of patients.5-7 The pulmonary fibrosis usually proves fatal by the fourth or fifth decade.8,9

Hermansky-Pudlak syndrome occurs with a high frequency in northwest Puerto Rico, where 1 in 21 individuals is a carrier and more than 400 people are affected because of an apparent founder effect.10 Recent studies have uncovered an HPS-causing gene on chromosome 10q23,11 and subsequent cloning of that gene, now called HPS1,12 demonstrated a coding sequence containing 2100 base pairs (bp) composed of 20 exons.13 HPS1 is predicted to produce a protein with a molecular weight of 79.3 kd. Although the
PATIENTS AND METHODS

PATIENTS

All patients were admitted to the National Institutes of Health Clinical Center, Bethesda, Md, and were enrolled in an institutional review board–approved study on the clinical and molecular characteristics of HPS. Forty-nine of the patients were included in a previous publication comparing groups of patients with HPS with and without the 16-bp duplication.7 Informed consent was obtained from all patients or their parents. The diagnosis of HPS was based on the finding of ocularcutaneous albinism, a history of increased bruising, and either absence of platelet dense bodies documented by electron microscopy or the presence of a 16-bp duplication in exon 15 of the HPS1 gene, documented by molecular analysis.7,13 Twenty-one non–Puerto Ricans from the mainland United States and 44 Puerto Rican patients ranging in age from 3 to 54 years were examined between November 1, 1995, and March 31, 1998. The 40 patients (21 females and 19 males) homozygous for the 16-bp duplication were older than the 25 patients (14 females and 11 males) without the 16-bp duplication (mean ± SD, 30 ± 14 vs 24 ± 10 years; P = .05). All patients underwent a complete skin examination, and all were photographed. A skin biopsy was performed when clinically indicated.

DERMATOLOGIC LESIONS

The degree of skin pigmentation was defined according to the Fitzpatrick classification.24 Lentigines were defined as uniform dark-brown to black stellate macules smaller than 1 cm on sun-exposed areas.7 Freckles were small (<5 mm), light-brown to medium-brown round macules with even pigmentation on sun-exposed areas.23 Dysplastic nevi were defined as irregularly contoured, pigmented papules with a diameter greater than 5 mm, a macular component, and variation in color.25 Cutis rhomboidalis nuchae was defined as thickening and furrowing of the skin of the nape of the neck in a rhomboidal pattern.25 Solar elastolytic bands of the forearms were cordlike plaques across the surface of the forearms.26 All squamous cell carcinomas and basal cell carcinomas were histologically confirmed. A total of 15 melanocytic nevi and 2 dysplastic nevi had histological verification.

MOLECULAR ANALYSIS

DNA was extracted from peripheral blood leukocytes of each patient, and the presence of the 16-bp duplication in exon 15 of the HPS1 gene was analyzed by polymerase chain reaction amplification, as previously described.7,13 Patients with the duplication gave a 285-bp fragment, with normal DNA yielding a 269-bp fragment. For patients lacking the duplication, single-strand conformational polymorphism analysis was performed, followed by sequencing of suspicious exons, as described.10

STATISTICAL ANALYSES

Student t test and the χ² distribution, with P values, were used to analyze the data.27

RESULTS

MOLECULAR STUDIES

Of 65 patients with HPS admitted to the National Institutes of Health, 40 were homozygous for the 16-bp duplication in exon 15 of HPS1. All of these patients had immediate ancestry in northwest Puerto Rico. Twenty-five patients exhibited no allele bearing the 16-bp duplication; only 4 of these had Puerto Rican heritage, and they were from the center of the island.21 Four non–Puerto Rican patients displayed a mutation in HPS1 different from the 16-bp duplication.18 One patient carried a T322insC mutation, leading to termination at codon 452, and the nonsense mutation E133X. Two affected siblings exhibited an S396delC mutation, resulting in termination at codon 398, and a T322delC mutation, causing termination at codon 330. One of these patients was either homozygous or heterozygous for the S396 mutation.18 In the remaining 21 patients, no mutation was found in the HPS1 gene.

GENERAL DERMATOLOGIC FEATURES

The Puerto Rican patients homozygous for the 16-bp duplication exhibited hair color ranging from white to light brown; 50% were blond. In contrast, only 28% of patients lacking the 16-bp duplication were blond, and 40%
had brown hair (Table 1). Two patients with the 16-bp duplication exhibited a reddish brown hair color. Eye color in the patients with HPS ranged from blue to brown, with 73% of the patients with the duplication and 56% of those without it having blue irises. All of the patients with the duplication displayed light skin color, but 5 patients without the duplication (20%) had skin with pigmentation similar to that of other family members. By history, hair and skin pigmentation increased as patients aged. Seventy percent of patients with the duplication and 36% of those without it had hypertrichosis of the eyelashes and trichomegaly of the arms and legs (Figure 1). A history of prolonged bleeding and bruising was present in patients with and without the 16-bp duplication. Multiple bruises were present in 86% of all the patients with HPS examined, whether or not they carried the 16-bp duplication. An illustrative patient with ecchymoses in different stages of development is shown in Figure 2. Twenty-nine percent of all our patients with HPS had acanthosis nigricans–like lesions (without pigment) on their necks and axillae (Figure 3). These patients lacked a history of diabetes, hyperandrogenemia, or intake of nico- tinic acid or triazinate. Serum glucose level was within normal limits, and luteinizing hormone, follicle-stimulating hormone, and testosterone levels were normal in all cases.

<table>
<thead>
<tr>
<th>Table 1. Dermatologic Findings in Patients With HPS With and Without the 16–Base Pair Duplication in HPS††</th>
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<tbody>
<tr>
<td><strong>No. (%)†</strong></td>
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<td>Hair color</td>
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<td>White with or without yellow tinge</td>
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<td>Blond</td>
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<td>Brown</td>
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<td>Gray</td>
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<tr>
<td>Freckles</td>
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<td>Lentigines</td>
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<td>Severe sun damage</td>
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<td>Solar keratoses</td>
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<td>Basal cell carcinoma</td>
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<td>Squamous cell carcinoma</td>
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<tr>
<td>Acanthosis nigricans</td>
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<tr>
<td>Hypertrichosis-trichomegaly</td>
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<td>Bruising</td>
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*HPS indicates Hermansky-Pudlak syndrome.
††Because of rounding, percentages may not all total 100.

Figure 1. Trichomegaly of eyelashes and bushy eyebrows in a 9-year-old boy homozygous for the 16–base pair duplication. (Reprinted in part with permission from Gahl et al.7 Copyright © 1998 Massachusetts Medical Society. All rights reserved.)

Figure 2. Ecchymoses at different stages of development on the legs of a 4-year-old boy homozygous for the 16–base pair duplication.

Figure 3. Acanthosis nigricans–like lesion in the axilla of an adult patient bearing the duplication in Hermansky-Pudlak syndrome.

**PIGMENTED LESIONS**

Melanocytic nevi were present in 33 (83%) of the 40 patients with the duplication and in 23 (92%) of the 25 pa-
patients without the duplication. Affected individuals had a variety of melanocytic nevi with different degrees of pigmentation, from skin colored to pink to black (Figure 4). Junctional, compound, intradermal, and halo nevi were found. Two patients with the duplication (5%) and 7 without it (28%) had atypical nevi, defined clinically as those with dysplastic features. Both groups of patients with HPS had multiple melanocytic lesions, and 1 patient in the duplication group and 1 in the nonduplication group had more than 50 lesions.

**SOLAR DAMAGE**

Every patient with sun-damaged skin manifested freckles and lentigines. Freckles and stellate black lentigines were present in 80% of patients bearing the 16-bp duplication, although the children examined (<18 years old) had not yet demonstrated this feature. Only 2 patients in the nonduplication group displayed these findings (Table 1). Six pairs of siblings with the 16-bp duplication and 5 pairs of siblings without it exhibited concordance for the presence of freckles, lentigines, and nevi.

Cutaneous manifestations of chronic and severe sun exposure (Figure 5) were present in approximately two thirds of the patients with the 16-bp duplication but were absent from patients without the 16-bp duplication. Sun-exposed areas, including the face, nuchae, arms, and anterior part of the neck, showed wrinkling and furrowing. Telangiectasias were also present, and the distribution of pigment was irregular. Cutis rhomboidalis nuchae was observed in 15 patients with the duplication (38%). Solar elastolytic bands of the forearms were found in 10 patients with the duplication (25%).

Multiple solar keratoses were present in 20 (50%) of 40 Puerto Rican patients with HPS bearing the 16-bp duplication. Squamous cell carcinoma and basal cell carcinoma were each present in 3 patients in the duplication group.

Could some of the findings related to solar damage have been worse in the 16-bp duplication group because this group was, on average, older than the nonduplication group? To investigate this possibility, we analyzed the findings related to solar damage separately in
all the adults with HPS (Table 2). The 33 adults with the 16-bp duplication had a mean ± SD age (35.9 ± 11.4 years) similar to that of the 12 adult patients with HPS without the 16-bp duplication (35.4 ± 8.6 years; \( P = .94 \)). Even in this comparably aged group, the patients with the duplication had significantly more signs of solar damage, including freckles, lentigines, and solar keratoses (Table 2).

### OPHTHALMOLOGIC FEATURES

All 65 patients with HPS examined had decreased visual acuity, photophobia, horizontal nystagmus, and some degree of iris hypopigmentation. Iris pigment correlated poorly with skin and hair pigment. Two Puerto Rican patients without the 16-bp duplication showed negligible to moderate transillumination,28 but patients with the duplication showed marked iris transillumination. Examples of hair, skin, iris, and fundus pigmentation are shown in Figure 6.

### COMMENT

Although the basic defect in HPS remains unknown, it is recognized that HPS melanocytes contain many morphologically normal melanosomes up to stage III. The HPS melanosomes are unusual in that they are spherical rather than oval and contain disorganized matrix fibers.79 Although giant melanosomes have been reported by 1 group,30 they were not found by several other investigators,31,32 nor were they present in 8 cases we examined by electron microscopy (data not shown). Albinism associated with HPS is considered to be tyrosinase positive, based on a positive reaction (melanin production) when hair bulbs are incubated with tyrosine or dopamine.30

Clinically, the dermatologic features of HPS are extremely variable. Patients exhibit different degrees of cutaneous and ocular pigmentation, ranging from nearly none to almost normal. This phenotypic variability occurs even within a group of patients with HPS that is entirely homogeneous with respect to the HPS-causing gene. This finding reflects the enormously complicated pathway that leads to melanin production. Clearly, many genes besides \( HPS1 \) contribute to the ultimate extent of pigmentation. The \( HPS1 \) gene product itself has no known function, but it contains 2 putative transmembrane domains and a presumed melanosomal localization signal. It is located within the cytoplasm of nonmelanotic cells and within the granular fraction of melanotic cells. \( HPS1 \) also has a small block of homology to the Chediak-Higashi gene product.13 Chediak-Higashi disease is another hypopigmentation–platelet store pool deficiency characterized by giant lysosomes and a susceptibility to infection.24 The molecular characteristics of \( HPS1 \), as well as the multiorganellar involvement in HPS, suggest that the \( HPS1 \) gene product is integrally involved in the trafficking of melanosomes, platelet dense bodies, and lysosomes.
Our patients homozygous for the 16-bp duplication manifested some dermatologic signs previously reported in Puerto Rican patients with HPS. For example, Witkop et al\textsuperscript{37} found that 100 (49\%) of 203 patients with HPS aged 10 years and older had solar keratoses; we found 20 (50\%) of 40 patients with solar keratoses (Table 1). Like Witkop et al, we found a small percentage of squamous cell and basal cell carcinomas. Witkop et al reported that more than 80\% of patients with HPS older than 10 years had freckles or lentigines; we described similar findings in this group of Puerto Rican patients. However, we also expanded the dermatologic findings of Puerto Rican patients with HPS, since we found a very high frequency of nevi among individuals homozygous for the 16-bp duplication. Furthermore, we report new findings seen in both groups of patients with HPS, such as a significant frequency of acanthosis nigricans—like lesions, hypertrichosis or trichomegaly, and dysplastic nevi.

Our group of patients without the 16-bp duplication arose from a wide variety of ethnic backgrounds and regions. Twenty-one of the 25 had no detectable mutation anywhere in the HPS gene. Hence, this syndrome is expected to be a molecularly heterogeneous one, consistent with the many genetically distinct mouse models displaying both pigment dilution and platelet storage pool deficiency.\textsuperscript{19,20}

As a group, the nonduplication group of patients with HPS displayed the same variability in cutaneous and ocular pigment as the duplication group, and a similar frequency of nevi. However, freckles and lentigines, solar keratoses, and squamous cell carcinomas were rare or absent in the nonduplication group (Table 1). This difference in solar damage between the duplication and nonduplication groups was maintained when only adult patients (with equivalent mean ages) were analyzed (Table 2), so it was not simply an age effect. However, the differences may be partly attributed to the less intense ultraviolet radiation to which patients from the mainland United States (ie, nonduplication group) were subjected in comparison with the patients in the duplication group, most of whom were exposed to tropical ultraviolet radiation on a daily basis. Four Puerto Rican patients lacked the 16-bp duplication and did not show manifestations of severe solar damage. Two of these individuals, aged 4 and 47 years,\textsuperscript{28} had resided in Philadelphia, Pa, and New York, NY, for all or most of their lives and did not have the same degree of sun exposure as the island residents. However, 2 other patients, aged 41 and 42 years, resided in Puerto Rico and had only mild lentigines and freckles.

The use of sunscreens to prevent\textsuperscript{33-36} or diminish\textsuperscript{37,38} photodamage in animal models has been reported.\textsuperscript{33-36} Kligman et al\textsuperscript{37} irradiated hairless albino mice with sunlamps emitting both UV-A and UV-B light and then applied sun protection factor 15 and sun protection factor 2 sunscreen to different groups of animals. Repair of collagen degeneration, glycosaminoglycan deposition, and solar elastosis were found with sunscreen use and were noted to occur to a greater extent with the product that had the higher sun protection factor. In addition, Harrison et al\textsuperscript{39} irradiated hairless albino mice with UV-A and UV-A/UV-B after applying sunscreen agents. They noted that UV-B induced histological changes, such as epidermal thickening, dermal inflammation, and elastic tissue changes. These histological changes were significantly reduced by UV-B sunscreen alone and further diminished by UV-A/UV-B sunscreen. A similar study in humans\textsuperscript{40} found that UV-A/UV-B sunscreen was effective in diminishing solar elastosis in human skin. This finding suggests a beneficial effect of sunscreen in the prophylaxis and reversal of photodamage in patients with HPS. However, it is unclear whether humans demonstrate the same extent of repair seen in mice.

Many of our patients (37 of 65) had hypertrichosis and trichomegaly. Hypertrichosis occurs in porphyria, acromegaly, Cushing disease, Stein-Leventhal syndrome, and tumors of adrenal, testicular, and ovarian origin. However, none of our patients had clinical features suggestive of these disorders. We also found that 36 of 65 patients with HPS had regular or dysplastic nevi. This high frequency is not characteristic of tyrosinase-negative oculocutaneous albinism, in which pigmented nevi\textsuperscript{41,42} and dysplastic nevus syndrome with amelanotic melanoma\textsuperscript{43} have been described only rarely. However, it is not unusual for tyrosinase-positive oculocutaneous albinism. The reason for this difference remains unknown.

Several issues related to the dermatologic findings in HPS pertain to the welfare of affected children. First, most children with HPS exhibit excessive bruises when they begin walking. This bruising can be mistaken for child abuse, so the correct and early diagnosis of HPS is essential. In northwest Puerto Rican patients, the diagnosis of HPS can be made molecularly, based on the presence of the 16-bp duplication. However, in patients lacking this mutation, the diagnosis is made by electron microscopy showing absence of platelet dense bodies, or by platelet studies showing absence of a secondary aggregation response in a hypopigmented individual. Another reason to make the diagnosis of HPS early is to initiate avoidance of aspirin-like products and prophylactic use of desmopressin to shorten the bleeding time,\textsuperscript{44} thus reducing the likelihood of severe bleeding episodes. In cases of emergency trauma or surgery, families and physicians should be aware of the platelet aggregation defect, and medical alert bracelets can be beneficial. Children are at particular risk of nonmelanoma skin cancer, since sun exposure during childhood accounts for an estimated 80\% of total lifetime exposure.\textsuperscript{44} Early sun protection will prevent the future development of premalignant and malignant skin cancer and will protect against the occurrence of severe photoaging. In addition to prompting surveillance for dermatologic complications, the early diagnosis of HPS encourages patients to avoid cigarettes and other lung irritants, which could hasten deterioration of pulmonary function. Finally, children with HPS have decreased visual acuity, which can impede learning, so parents and teachers should be informed about the availability of aids for the visually impaired.

Future research into HPS will undoubtedly make use of mouse models of this disorder.\textsuperscript{45} Clearly, the cloning of the murine genes responsible for these HPS phenocopies will facilitate isolation of more human genes causing the disease. Currently, $ep$ (for pale ear) is recognized as the mouse homolog of HPS, and the pale ear
mouse can serve as a model for pathologic and therapeu-
tic studies of the complications of HPS, including der-
matologic involvement. Another example is pearl, whose
gene has been identified as the b3A subunit of adaptor
complex-3 and whose human counterpart has been re-
cently identified.46

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Reprints: Maria Turner, MD, Dermatology Branch, Na-
tional Cancer Institute, Bldg 10, Room 12N-238, 10 Cen-
tral Dr, MSC 1908, Bethesda, MD 20892-1908 (e-mail: Mltturner@box-m.nih.gov).

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