GENETIC DEFECTS AND CLINICAL CHARACTERISTICS OF PATIENTS WITH A FORM OF OCULOCUTANEOUS ALBINISM (HERMANSKY–PUDLAK SYNDROME)

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ABSTRACT

Background Hermansky–Pudlak syndrome is characterized by oculocutaneous albinism, a storage-pool deficiency, and lysosomal accumulation of ceroid lipofuscin, which causes pulmonary fibrosis and granulomatous colitis in some cases. All identified affected patients in northwest Puerto Rico are homozygous for a 16-bp duplication in exon 15 of a recently cloned gene, *HPS*. We compared the clinical and laboratory characteristics of these patients with those of patients without the 16-bp duplication.

Methods Forty-nine patients — 27 Puerto Ricans and 22 patients from the mainland United States who were not of Puerto Rican descent — were given a diagnosis on the basis of albinism and the absence of platelet dense bodies. We used the polymerase chain reaction to determine which patients carried the 16-bp duplication.

Results Twenty-five of the Puerto Rican patients were homozygous for the 16-bp duplication, whereas none of the non–Puerto Rican patients carried this mutation. Like the patients without the duplication, the patients with the 16-bp duplication had a broad variation in pigmentation. Nine of 16 adults with the duplication, but none of the 10 without it, had a diffusing capacity for carbon monoxide that was less than 80 percent of the predicted value. High-resolution computed tomography in 12 patients with the 16-bp duplication revealed minimal fibrosis in 8, moderate fibrosis in 1, severe fibrosis in 1, and no fibrosis in 2. Computed tomography in eight patients without the duplication revealed minimal fibrosis in three and no fibrosis in the rest. Inflammatory bowel disease developed in eight patients (four in each group) between 3 and 25 years of age.

Conclusions The 16-bp duplication in exon 15 of *HPS*, which we found only in Puerto Rican patients, is associated with a broad range of pigmentation and an increased risk of restrictive lung disease in adults. (N Engl J Med 1998;338:1258-64.)

HERMANSKY–PUDLAK syndrome, an autosomal recessive disorder, consists of oculocutaneous albinism, a storage-pool deficiency, and lysosomal accumulation of ceroid lipofuscin.[1-3] The albinism causes congenital nystagmus, a visual acuity approximating 20/200,[4] transillumination of the iris, and mild-to-striking dilution of skin and hair pigmentation. The storage-pool defect arises from the absence of platelet dense bodies, whose contents (adenosine diphosphate, adenosine triphosphate, calcium, and serotonin) trigger the secondary aggregation response of platelets.[2] Patients with Hermansky–Pudlak syndrome have easy bruisability of soft tissues and prolonged bleeding after dental extraction and surgical procedures; prophylaxis with desmopressin can be effective,[5] and avoidance of aspirin products is essential. The accumulation of ceroid lipofuscin, an amorphous lipid–protein complex, is associated with pulmonary fibrosis[6,7] and granulomatous colitis.[8] The pulmonary disease begins with a restrictive component and progresses inexorably to death, usually in the fourth or fifth decade.[2]

Most information concerning Hermansky–Pudlak syndrome has been obtained from the study of patients in northwest Puerto Rico, where the gene frequency approximates 1 in 18 and more than 300 persons are affected.[9] Linkage analysis of Puerto Rican families mapped a gene causing Hermansky–Pudlak syndrome to chromosome 10q23.[10] The gene, *HPS*, has 20 exons coding for a 79.3-kd protein of 700 amino acids whose function is unknown and that is not homologous to any known proteins.[11] Thus, the actual gene product is not known. In the report describing *HPS*,[11] all Puerto Rican patients who were studied were homozygous for a 16-bp duplication in exon 15, reflecting a founder effect. A Japanese patient whose parents were consanguineous had a single-base duplication in codon Ala441, and six Swiss patients and one Irish patient were homozygous for a single-base duplication in codon Pro324.[11]

The availability of molecular genotyping has enabled us to document the phenotype associated with homozygosity for the 16-bp duplication. We also determined its frequency among non–Puerto Rican patients and compared the clinical and laboratory characteristics of patients with the 16-bp duplication and those without the duplication.

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METHODS

Patients

Forty-nine patients ranging in age from 3 to 54 years were enrolled in the study, which was conducted between November 1995 and February 1997. Hermansky–Pudlak syndrome was diagnosed on the basis of oculocutaneous albinism and a storage-pool deficiency (the absence of platelet dense bodies on electron microscopy)[12] in all but two patients. These two patients had albinism and were siblings of a patient who met the diagnostic criteria. In the case of 41 patients, electron microscopy of the platelets was performed by Dr. James G. White (University of Minnesota) before the study. Documentation of ceroid lipofuscinosis was not required for the diagnosis.

Twenty-two of the patients (from 17 families) lived in the mainland United States and were neither native Puerto Ricans nor of Puerto Rican descent; two of these patients have been described previously.[13,14] The other 27 patients (from 22 families) were Puerto Ricans and included children who were similar in age to the non–Puerto Rican children. Some of the Puerto Rican patients could not travel to the National Institutes of Health Clinical Center for testing because of severe pulmonary disease. We have previously described 2 of the Puerto Rican patients[15]; as many as 19 others were identified by the late Dr. Carl Witkop and may have been described previously.[3,6,9]

The protocol was approved by the institutional review board of the National Institute of Child Health and Human Development, and all patients or their parents provided written informed consent.

Clinical and Laboratory Evaluations

The best corrected visual acuity of patients six years old or older was measured with the Early Treatment Diabetic Retinopathy Study chart and recorded as the Snellen equivalent. Photographs of the transillumination of the fundus and iris were taken in each patient to show the degree of pigmentation.

Glomerular function was estimated according to the equation of Schwartz et al.[16]: 0.55 × height (in centimeters) ÷ serum creatinine (in milligrams per deciliter) = creatinine clearance (in milliliters per minute per 1.73 m^2). Urine samples were also obtained from 45 patients, and the clearance values calculated on the basis of urine and serum creatinine concentrations supported the findings calculated with the use of this equation.

Renal tubular dysfunction was quantified with the Fanconi's syndrome index. In this index the daily urinary excretion of 21 amino acids is measured by ion-exchange chromatography[17] and expressed as micromoles per kilogram of body weight per day. The greater the index, the more severe the defect in tubular reabsorption. At least two 24-hour urine collections of reasonable volumes were used to calculate the index. Plasma lipids were assayed with the Gilchem reagent system (Gilford Diagnostics, Cleveland) in blood obtained from the patients after an overnight fast.[17]

Molecular Studies

To assess samples for the 16-bp duplication, DNA was extracted from lymphocytes.[18] A 269-bp fragment spanning exon 15 of *HPS* was amplified by the polymerase chain reaction (PCR) in a 50-μl reaction mixture containing 50 mM potassium chloride, 1.5 mM magnesium chloride, 5 mM TRIS (pH 8.3), 200 mM of each deoxynucleoside triphosphate, 0.01 percent gelatin, 0.6 mM primers (5′GATGGTCCACAAAGGACGAG3′ and 5′GCGTGAAGGAAGTACGGGCC3′), 2.5 U of *Taq* polymerase, and 500 ng of template DNA. After an initial period of denaturation at 94°C for 2 minutes, amplification was performed for 30 cycles consisting of 1 minute of denaturation at 94°C, 30 seconds of annealing at 60°C, 1 minute of extension at 72°C, and a final 10-minute period of elongation at 72°C. PCR products were subjected to electrophoresis on 2 percent agarose gel and stained with ethidium bromide.

Statistical Analysis

Student's t-test with two-tailed P values, Fisher's exact test with a chi-square distribution, and the Wilcoxon rank-sum test were used to analyze the data.[19]

RESULTS

The 16-bp Duplication

Of the 49 patients, all 25 who were homozygous for the 16-bp duplication in exon 15 of the *HPS* gene (Fig. 1) were from northwest Puerto Rico. The other 2 Puerto Rican patients,[15] as well as all 22 of the non–Puerto Rican patients, had no alleles containing the duplication. The two groups of patients were analyzed separately. Of the 25 patients with the 16-bp duplication, 13 were male and 12 were female (mean [±SD] age, 24±15 years). Of the 24 patients without the duplication, 11 were male and 13 were female (mean age, 19±13 years).

Pigmentation

Both groups of patients had hypopigmentation, with skin color ranging from tan to light and hair color from brown to white (Fig. 2, top panels). The degree of iris pigmentation, as assessed by transillumination (Fig. 2, middle panels), and retinal and choroid pigmentation (Fig. 2, bottom panels) correlated poorly with the degree of skin and hair pigmentation. The extent of pigmentation of the iris and fundus varied considerably. One of the Puerto Rican patients without the 16-bp duplication had nearly complete pigmentation of the iris with negligible transillumination; the other had substantial pigmentation of the iris with diffuse, irregular transillumination.[15]

Ophthalmic Findings

The median visual acuity was similar in the two groups (Table 1). The poorest acuity of the better eye was 20/250 in the 21 patients with the 16-bp duplication in whom it was measured and 20/200 in 20 patients without the duplication. In 12 patients, 8 of whom were homozygous for the 16-bp

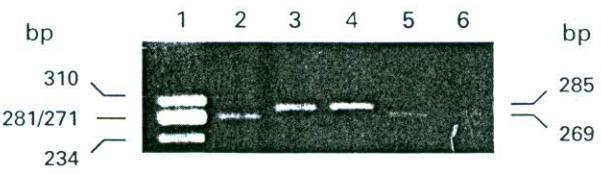


Figure 1. Representative Agarose Gel Showing the 16-bp Duplication in Exon 15 of *HPS*.

PCR amplification yielded a normal 269-bp fragment in control DNA from a subject who did not have Hermansky–Pudlak syndrome (lane 2) and from two patients with the syndrome but without the 16-bp duplication (lanes 5 and 6). A 285-bp fragment was identified in two other patients with the 16-bp duplication (lanes 3 and 4). Lane 1 shows a size marker.

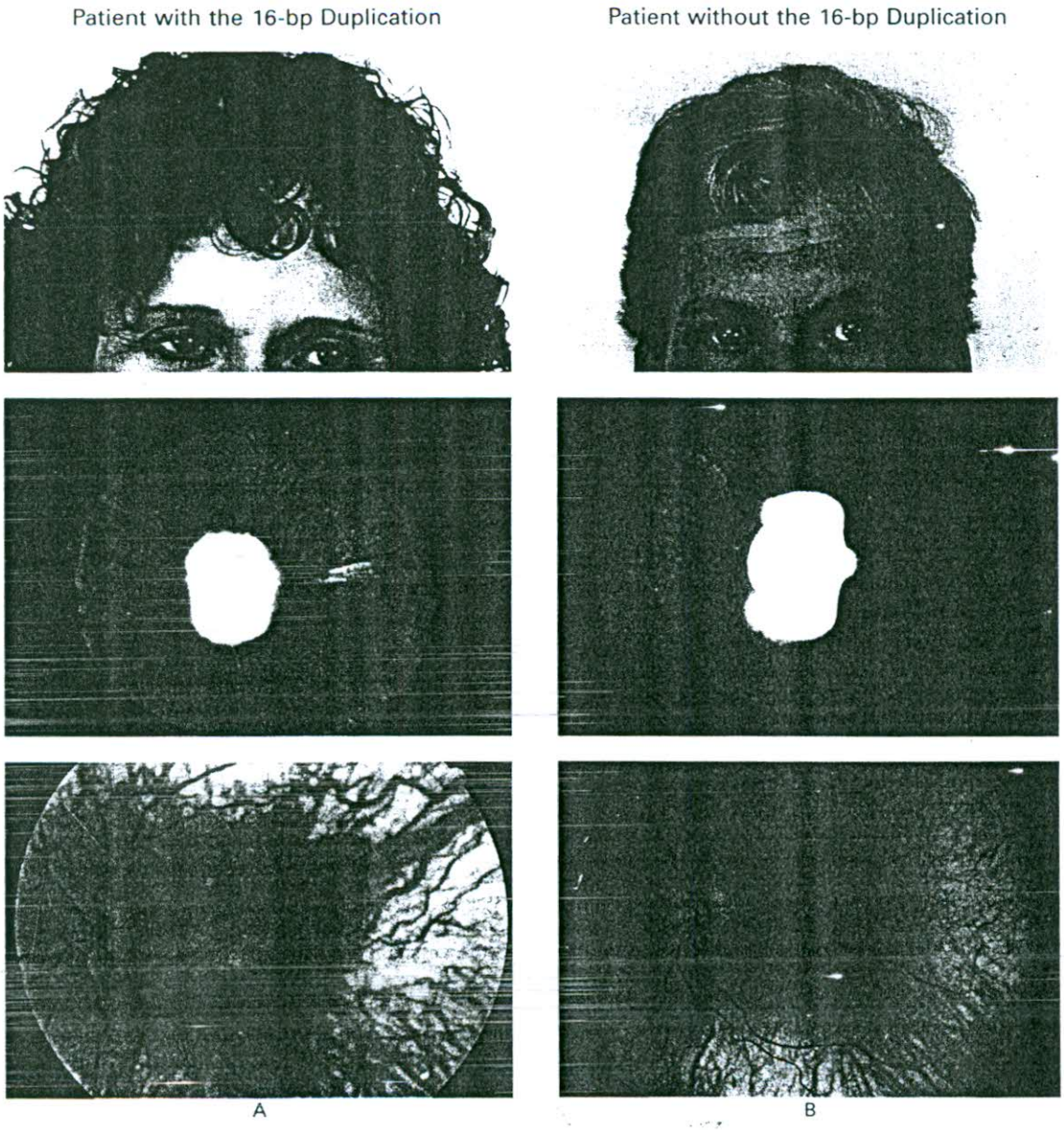


Figure 2. Variability in Pigmentation in Three Patients with Hermansky–Pudlak Syndrome.

The top panels show skin and hair pigmentation, the middle panels iris transillumination, and the bottom panels choroid and retina pigmentation. Two of the patients are homozygous for the 16-bp duplication (Panels A and C), and one patient does not have the duplication (Panel B). The degree of pigmentation varied widely in both types of patients and did not distinguish members of one group from those of the other. In normal persons, pigment prevents transillumination of the iris and light appears only through the pupil. In patients with Hermansky–Pudlak syndrome, light transilluminating the iris appears orange and the areas of residual pigmentation are black.

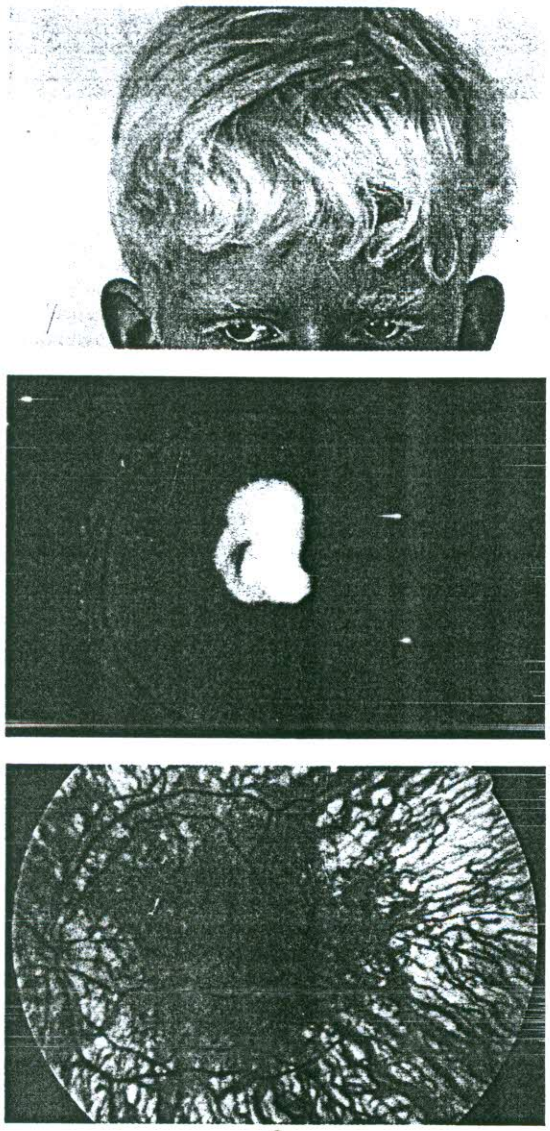
duplication and 4 of whom did not have the mutation, visual acuity in both eyes was 20/200 or less. Visual acuity of the better eye was between 20/100 and 20/80 in eight patients with the 16-bp duplication (38 percent) and nine patients without the duplication (45 percent). Visual acuity was similar in adults and children.

All patients had nystagmus at the primary position except one three-year-old girl who had neonatal nystagmus that decreased over time. All patients had horizontal nystagmus, and 18 also had a rotatory component.

Bleeding

All 49 patients reported excessive bruising in infancy; it generally began when they learned to walk.

Patient with the 16-bp Duplication



C

Three patients with the 16-bp duplication and seven patients without the duplication had frequent (more than twice per month) or prolonged (more than one hour) episodes of epistaxis. A major bleeding event — one that was life-threatening, lasted more than 12 hours, or required a transfusion, treatment with desmopressin, cautery, or hospitalization — had occurred in 12 patients with the 16-bp duplication (5 patients after dental extractions) and 8 patients without the duplication (2 after dental extractions). Two women in each group had had increased menstrual bleeding that required medical intervention. Two of the women with the 16-bp duplication had borne a total of four children; one had had postpartum bleeding. Two of the women without the duplication had borne a total of six children without bleeding complications. Four patients with the 16-bp duplication and five patients without the duplication had required a transfusion of either platelets or whole blood.

The mean platelet counts, prothrombin times, and partial-thromboplastin times were normal in both groups of patients (Table 2).

Pulmonary Function

Pulmonary function was assessed in all patients over the age of nine and in 8 of the 15 patients under the age of nine. Although the patients with the 16-bp duplication had lower mean values for each pulmonary-function test, the absolute and age-adjusted differences between groups were not significant (Table 1). However, because of the poor reliability of pulmonary-function tests in children, the data on the 16 adult patients with the 16-bp duplication (50 percent of whom were women) and the 10 adult patients without the duplication (60 percent of whom were women) were analyzed separately. The mean ages of the two groups (33.5 and 31.7 years, respectively) were similar, and no patient was employed in a profession associated with pneumoconiosis. The adults with the 16-bp duplication had lower mean ($\pm$SD) values for forced vital capacity (82 ± 20 vs. 100 ± 13 percent of the predicted value, $P=0.02$), forced expiratory volume in one second (86 ± 20 vs. 104 ± 16 percent of the predicted value, $P=0.01$), total lung capacity (85 ± 19 vs. 96 ± 10 percent of the predicted value, $P=0.07$), and diffusing capacity for carbon monoxide (82 ± 23 vs. 108 ± 12 percent of the predicted value, $P<0.001$). Nine of the 16 adults with the 16-bp duplication, as compared with none of the 10 adults without the 16-bp duplication, had values for the diffusing capacity for carbon monoxide that were less than 80 percent of the predicted value, indicating significantly impaired gas exchange ($P=0.004$ by Fisher's exact test). The diffusing capacity for carbon monoxide did not correlate with visual acuity, frequency of bleeding, or age.

Pulmonary fibrosis was assessed in 20 adult patients by thin-section, high-resolution computed tomography of the lung by a physician who was unaware of the patients' conditions.[20,21] Three smokers (one with the duplication and two without it) were excluded from the analysis. Normal lung was assigned a score of 0. A score of 1 indicated a ground-glass appearance or mild fibrosis; a score of 2 a ground-glass or reticular pattern, or moderate fibrosis; and a score of 3 a reticular pattern, or severe fibrosis. Twelve patients with the 16-bp duplication (mean [$\pm$SD] age, 37 ± 10 years) had a mean score of 1.08 ± 0.79, as compared with a score of 0.38 ± 0.52 ($P=0.02$) for eight patients without the duplication (mean age, 31 ± 12 years). Eight of the 12

TABLE 1. CLINICAL CHARACTERISTICS OF 49 PATIENTS WITH HERMANSKY–PUDLAK SYNDROME.*

CHARACTERISTIC	PATIENTS WITH THE 16-bp DUPLICATION (N=25)	PATIENTS WITHOUT THE DUPLICATION (N=24)	P VALUE	
			UNADJUSTED	ADJUSTED FOR AGE
Age (yr)	24.3±15.2	18.7±13.3	0.17	—
Best corrected visual acuity†				
Median	20/125	20/100	0.35	—
Range	20/250–20/80	20/200–20/50		
Pulmonary function (% of predicted)				
Forced vital capacity‡	88±21	97±19	0.13	0.21
Forced expiratory volume in 1 second‡	89±19	94±22	0.45	0.32
Total lung capacity§	88±21	96±16	0.23	0.41
Carbon monoxide diffusing capacity§	80±22	91±25	0.19	0.06
Creatinine clearance (ml/min/1.73 m²)¶	101±23	113±28	0.11	0.22

*Plus–minus values are means ±SD. All patients who were homozygous for the 16-bp duplication in the *HPS* gene were Puerto Rican. There were four sets of siblings. The patients without the 16-bp duplication were of Irish, German, Polish, Russian, English, Swiss, Ukrainian, Italian, Dutch, French, Swedish, Greek, Indian, Hungarian, Lithuanian, Romanian, Scotch, and Puerto Rican descent. There were five sets of siblings.

†Data were missing for four patients in each group. The Wilcoxon rank-sum test was used to calculate the unadjusted P value.

‡Data were available for 21 patients in each group.

§Data were available for 18 patients in each group.

¶Creatinine clearance was calculated according to the method of Schwartz et al.[16] To convert values to milliliters per second per 1.73 m², multiply by 0.01667.

patients with the 16-bp duplication had mild fibrosis, 1 had moderate fibrosis, 1 had severe fibrosis, and 2 did not have fibrosis; 3 of the 8 patients without the duplication had mild fibrosis, and the rest did not have fibrosis. In the seven patients with no fibrosis the mean (±SE) forced vital capacity was 100±8 percent of the predicted value. Mean forced vital capacity was 95±7 percent of the predicted value in the 11 patients with mild fibrosis, 67 percent of the predicted value in the patient with moderate fibrosis, and 37 percent of the predicted value in the patient with severe fibrosis.

Gastrointestinal Findings

Diarrhea was reported by 12 patients, 8 of whom were given a diagnosis of inflammatory bowel disease. Four patients with the 16-bp duplication presented at the ages of 11, 22, 24, and 25 years with disease confined to the large intestine. Three required either a subtotal or total colectomy, resulting in a colostomy. Four patients without the duplication had inflammatory bowel disease, with symptoms beginning at the ages of 3, 5, 8, and 14 years. Two had colitis alone, and two had disease of both the small and large intestines. None required surgery. The remaining four patients (two in each group) had symptoms of lactase deficiency. Breath hydrogen testing was positive for lactose intolerance in one of the patients with the 16-bp duplication and for bacterial overgrowth in the two patients without the duplication.

Renal Function

The estimated mean (±SD) creatinine clearance was 101±23 ml per minute per 1.73 m² (1.68±0.38 ml per second per 1.73 m²) in the patients with the 16-bp duplication and 113±28 ml per minute per 1.73 m² (1.88±0.47 ml per second per 1.73 m²) in the patients without the duplication (age-adjusted P=0.22) (Table 1). Creatinine clearance was below normal (90 ml per minute per 1.73 m² [1.50 ml per second per 1.73 m²]) in seven of the patients with the 16-bp duplication, as compared with two of the patients without the duplication (P=0.08). The mean serum creatinine concentration was 0.90±0.31 mg per deciliter (80±28 μmol per liter) in the patients with the 16-bp duplication and 0.78±0.26 mg per deciliter (70±23 μmol per liter) in those without the duplication (P=0.13).

The mean (±SE) Fanconi's syndrome index was 71±7 μmol per kilogram per day in the 21 patients with the 16-bp duplication in whom it was measured (normal, 95±45 μmol per kilogram per day[17]) and 74±7 μmol per kilogram per day in 24 patients without the duplication (P=0.77).

Other Laboratory Values

There were no significant differences between groups in any of the laboratory variables examined (Table 2). All values were within the normal range, except the mean serum phosphate concentration, which was slightly elevated in the patients without the 16-bp duplication.

TABLE 2. LABORATORY VALUES IN 49 PATIENTS WITH HERMANSKY–PUDLAK SYNDROME.*

VARIABLE	PATIENTS WITH THE 16-bp DUPLICATION (N=25)	PATIENTS WITHOUT THE DUPLICATION (N=24)	NORMAL RANGE
Platelet count ($\times 10^{-3}$/mm^3)	271±13	270±19	162–380
Prothrombin time (sec)	12.1±0.1	12.3±0.1	11.2–12.8
Partial-thromboplastin time (sec)	30.1±0.7	30.9±0.8	23.7–35.0
Total cholesterol (mg/dl)	175±7	186±8	100–200
Low-density lipoprotein cholesterol (mg/dl)	116±6	117±7	65–129
Triglycerides (mg/dl)	75±9	89±11	<160
Hemoglobin (g/dl)	13.8±0.3	13.5±0.3	11.1–15.0
Leukocytes ($\times 10^{-3}$/mm^3)	7.0±0.4	6.3±0.6	3.4–9.6
Aspartate aminotransferase (U/liter)	24±1	28±2	9–34
Calcium (mmol/liter)	2.32±0.02	2.31±0.02	2.05–2.50
Phosphate (mg/dl)	4.0±0.2	4.5±0.2	2.3–4.3
Ceruloplasmin (mg/liter)	388±13	382±14	201–575
Erythrocyte sedimentation rate (mm/hr)	19±3	17±3	0–42
Free thyroxine (ng/dl)	1.4±0.1	1.3±0.1	1.0–1.9
Vitamin A (μg/dl)	50±2	59±4	36–120
Carotene (μg/dl)	107±8	101±10	48–200

*Plus–minus values are means ±SE. To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129; to convert values for phosphate to millimoles per liter, multiply by 0.3229; to convert values for free thyroxine to picomoles per liter, multiply by 12.87; to convert values for vitamin A to micromoles per liter, multiply by 0.03491; and to convert values for carotene to micromoles per liter, multiply by 0.01863.

When the mean total cholesterol concentrations were expressed in terms of percentiles for age,[22] the mean (±SE) percentile was 48±7 for the group with the 16-bp duplication and 65±6 for the group without the duplication (P=0.07). All 7 patients over the age of 40 and 4 of 11 children (2 with the 16-bp duplication) who were under the age of 8 had total cholesterol values of at least 200 mg per deciliter (5.15 mmol per liter). The total cholesterol concentrations in three young patients without the duplication, ages 4, 6, and 7, were greater than those of their unaffected siblings (ages 6, 7, and 7) by 24, 31, and 70 mg per deciliter (0.62, 0.80, and 1.81 mmol per liter), respectively.

DISCUSSION

Among 49 patients with Hermansky–Pudlak syndrome, homozygosity for a 16-bp duplication in exon 15 of *HPS* was a substantial risk factor for clinically significant restrictive pulmonary disease in adults. The onset and the rate of progression of pulmonary fibrosis can be monitored by pulmonary-function tests and high-resolution computed tomography of the lung. Renal reabsorptive capacity was normal in the patients with the 16-bp duplication despite reports of the accumulation of ceroid lipofuscin in tubular epithelial cells of patients with Hermansky–Pudlak syndrome.[23]

The degree of pigmentation of skin, hair, iris, and fundus differed enormously among the patients with the 16-bp duplication (Fig. 2), indicating that other gene products besides that of *HPS* affect melanogenesis. However, a defective HPS protein could cause variations in melanin production if it interfered with the formation of melanosomes. A similar mechanism may underlie the lack of platelet dense bodies and lysosomal impairment that are characteristic of Hermansky–Pudlak syndrome. These vesicles share an integral membrane protein (referred to as granulophysin,[24] or CD63, in dense bodies; ME 491[25] in melanosomes; and limp-1 or lamp-3[26] in lysosomes), and their genesis may require a common mechanism involving, for example, the protein product of *HPS*.

There are scant data on Hermansky–Pudlak syndrome in non–Puerto Ricans. The mutation identified in a family in Valais, Switzerland[27] — the insertion of a C at codon Pro 324[11] — is reportedly associated with normal life expectancy,[28] but no studies of pulmonary or renal function in persons with the mutation have been published. Pulmonary fibrosis has not been reported in most other patients with Hermansky–Pudlak syndrome[2] but was described in one of the original Czechoslovakian patients,[1] a 34-year-old Japanese man,[29] a Belgian family,[30] and an English family.[31] Colitis has been reported in only one non–Puerto Rican child[14] (one of the patients we studied), although pseudomel-

anosis coli was diagnosed post mortem in a Japanese patient.[29]

None of the 22 non–Puerto Rican patients that we studied carried the 16-bp duplication, and 2 Puerto Rican patients had no evidence of a mutation in *HPS*.[15] This apparent heterogeneity in the disease locus is consistent with the finding that there are many different loci that give rise to pigment dilution and a storage-pool defect in mice.[32] One mouse gene, pale ear or *ep*, is homologous with the human *HPS*,[33,34] whereas another, pearl or *pe*, codes for the β3A subunit of the adaptor-related protein complex AP-3.[35] This heterotetrameric complex[36] comprises part of the coat of transport vesicles that create intracellular organelles.

Patients without the 16-bp duplication had the same range of pigmentation as patients with the duplication (Fig. 2) and the same frequency of early inflammatory bowel disease. The absence of pulmonary fibrosis in adult patients without the duplication might reflect the presence of a mutation in *HPS* that causes only a mild form of Hermansky–Pudlak syndrome, as is presumed for the Swiss isolate,[11] or the presence of defects at entirely different loci. The age at onset of pulmonary fibrosis may also be later in these patients.

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