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Hypopigmentation: A Common Feature of Prader-Labhart-Willi Syndrome

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Summary

In order to determine the frequency and characterization of hypopigmentation in Prader-Labhart-Willi syndrome (PLWS), clinical, cytogenetic and biochemical findings are reported in 56 PLWS individuals. Forty-eight percent of the individuals with PLWS met the criteria for hypopigmentation. Hypopigmentation in PLWS individuals appears to be as common as previously recognized features such as behavioral problems and dental abnormalities. Significant differences in hair color, sun sensitivity, and complexion were found between those PLWS patients with the chromosome 15 deletion and those with normal chromosomes. Individuals with the deletion frequently had lighter hair color, more sun sensitivity, and fairer complexion than did either other family members or nondeletion PLWS patients. No significant differences in biochemical findings (phenylalanine, tyrosine, catecholamines, or β-melanocyte-stimulating hormone) were found between deletion and nondeletion PLWS patients or between hypopigmented and normally pigmented patients. The data suggest that a gene(s) controlling the activity of tyrosinase or other enzymes required for melanin production is located on proximal 15q.

Introduction

Prader-Labhart-Willi syndrome (PLWS) is the most common dysmorphic/genetic form of human obesity, and more than 700 cases have been reported (Butler 1989). It has been characterized by infantile hypotonia, early childhood obesity, short stature, small hands and feet, hypogonadism, mental deficiency, and a characteristic facial appearance. About 50% of patients with PLWS have an interstitial deletion of the proximal long arm of chromosome 15 (Ledbetter et al. 1982; Mattei et al. 1984; Butler et al. 1986; Wenger et al. 1987; Butler 1989).

Decreased oculocutaneous pigmentation has been observed in clinical studies in several individuals with PLWS (Hittner et al. 1982; Butler et al. 1986; Wiesner et al. 1987; Phelan et al. 1988). In 1982, Hittner et al. described hypopigmentation in nine PLWS individuals with the 15q deletion but did not compare them with PLWS patients with normal chromosomes. Butler et al. (1986) found in 39 PLWS individuals that those individuals with the chromosome 15 deletion had lighter hair and eye color, fairer skin complexion, and greater sun sensitivity than did PLWS individuals with normal chromosomes. They proposed that a DNA segment on proximal 15q, which is deleted in about 50% of PLWS patients, may play a role in both melanin production and decreased pigmentation. Recently, Wiesner et al. (1987) studied 29 PLWS patients and found decreased cutaneous and ocular pigmentation in 48% of their patients. They also reported abnormal melanosomes in one PLWS patient. Misrouting of optic fibers, a finding consistent with oculocutaneous or ocular albinism, was also found in several PLWS patients reported by Creel et al. (1986). Wiesner et al. (1987) reported that hypopigmentation was also correlated with the 15q deletion, although Wenger et al. (1987) did not identify such a correlation in their PLWS patients. Wiesner et al. (1987) concluded that the mechanism for hypopigmentation in PLWS is unknown, although hairbulb tyrosinase activity and glutathione levels (both important for production of melanin) were low in PLWS

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patients. Butler et al. (1987) also studied 12 PLWS patients and did not find a difference in plasma β-melanocyte-stimulating hormone levels in those with or without hypopigmentation. An error in amino acid metabolism (e.g., phenylalanine and tyrosine, which are utilized in melanin production) may exist in PLWS, as supported by low tyrosinase activity, albinism (Wiesner et al. 1987; Phelan et al. 1988), and tyrosinemia (Fernhoff et al. 1984). Additional features found in PLWS individuals (e.g., hyperphagia, obesity, and hypertension) may also be related to metabolic disturbances (e.g., catecholamine synthesis).

Herein, the frequency and characterization of the hypopigmentation in 56 PLWS patients, as well as clinical, biochemical, and cytogenetic findings, are reported in order to better delineate the cause of hypopigmentation in PLWS individuals.

Material and Methods

Subjects

Fifty-six Caucasian PLWS patients (29 males and 27 females with an average age of 13.9 years and a range of 1.5–39.0 years) were studied. The patients were diagnosed as having PLWS on the basis of hypotonia, hypogenitalism, early childhood obesity, small hands and feet, short stature, and delayed psychomotor development and/or mental retardation. During the physical examination, special attention was given to the pigment status (skin, hair, and eye color) and eye examination of each PLWS patient and his or her first-degree relatives. Fifty-one of the 56 PLWS patients were studied with high-resolution chromosome procedures; and 29 patients were identified as having the 15q11–12 deletion, while 22 patients had normal chromosomes.

Hair, Eye, and Skin Examination

Hair color was compared with a set of standard hair samples scaled for color from 0 (white-blond) to 7 (black). Skin was classified into four categories, depending on tanning ability, on the basis of Fitzpatrick criteria: type 1 skin (always burned and never tanned), type 2 skin (usually burned and tanned less than average), type 3 skin (sometimes burned mildly and tanned an average amount), and type 4 skin (rarely burned and tanned with ease) (Pathak et al. 1987). Skin complexion was judged as either normal or fairer than that of other family members. An eye examination for iris color, strabismus, nystagmus, and the presence or absence of both iris translucency and retinal abnormalities was undertaken. Iris color was scored from 1 (light blue) to 15 (dark brown) by comparison with a color chart for artificial eyes (Mager and Gougelman, Inc., Minneapolis). For this study an individual was considered to be hypopigmented when (1) skin type was 1 or 2; (2) skin complexion was fairer than that of other family members at comparable ages, by history and/or examination; (3) eye color was scored $\leqslant 5$; and (4) hair color was rated $\leqslant 4$.

Laboratory Findings

Random daytime fasting (6–12 h) plasma samples from several of the PLWS patients were obtained for various biochemical tests to directly or indirectly analyze melanin synthesis or for metabolic disturbances. Routine amino acid levels of phenylalanine and tyrosine, β-melanocyte-stimulating hormone levels ([by radioimmunoassay using antiserum R2489/12] [Nicholson et al. 1984; Butler et al. 1987]), catecholamines (norepinephrine, epinephrine, and dopamine—indirectly related to melanin synthesis and produced by the metabolism of tyrosine by tyrosine hydroxylase) were analyzed. Independent *t*-tests, Pearsonian product-moment and Spearman rank correlations, and Mann-Whitney U- and χ^2 tests were used throughout this study for statistical analysis of the biochemical and clinical findings.

Results

Twenty-seven (48%) of 56 PLWS patients were judged to have hypopigmentation on the basis of criteria established from skin type and complexion as well as from hair and eye color. The clinical, cytogenetic, and biochemical data for 56 PLWS patients are shown in table 1.

Deletion versus Nondeletion PLWS Individuals

The mean ages were 15.9 years for the 29 deletion PLWS patients and 12.0 years for the 22 nondeletion PLWS patients, i.e., not significantly different. Thirty-two percent of the nondeletion PLWS patients and 62% of deletion PLWS patients were classified as having hypopigmentation. The average eye-color rating was 3.7 (dark blue–light green) for all 56 PLWS patients; the average eye-color rating was 3.4 (dark blue) for the deletion PLWS patients and 4.0 (light green) for the nondeletion PLWS patients. The average hair-color rating was 3.1 (red) for all PLWS patients and was 2.6 (dark blond–red) for the deletion PLWS patients and 3.7 (red–light brown) for the nondeletion patients. The av-

Table 1

Pigmentation Status with Clinical, Cytogenetic, and Biochemical Findings in Individuals with Prader-Labhart-Willi Syndrome

				Hair			Skin	Eye				Biochemical						
Case	Sex	Age (years)	Chromosome Status	Color	Scale[a] (0–7)	Type[a] (1–4)	Complexion[b]	Color	Scale (1–15)	Strabismus	Nystagmus	Phenylalanine[c] (nmol/ml)	Tyrosine[d] (nmol/ml)	β-Melanocyte-stimulating Hormone[e] (pg/ml)	Epinephrine[f] (pg/ml)	Norepinephrine[g] (pg/ml)	Dopamine[h] (pg/ml)	Pigment Status[b]
1.....	M	1.5	del(15q)	Dark blond	2	2	Fair	Dark blue	3	–	–							Hypo
2.....	M	4.0	del(15q)	Blond	1	1	Fair	Dark blue	3	+	–	82	100	15	11	183	33	Hypo
3.....	M	5.0	del(15q)	Light blond	0	2	Fair	Dark blue	3	+	–							Hypo
4.....	M	9.0	del(15q)	Light blond	0	1	Fair	Dark blue	3	+	–							Hypo
5.....	M	12.0	del(15q)	Brown	5	4	Normal	Medium blue	2	+	–	70	47	29	30	275	12	Normal
6.....	M	13.0	del(15q)	Dark blond	2	1	Fair	Medium blue	2	+	–							Hypo
7.....	M	14.0	del(15q)	Light brown	4	4	?	Medium green	5			62	71					Normal
8.....	M	15.0	del(15q)	Light brown	4	2	Fair	Dark blue	3	+	–							Hypo
9.....	M	17.0	del(15q)	Light blond	0	2	Fair	Dark blue	3	+	–							Hypo
10.....	M	18.0	del(15q)	Light brown	4	1	Normal	Dark green	6			69	79					Normal
11.....	M	18.0	del(15q)	Blond	1	2	Fair	Medium blue	2	+	–							Hypo
12.....	M	18.0	del(15q)	Blond	1	3	Fair	Medium blue	2	–	–	57	55					Normal
13.....	M	20.0	del(15q)	Light brown	4	2	Fair	Dark blue	3	–	–	37	39	5	13	120	13	Hypo
14.....	M	39.0	del(15q)	Light brown	4	3	Normal	Dark blue	3	+	–							Normal
15.....	F	5.0	del(15q)	Light blond	0	1	Fair	Medium blue	2	+	–	84	87	31	19	315	10	Hypo
16.....	F	5.0	del(15q)	Blond	1	2	Fair	Dark blue	3	–	–	72	101					Hypo
17.....	F	6.0	del(15q)	Light brown	4	1	Fair	Medium blue	2	+	–							Hypo
18.....	F	7.0	del(15q)	Light blond	0	3	Normal	Medium brown	11	+	–							Normal
19.....	F	13.0	del(15q)	Dark blond	2	2	Fair	Dark blue	3	+	–							Hypo
20.....	F	16.0	del(15q)	Dark blond	2	2	?	Dark blue	3			65	65					Hypo
21.....	F	17.0	del(15q)	Light brown	4	2	Fair	Dark blue	3	–	–							Hypo

22.....	F	17.0	del(15q)	Dark blond	2	2	Fair	Dark blue	3	+	–							Hypo
23.....	F	20.0	del(15q)	Light brown	4	2	Fair	Medium blue	2	+	–	101	111	24	10	105	17	Hypo
24.....	F	20.0	del(15q)	Dark blond	2	3	?	Medium blue	2			75	59					Normal
25.....	F	22.0	del(15q)	Dark blond	2	2	Fair	Dark blue	3	–	–							Hypo
26.....	F	23.0	del(15q)	Dark blond	6	2	?	Dark green	6	–	–	35	46					Normal
27.....	F	24.0	del(15q)	Light brown	4	3	Normal	Dark blue	3	–	–							Normal
28.....	F	27.0	del(15q)	Light brown	4	3	Fair	Dark blue	3	+	–							Normal
29.....	F	35.0	del(15q)	Brown	5	3	Fair	Dark green	6	–	–	53	41		13	568	14	Normal
N		29			29	29			29			13	13	5	6	6	6	
Mean		15.9			2.55	2.17			3.38			66	69	21	16	262	16	
SD		8.9			1.78	0.85			1.88			18	24	11	8	172	8	
30.....	M	3.0	Normal	Red	3	3	Normal	Medium/ dark brown	12	–	–							Normal
31.....	M	3.0	Normal	Brown	5	3	Normal	Medium blue	2	+	–							Normal
32.....	M	6.0	Normal	Blond	1	2	Fair	Dark blue	3	+	–							Hypo
33.....	M	7.0	Normal	Brown	5	4	?	Medium blue	2	+	–	96	88					Normal
34.....	M	8.0	Normal	Light brown	4	3	Fair	Dark blue	3	+	–							Normal
35.....	M	8.0	Normal	Dark brown	6	4	Normal	Dark blue	3	–	–							Normal
36.....	M	8.0	Normal	Light brown	4	3	Normal	Dark blue	3	+	–							Normal
37.....	M	11.0	Normal	Dark blond	2	3	Normal	Dark blue	3	–	–	89	100	21	27	221	31	Normal
38.....	M	16.0	Normal	Dark brown	6	4	Normal	Medium/ dark brown	12	–	–							Normal
39.....	M	17.0	Normal	Dark brown	6	3	Normal	Medium/ dark brown	12	+	–							Normal
40.....	M	19.0	Normal	Light brown	4	1	?	Dark blue	3	+	–	54	46					Hypo
41.....	M	20.0	Normal	Red	3	2	Fair	Medium blue	2	+	–	48	53	16	23	173	2	Hypo
42.....	M	24.0	Normal	Light brown	4	2	Fair	Dark blue	3	–	–	87	66	18	11	373	9	Hypo
43.....	F	3.0	Normal	Dark blond	2	3	Normal	Medium green	5	+	–	90	70	24	56	284	20	Normal
44.....	F	7.0	Normal	Light brown	4	4	Normal	Dark blue	3	+	–							Normal

(continued)

Table 1 (continued)

Pigmentation Status with Clinical, Cytogenetic, and Biochemical Findings in Individuals with Prader-Labhart-Willi Syndrome

				Hair		Skin		Eye				Biochemical						
Case	Sex	Age (years)	Chromosome Status	Color	Scale[a] (0–7)	Type[a] (1–4)	Complexion[b]	Color	Scale (1–15)	Strabismus	Nystagmus	Phenylalanine[c] (nmol/ml)	Tyrosine[d] (nmol/ml)	β-Melanocyte-stimulating Hormone[e] (pg/ml)	Epinephrine[f] (pg/ml)	Norepinephrine[g] (pg/ml)	Dopamine[h] (pg/ml)	Pigment Status[b]
45.....	F	11.0	Normal	Blond	1	2	?	Medium blue	2	+	–	68	58					Hypo
46.....	F	13.0	Normal	Light brown	4	2	?	Medium blue	2									Normal
47.....	F	14.0	Normal	Dark brown	6	2	Normal	Dark blue	3	+	–	106	81	21	21	153	24	Normal
48.....	F	15.0	Normal	Blond	1	2	Normal	Medium green	5	+	–							Hypo
49.....	F	16.0	Normal	Dark brown	6	3	Normal	Medium green	5	+	–	39	54	46	19	241	10	Normal
50.....	F	17.0	Normal	Light brown	4	3	?	Medium hazel	8			53	55					Normal
51.....	F	18.0	Normal	Blond	1	1	Fair	Dark blue	3	+	+							Hypo
52.....	M	5.0	Unknown	Red	3	2	?	?										Hypo
53.....	M	8.0	Unknown	Blond	1	2	?	Dark blue	3									Hypo
54.....	F	8.0	Unknown	Dark brown	6	3	?	Dark hazel	9									Normal
55.....	F	11.0	Unknown	Dark blond	2	3	?	Dark blue	3									Normal
56.....	F	23.0	Unknown	Brown	5	4	?	Medium/dark brown	12									Normal
N[i]		22			22	22			22			10	10	6	6	6	6	
Mean		12.0			3.73	2.68			4.05			73	67	24	26	241	16	
SD		6.0			1.78	0.89			2.94			23	17	11	16	80	11	

[a] Significant difference ($P < .05$; Mann-Whitney U-test) between deletion PLWS patients and nondeletion PLWS patients.
[b] Significant difference ($P < .001$; χ^2 test) between deletion PLWS patients and nondeletion PLWS patients.
[c] Normal adult level 39–78 nmol/ml.
[d] Normal adult level 33–91 nmol/ml.
[e] Normal adult level <50 pg/ml.
[f] Normal adult level <65 pg/ml.
[g] Normal adult level 75–480 pg/ml.
[h] Normal adult level <100 pg/ml.
[i] PLWS individuals with normal chromosomes.

erage skin type was 2.4 for all PLWS patients and was 2.2 for the deletion PLWS patients and 2.7 for the nondeletion PLWS patients. There were significant differences ($P < .05$; Mann-Whitney U-test) for both hair color and skin type—but not for eye color—between the deletion PLWS patients and the nondeletion patients (table 1).

Sixty percent of all PLWS patients—80% of deletion PLWS patients and 29% of nondeletion PLWS patients—were found to have skin complexion fairer than that of other family members; this result showed significant difference ($P < .001$; χ^2 test) between the two chromosome subgroups. Therefore, deletion PLWS patients had significantly lighter hair, fairer skin complexion, and more sun sensitivity than did nondeletion PLWS patients. There was no difference in strabismus, nystagmus, or iris translucency between deletion PLWS patients and nondeletion PLWS patients. Strabismus was found in 64% of deletion PLWS patients and in 75% of nondeletion PLWS patients. Also, no differences in biochemical findings (β-melanocyte-stimulating hormone, phenylalanine, tyrosine, or catecholamine levels) were found between the deletion PLWS patients and nondeletion PLWS patients (table 1).

Hypopigmented versus Normally Pigmented PLWS Individuals

Significant differences ($P < .001$; Mann-Whitney U-test) were found between hypopigmented PLWS patients and normally pigmented PLWS patients, with lighter hair color, fairer skin complexion, and more sun sensitivity being found in the hypopigmented PLWS patients. There was no difference in age between hypopigmented PLWS patients and normally pigmented PLWS patients. There also was no significant difference in biochemical findings (β-melanocyte-stimulating hormone, phenylalanine, tyrosine, or catecholamine levels), strabismus, nystagmus, or consistent iris translucency or retinal abnormalities between the hypopigmented PLWS patients and the normally pigmented PLWS patients. Strabismus was found in 75% of hypopigmented PLWS patients and in 62% of normally pigmented PLWS patients. The average hair-color rating was 2.0 (dark blond) for the hypopigmented PLWS patients and 4.1 (light brown) for those judged to have normal pigmentation. The average eye-color score was 2.8 (dark blue) for the hypopigmented PLWS patients and 4.5 (light green–medium green) for those with normal pigmentation. The average skin type was determined to be 1.7 for the hypopigmented group and 3.0 for the normally pigmented patients. Ninety-five percent of the hypopigmented PLWS patients were found to have fairer complexion than did other family members, compared with 20% of the normally pigmented PLWS patients.

Discussion

Forty-eight percent of the 56 PLWS patients in this study met the criteria for hypopigmentation. Therefore, hypopigmentation appears as common as other features recognized in PLWS individuals. For example, in a review of 555 PLWS patients, behavioral problems and dental abnormalities were reported in 53% and 48% of PLWS patients, respectively (Butler 1989).

There was a significant positive correlation ($P < .05$) between darker hair color and advanced age. Hypopigmentation was also positively correlated with the presence of the chromosome deletion. Hypopigmentation in nondeletion PLWS patients may be due to a submicroscopic deletion of proximal 15q, which may play a role in melanin production. Although no quantitative differences were identified in phenylalanine, tyrosine, β-melanocyte-stimulating hormone, and catecholamine plasma levels between deletion PLWS patients and nondeletion PLWS patients or between hypopigmented PLWS patients and normally pigmented PLWS patients, more research is needed on the synthesis and deposition of melanin.

Additional evidence that chromosome 15 may be involved in pigment formation is Angelman syndrome, a syndrome characterized by mental retardation, ataxic gait, inappropriate laughter, seizures, and a characteristic facies (Willems et al. 1987). Angelman syndrome patients may also have hypopigmentation (fair hair (Willems et al. 1987) and lightly pigmented irides [Massey and Roy 1973; Williams and Frias 1982; Magenis et al. 1987]). Recently, a deletion of the proximal long arm of chromosome 15, similar to the deletion seen in PLWS patients, has been identified in Angelman syndrome patients (Magenis et al. 1987).

In summary, the clinical and biochemical data in both this study and other reports indicate that there is decreased pigment in approximately one-half of the PLWS patients—a finding that correlates with the chromosome 15 deletion, although the hypopigmentation is not as severe as in individuals with oculocutaneous albinism. The genetic, molecular, and physiologic mechanism of pigment formation and deposition in humans is not fully understood, but chromosome 15 may contain structural and/or regulatory genes for development of normal hair, eye, and skin pigment. More biochemical and DNA research is needed to identify and classify

the cause(s) of the pigmentary disturbance and its relationship to the chromosome 15 deletion seen in PLWS and in Angelman syndrome.

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