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Molecular subtype and growth hormone effects on dysmorphology in Prader–Willi syndrome

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Abstract

Prader–Willi syndrome (PWS) affects 1/15,000–1/30,000 live births and is characterized by lack of expression of paternally inherited genes on 15q11.2-15q13 caused by paternal deletions, maternal uniparental disomy (UPD), or imprinting defects. Affected individuals have distinct physical features, and growth hormone (GH) deficiency occurs in some individuals with PWS. The aim of this study is to test the hypotheses that (a) individuals with deletions and UPD have different physical and dysmorphic features, (b) individuals treated with GH have different physical and dysmorphic features than those not treated, and (c) GH treatment effects are different for individuals with UPD in comparison to those with deletions. Study participants included 30 individuals with deletions or UPD, who did or did not have GH treatment. Participants' molecular abnormalities were determined by molecular and cytogenetic analysis. Clinical data were obtained by a single dysmorphologist. Individuals with deletions were found to be heavier (p = .001), taller (p = .031), with smaller head circumferences (p = .042) and were more likely to have fair skin and hair than their family members (p = .031, .049, respectively) compared to UPD patients. Females with deletions more commonly had hypoplastic labia minora (p = .009) and clitoris (.030) in comparison to those with UPD. Individuals who received GH in both deletion and UPD groups were taller (p = .004), had larger hands (p = .011) and feet (p = .006) and a trend for a larger head circumference (p = .103). Interestingly, the GH-treated group also had a lower rate of strabismus (esotropia [p = .017] and exotropia [p = .039]). This study showed statistically significant correlations between phenotype and molecular subtypes and also between phenotype and GH treatment.

KEYWORDS

dysmorphology, GH, imprinting disorders, microdeletion, Prader–Willi syndrome, uniparental disomy

1 | INTRODUCTION

1.1 | Background

Prader–Willi syndrome (PWS) was one of the first described complex neurodevelopmental disorders (Prader, Labhart, & Willi, 1956a). It is characterized by an array of symptoms including hypotonia at birth, hypogonadism, short stature, and hyperphagia beginning in childhood leading to morbid obesity (Prader, Labhart, & Willi, 1956b). PWS is the most common genetic syndrome associated with obesity and obesity-related morbidity and mortality (Butler, 1990; Crino, Fintini, Bocchini, & Grugni, 2018).

PWS affects about 1/15,000–1/30,000 individuals (reviewed in Butler, 1990; Cassidy, Schwartz, Miller, & Driscoll, 2012;

Cassidy & Driscoll, 2009) and is equally distributed throughout all genders and ethnic groups (Whittington et al., 2001). PWS was the first recognized disorder in humans caused by an error in genomic imprinting (Reik, 1989). It is characterized by lack of expression of genes on the paternally inherited chromosome 15q11.2-15q13 (Cassidy & Driscoll, 2009; Ledbetter et al., 1981; Muscogiuri et al., 2019; Nicholls, Knoll, Butler, Karam, & Lalande, 1989). Genomic imprinting is the modification of genes based on the parent of origin, leading to differential expression of maternal and paternal genes in the zygote (Monk, 1988). The majority of the genes in this region are involved in RNA and protein processing of neuroregulators and hormones; thus disruption in this region negatively affects neuronal development and endocrine function (Bittel & Butler, 2005). Three types of molecular lesions are known to cause PWS, all involving chromosome 15. Paternally inherited interstitial deletions in chromosome 15 are found in 65–75% of affected individuals (Cassidy & Driscoll, 2009; Ledbetter et al., 1981). Maternal uniparental disomy (UPD) of chromosome 15, first described in 1989 by Nicholls et al., occurs in 20–30% of affected patients (Cassidy & Driscoll, 2009; Nicholls et al., 1989). Sporadic deletions or microduplications in chromosome 15 imprinting centers, regions that appear to control regional methylation patterns, occur in about 2–5% of affected patients (reviewed in Cassidy & Driscoll, 2009; Buiting et al., 1995).

1.1.1 | Facial dysmorphology and physical features

When Prader et al. first described the syndrome in 1956, they reported several distinct facial and physical features associated with PWS, including distinct eyes, small hands and feet, hypogonadism, short stature, and obesity (Prader et al., 1956b). Typical PWS facial and physical features have been since noted to include narrow bifrontal diameter, almond-shaped palpebral fissures, narrow nasal bridge, thin upper lip with downturned mouth, small hands and feet, and scoliosis (Cassidy & Driscoll, 2009). The average height of individuals with PWS is below the third centile of the general population height beginning around 3 years of age, and the weight for affected individuals older than 2 years of age increases significantly compared to the general population average (Wollmann, Schultz, Grauer, & Ranke, 1998) if uncontrolled externally.

1.1.2 | Growth hormone treatment and benefits

One of the first comprehensive studies to measure benefits of growth and body composition with use of GH on individuals with PWS was completed by Lindgren et al. (1997). All 27 enrolled individuals showed an increase in height and muscle mass and a decrease in body fat percentage, regardless of time on GH. The study also suggested that GH treatment improved the adverse behavioral and psychiatric issues that are associated with PWS (Lindgren et al., 1997).

Bakker et al. (2017) described the largest international cohort of 522 prepubertal children with PWS who received GH therapy for three consecutive years and 173 adolescents who reached adult height after 8 years of GH treatment with a mean dose of 0.22 mg/kg/week. Significant improvement in linear growth and adult height was reported (Bakker et al., 2017). These studies, and others, demonstrate the benefits of GH treatment in patients with PWS, and prompted the U.S. Food and Drug Administration to approve injectable somatropin (GH) as a standard of care treatment for children with PWS who growth failure (Deal et al., 2013; Heksch, Kamboj, Anglin, & Obrynba, 2017).

Although prior authors demonstrate improvements in physical characteristics in PWS-affected individuals following GH therapy, none have quantified this change in terms of dysmorphic features. The goals of this study were to determine if individuals with deletions were more likely to have dysmorphic features than those with UPD, to determine the effects of GH treatment on dysmorphic features in patients with PWS, and to determine if individuals with maternal UPD versus those with deletions respond differently to GH treatment.

2 | MATERIALS AND METHODS

Study participants were recruited for a genotype–phenotype study in 2000–2003 at the University of California, Irvine (HS#: 2000-1405). Participants were recruited through notices on the websites for Prader–Willi Syndrome Association, USA and the statewide Prader–Willi California Foundation. Many participants contacted the project coordinator to participate, unsolicited, via the internet. After the protocol was fully explained and all questions were answered, informed consent was signed by each participant and/or a legal guardian.

Clinical and genetic data were obtained by standardized measurement of physical variables including facial features, as well as participants description by a single dysmorphologist (SBC).

2.1 | Dysmorphology evaluation

Physical and facial features, including continuous and categorical variables, were assessed. Continuous variables include measurements of height, weight, BMI, head circumference, facial features, arm span, hand and foot length, and penile length. For statistical purpose, this data were converted into age and gender-adjusted centiles using the WHO reference tables. Categorical variables of interest included presence of facial features (eye esotropia and exotropia, narrow nasal bridge, flat philtrum, downturned upper lip, thick and hypopigmented hair), and physical characteristics including height, head circumference, and other measures.

2.2 | Data analysis

The data were summarized using mean and *SD* for continuous variables, such as height, weight, head circumference. Continuous variables were analyzed using a two-sample *t* test and categorical variables were analyzed using Pearson's chi-square tests and Fisher's

TABLE 1 Phenotypic characteristics of the study population according to molecular subtype and GH treatment

Physical measurements	Molecular subclass					Growth hormone treatment				
	UPD		Deletion		*p*-value	No GH		GH		*p*-value
	N	Mean (*SD*) or % frequency	*N*	Mean (*SD*) or % frequency		*N*	Mean (*SD*) or % frequency	*N*	Mean (*SD*) or % frequency	
Height %ile	30	21.1 (28.0)	34	36.7 (28.3)	**.031**	33	19.4 (25.5)	31	40.0 (29.2)	**.004***
Weight %ile	30	63.9 (33.1)	34	87.4 (18.2)	**.001***	33	74.5 (32.3)	31	78.4 (24.5)	.586
Weight % for height	29	80.7 (23.6)	31	91.6 (12.6)	**.033**	30	87.5 (22.0)	30	85.1 (16.6)	.641
BMI	30	23.5 (7.6)	34	26.6 (8.0)	.114	33	25.8 (8.5)	31	24.4 (7.3)	.467
Head circumference %ile	30	57.0 (31.8)	32	39.9 (33.1)	**.042**	32	41.5 (30.8)	30	55.4 (34.9)	.103
Innercanthal distance %ile	30	53.23	33	48 (5.3)	.904	32	47.3 (5.5)	31	54.5 (5.4)	.37
Interpupillary distance %ile	30	44.4 (5.7)	33	56 (5.6)	.920	32	50 (5.8)	31	51 (5.9)	.832
Outercanthal distance %ile	30	5.7 (2.1)	33	12.8 (4.4)	.934	32	6.6 (2.4)	31	12.4 (4.5)	.242
Palpebral fissure length %ile	30	17.1 (5.1)	32	20.5 (4.5)	.748	31	16.1 (3.2)	31	22.4 (6.1)	.365
Right ear length %ile	28	41.7 (23.2)	32	43.5 (26.1)	.784	30	43.8 (24.6)	30	41.5 (25.0)	.728
Chest: internipple distance (cm)	25	20.2 (16.3)	27	17.1 (4.3)	.372	24	16.9 (4.8)	28	20.0 (15.2)	.315
Chest: circumference (cm)	26	72.5 (22.2)	27	77.7 (17.8)	.353	24	76.0 (20.5)	29	74.5 (20.0)	.797
Right hand length %ile	28	29.5 (28.0)	33	37.0 (27.5)	.297	30	24.4 (28.3)	31	42.3 (24.5)	**.011***
Right middle finger length %ile	28	16.7 (17.5)	33	29.8 (25.1)	**.020**	30	19.3 (22.2)	31	28.1 (22.8)	.129
Right middle finger as % of hand	28	18.7 (21.7)	33	30.7 (28.5)	.067	30	28.3 (26.4)	31	22.1 (25.8)	.360
Right foot length %ile	27	20.2 (23.7)	32	17.5 (20.6)	.643	29	10.9 (17.0)	30	26.3 (24.3)	**.006***
Right male testis size (ml)	9	2.0 (1.1)	10	1.6 (0.8)	.373	9	1.5 (0.9)	10	2.1 (0.9)	.134
Male: penis length %ile	13	1.7 (2.5)	15	1.6 (17.8)	.057	16	4.1 (12.2)	12	10.9 (15.4)	.218
Hair: color normal for family	30	96.7	30	80.0	**.044**	30	83.3	30	93.3	.228
Hair: hypopigmented	11	18.2	12	58.3	**.049**	17	35.3	6	50.0	.526
Hair: thick	14	71.4	20	80.0	.226	15	60.0	19	89.5	**.009***
Eyes: esotropia	28	17.9	32	9.4	.335	29	24.1	31	3.2	**.017**
Eyes: exotropia	29	10.3	33	3.0	.242	31	12.9	31	0.0	**.039**
Nose: narrow	30	30.0	32	56.2	**.037**	31	61.3	31	25.8	**.005***
Mouth: dentition carious	27	7.4	27	33.3	**.018**	26	26.9	28	14.3	.249
Mouth: philtrum flat	30	3.3	33	9.1	.349	32	12.5	31	0.0	**.042**
Mouth: upper lip downturned	30	53.3	31	51.6	.893	31	67.7	30	36.7	**.015**
Mouth: dentition grinding	28	7.1	30	23.3	.089	27	25.9	31	6.5	**.041**
Ears: normal	29	86.2	33	100.0	**.027**	31	93.5	31	93.5	1.000
Chest: normal	28	100.0	33	84.8	**.032**	30	90.0	31	93.5	.614
Genu valgus	25	12.0	29	41.4	**.050**	26	38.5	28	17.9	.211
Skin: fair	29	37.9	32	65.6	**.031**	31	64.5	30	40.0	.055
Male: scrotum rugation poor	7	43.8	2	11.8	**.039**	19	31.6	14	21.4	.518
Male: scrotum hypoplastic	15	53.3	17	58.8	.755	18	77.8	14	28.6	**.005***
Female: labia minora hypoplastic	12	33.3	13	84.6	**.009***	9	66.7	16	56.2	.610
Female: clitoris hypoplastic	11	36.4	11	81.8	**.030**	9	77.8	13	46.2	.138
Female: clitoris normal	10	70.0	11	36.4	.123	6	16.7	15	66.7	**.038**
Palmar creases single	17	17.6	11	9.1	.203	11	36.4	17	0.0	**.027**
Neuro: Babinski	25	8.0	23	17.4	.218	25	24.0	23	0.0	**.015**
Neuro: muscle bulk increased	22	0.0	19	5.3	.276	19	0.0	22	4.5	.347

p values <.05 in bold and <.01 in asterix.

exact tests. When data were compared between subgroups classified by both molecular subtype and GH treatment, categorical variables were analyzed using Mantel–Haenszel chi-square test to test for GH effect after adjusting for molecular subtypes. For continuous variables, a differential effect of GH treatment would be detected by a significant interaction between the two independent variables molecular subtype and GH treatment within the analysis of variance test (Table 2). For categorical variables, the Mantel–Haenszel test determined whether there is an overall effect for GH treatment after adjusting for any differences due to molecular subtype. Statistical significance was considered at $p < .05$.

3 | RESULTS

3.1 | Study participants

The study included 64 participants, 34 with deletions and 30 with UPD. Fifty percent (17/34) with deletions and 47% (14/30) with UPD had received GH treatment. Among the 64 participants there were 56 Caucasian, six Hispanic, one Iranian, and one Indian. Further details on the participants' gender, average age, molecular subtype, GH treatment are presented in Table 1. For individuals with deletions, the average age at time of entry into the study was 9.2 years (range 4–16 years) for those treated and 12.1 years for those not treated with GH. GH treatment was started at average age of 6.4 years and was administered for an average of 2.3 years (range = 1 month–8 years) by the time of the study. For individuals with UPD, the average age at time of entry into the study was 11.8 years (range 3–29 years) for those treated and 9.9 years for those not treated with GH by the time of the study. GH treatment was started at average age of 8.3 years and was given for an average of 2.9 years (range = 1–6 years). These individuals were still receiving growth hormone at the time of enrollment.

3.2 | Comparison between the deletion and uniparental disomy molecular subgroups

Patients with the deletion subtype when compared with the UPD subgroup were found to be taller with a mean height percentile of 36.7 ± 28.3 versus 21.1 ± 28 (p value = .031), heavier with mean weight percentile 87.4 ± 18.2 versus 63.9 ± 33.1 (p value .001), a higher weight for height percentile (91.6 ± 12.6 vs. 80.7 ± 23.6 p value = .033) and a smaller head circumference percentile (39.9 ± 33 vs. 1 57 ± 31.8, p value = .042). There was a trend for increased frequency of narrow

TABLE 2 Effect of GH treatment between molecular subtypes

Physical measurements	UPD					Deletion				
	No GH		GH		*p* value (GH-no GH)	No GH		GH		*p* value (GH-no GH)
	N	Mean (*SD*)	*N*	Mean (*SD*)		*N*	Mean (*SD*)	*N*	Mean (*SD*)	
Height %ile	16	57.7 (27.9)	14	38.7 (32.5)	**.002***	17	32.3 (29.6)	17	41.1 (27.2)	.375
Weight %ile	16	62.0 (38.4)	14	66.0 (26.6)	.742	17	86.2 (19.4)	17	88.6 (17.5)	.710
Weight for height %ile	15	80.1 (29.0)	14	81.4 (17.1)	.879	15	94.9 (6.5)	16	88.4 (15.9)	.147
BMI	16	24.3 (9.3)	14	22.5 (5.2)	.511	17	27.2 (7.7)	17	25.9 (8.4)	.635
Head circumference %ile	16	47.6 (31.5)	14	67.8 (29.6)	.081	16	35.3 (29.9)	16	44.5 (36.4)	.441
Upper/lower segment ratio	16	1.1 (0.1)	14	1.0 (0.1)	**.031**	15	1.1 (0.1)	16	1.1 (0.1)	.719
Arm/span height ratio	15	1.0 (0.03)	14	1.0 (0.1)	.683	15	1.0 (0.03)	16	1.0 (0.02)	.892
Innercanthal distance %ile	16	2.8 (0.4)	14	3.1 (0.3)	**.042**	16	2.9 (0.3)	17	2.9 (0.4)	.982
Interpupillary distance %ile	16	5.2 (0.7)	14	5.4 (0.5)	.415	16	5.3 (0.5)	17	5.3 (0.5)	.953
Outercanthal distance %ile	16	8.1 (1.0)	14	8.4 (0.7)	.329	16	8.1 (0.8)	17	8.3 (0.7)	.626
Palpebral fissure length %ile	16	2.6 (0.3)	14	2.7 (0.3)	.156	15	2.6 (0.3)	17	2.6 (0.2)	.791
Right ear length %ile	15	9.5 (22.5)	13	44.2 (24.6)	.605	15	48.0 (26.5)	17	39.5 (25.9)	.366
Chest: internipple distance %ile	13	17.0 (5.2)	12	23.6 (22.9)	.346	11	16.8 (4.6)	16	17.4 (4.1)	.772
Chest: circumference %ile	13	76.1 (24.5)	13	68.9 (20.0)	.420	11	75.8 (15.8)	16	79.1 (19.4)	.633
Right hand length %ile	14	17.8 (26.1)	14	41.1 (25.5)	**.024**	16	30.2 (29.7)	17	43.3 (24.4)	.180
Right middle finger length %ile	14	8.1 (10.0)	14	25.2 (19.5)	**.009***	16	29.0 (25.4)	17	30.5 (25.5)	.864
Right middle finger as % hand	14	20.7 (21.9)	14	16.6 (22.1)	.628	16	34.9 (28.9)	17	26.6 (28.3)	.412
Right foot length %ile	14	9.7 (11.7)	13	31.5 (28.3)	**.020**	15	12.1 (19.9)	17	22.3 (20.7)	.165
Right male testis size	4	1.6 (1.0)	5	2.4 (1.1)	.261	5	1.4 (0.9)	5	1.8 (0.7)	.419
Male: penis length	9	1.0 (0.0)	4	3.2 (4.5)	—	7	8.0 (18.5)	8	14.8 (17.7)	.485

Note: All measurements are in percentiles. p values <.05 in bold and <.01 in asterix.

bifrontal diameter. Patients with the deletion subtype were more fair skinned and fair-haired (p = .031 and p = .049, respectively) than their family members, attributed to loss of a single copy of the *OCA2* albinism gene in the 15q11-13 region. The deletion group had a higher incidence of carious dentition 33.3% versus 7.4% (p = .018). They also had a higher incidence of hypoplastic labia minora 84.6% versus 33.3% (p = .009), and clitoris 81.8% versus 36.4% (p = .03), with a trend for hypoplastic genitalia in males with deletions but no other significant differences in scrotal or penile anomalies.

3.3 | Comparison between GH treated and non-GH treated groups

The study participants were grouped by GH treatment (treated vs. not treated), irrespective of molecular subtype. Table 1 compares the results of continuous and categorical variables. Statistically significant differences between GH treated versus nontreated were found for height (p = .004), and foot length (p = .006), but not weight or head circumference. The prevalence of features including narrow nasal bridge (p = .005), dentition grinding (p = .041) and thickness of hair (p = .009) was higher in the GH treated group. The difference in skin fairness between the GH treated and untreated groups appeared to be higher for participants without treatment, however this difference did not reach statistical significance (p = .055). The prevalence of hypoplastic scrotum was higher in the nontreated group (p = .005).

3.4 | Comparison of GH effect between molecular subtypes

Analysis of effects of GH treatment was also undertaken for each individual molecular subtype separately (Table 2) for each variable. Based on the results of the analyses, there were no statistically significant differences by the Mantel–Haenszel chi-square tests between molecular subtypes in the effect of GH treatment on physical characteristics. In the deletions group, the individuals on GH appear to be proportionately taller (126.3 ± 23.5) than those who are on GH with UPD (115.8 ± 24) although this difference did not reach statistical significance (p = .068).

4 | DISCUSSION

Our studies suggest benefits of GH therapy treatment in individuals with PWS. Individuals being treated with GH, irrespective of molecular subtype, are taller, have bigger hands and feet, thicker hair, have a lower prevalence of esotropia, exotropia, narrow nose, flat philtrum, downturned upper lip, dentition grinding, single palmar crease, fair skin, and hypoplastic scrotum. It has previously been suggested that the facial features and physical characteristics of PWS may differ in the three different molecular subtypes. Individuals with UPD were previously reported to have a lower frequency of dysmorphic facial features (Cassidy et al., 1997; Gillessen-Kaesbach et al., 1995). This provided an explanation for why individuals with UPD were diagnosed later than those with deletions, at an average age of 9.29 years compared with 3.76 years respectively (Gunay-Aygun, Heeger, Schwartz, & Cassidy, 1997). Dobrescu, Chirita-Emandi, Andreescu, Farcas, and Puiu (2016), however reported that the delayed age at diagnosis in their cohort was not related to the genotype but was attributable to the lack of medical expertise and molecular diagnostic tests in different regions.

The analyses presented here include results from between genotype and phenotype correlation studies as assessed by a single observer blinded to molecular subtype. Because the study sample included both participants on GH treatment as well as those who are not on treatment, this was also an opportunity to investigate the effect of GH treatment on patients' physical characteristics and the possibility of different effects of GH treatment on different molecular subtypes. Our study has shown that individuals with deletions are taller, weigh more, have smaller head circumferences, longer middle finger length, and a higher prevalence of narrow nasal bridges, carious dentition, genu valgus, hypopigmentation, and hypoplastic genitalia in the females. Previous studies have shown that individuals with deletions have a higher frequency of hypopigmentation (Butler, 1989), increased weight, and a higher prevalence of characteristic facial features, including narrow bifrontal diameter, almond shaped palpebral fissures, narrow nasal bridge, and downturned mouth with thin upper lip (Cassidy et al., 1997). Lin et al. also reported that individuals with deletions tend to have smaller hands and feet and increased frequency of hypoplastic genitalia in females (Lin et al. 2007).

Costeff, Holm, Ruvalcaba, and Shaver (1990) have reported that poor growth and obesity in PWS are at least partly due to GH deficiency (Costeff et al., 1990). Additionally the body habitus including decreased lean muscle mass, increased fat mass, and short stature in individuals with PWS are more similar to those of individuals with GH deficiency than to those with simple obesity (Brambilla et al., 1997). The association between obesity and reduction in GH secretion was first described by Roth, Glick, Yalow, and Berson (1963). Lindgren et al. (1997) have shown that individuals treated with GH have increased height and muscle mass, along with decreased body fat and BMI. Eiholzer et al. (1998) supported these findings and further showed that individuals treated with GH have increased hand and foot length, arm span, and lean body mass, associated with decreased weight and skin fold thickness. Although Whitman, Myers, Carrel, and Allen (2002) allude to a normalization of the appearance of affected individuals with PWS following the use of GH treatment; no studies have been conducted to measure differences specifically for facial dysmorphic features. The lack of correlation with other studies may be due to different study population, small sample size, and limited statistical power. Alternatively, improved study design (single observer blind to molecular subtype) may be responsible for detection of differences not detected in other studies.

This study examines whether the effect of GH treatment differed depending on molecular etiology. We did not identify any significantly different effects of GH treatment between the two molecular subgroups for any of the dysmorphology variables or physical measurements.

The results of this study suggest the possibility of a difference in height centile between individuals with UPD compared with individuals with deletions (p = .031) irrespective of GH treatment. Results also support a significant difference in height percentile associated with GH treatment (p = .004). These findings, together with the results for height percentile in Table 2, suggest that there may be a complex relationship between molecular subtype and GH treatment for this variable. While untreated individuals with UPD appear shorter on average than untreated individuals in the deletion group, the increase in height associated with GH treatment appears to be greater in the UPD than in the deletion group. Larger studies will be needed to confirm this suggestive finding.

4.1 | Study limitations

Our study has some limitations including its retrospective design. The sample size of our study is relatively small, but this could be justified by the rarity of PWS. Our study results could be affected by variability of GH therapy dose and duration, and some of the observed differences may be significant due to chance and not reflective of a true difference between the groups due to presence of some confounding variables.

4.2 | Conclusions

This study although small, shows statistically significant genotype–phenotype correlations between 34 individuals with Prader–Willi syndrome due to paternal deletions and 30 individuals with maternal uniparental disomy for several growth measurements and physical anomalies. The deletion group is more likely to be taller and weigh more, have smaller head circumferences, have fair skin, and hypoplastic genitalia compared to the UPD group.

The study also shows significant differences between 31 individuals with PWS who have been treated with GH and 33 individuals who have not been treated with GH. Those individuals on GH are more likely to be taller, have larger hands and feet, and interestingly a lower frequency of esotropia and had a lower frequency of fair skin (p = .055). Finally, there were no significant findings in regards to the differential effects of GH treatment between the molecular subtypes, although it appeared that GH treatment had a larger effect for individual with uniparental disomy when compared to those with deletions.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

Bakker, N. E., Lindberg, A., Heissler, J., Wollmann, H. A., Camacho-Hubner, C., Hokken-Koelega, A. C., & Committee, K. S. (2017). Growth hormone treatment in children with Prader-Willi syndrome: Three years of longitudinal data in Prepubertal children and adult height data from the KIGS database. *The Journal of Clinical Endocrinology and Metabolism*, *102*(5), 1702–1711.

Bittel, D. C., & Butler, M. G. (2005). Prader-Willi syndrome: Clinical genetics, cytogenetics and molecular biology. *Expert Reviews in Molecular Medicine*, *7*(14), 1–20.

Brambilla, P., Bosio, L., Manzoni, P., Pietrobelli, A., Beccaria, L., & Chiumello, G. (1997). Peculiar body composition in patients with Prader-Labhart-Willi syndrome. *The American Journal of Clinical Nutrition*, *65*(5), 1369–1374.

Buiting, K., Saitoh, S., Gross, S., Dittrich, B., Schwartz, S., Nicholls, R. D., & Horsthemke, B. (1995). Inherited microdeletions in the Angelman and Prader-Willi syndromes define an imprinting Centre on human chromosome 15. *Nature Genetics*, *9*(4), 395–400.

Butler, M. G. (1989). Hypopigmentation: A common feature of Prader-Labhart-Willi syndrome. *American Journal of Human Genetics*, *45*(1), 140–146.

Butler, M. G. (1990). Prader-Willi syndrome: Current understanding of cause and diagnosis. *American Journal of Medical Genetics*, *35*(3), 319–332.

Cassidy, S. B., & Driscoll, D. J. (2009). Prader-Willi syndrome. *European Journal of Human Genetics*, *17*(1), 3–13.

Cassidy, S. B., Forsythe, M., Heeger, S., Nicholls, R. D., Schork, N., Benn, P., & Schwartz, S. (1997). Comparison of phenotype between patients with Prader-Willi syndrome due to deletion 15q and uniparental disomy 15. *American Journal of Medical Genetics*, *68*(4), 433–440.

Cassidy, S. B., Schwartz, S., Miller, J. L., & Driscoll, D. J. (2012). Prader-Willi syndrome. *Genetics in Medicine*, *14*(1), 10–26.

Costeff, H., Holm, V. A., Ruvalcaba, R., & Shaver, J. (1990). Growth hormone secretion in Prader-Willi syndrome. *Acta Paediatrica Scandinavica*, *79*(11), 1059–1062.

Crino, A., Fintini, D., Bocchini, S., & Grugni, G. (2018). Obesity management in Prader-Willi syndrome: Current perspectives. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, *11*, 579–593.

Deal, C. L., Tony, M., Hoybye, C., Allen, D. B., Tauber, M., Christiansen, J. S., & Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants. (2013). GrowthHormone research society workshop summary: Consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *The Journal of Clinical Endocrinology and Metabolism*, *98*(6), E1072–E1087.

Dobrescu, A. I., Chirita-Emandi, A., Andreescu, N., Farcas, S., & Puiu, M. (2016). Does the genetic Causof Prader-Willi syndrome explain the highly variable phenotype? *Maedica (Buchar)*, *11*(3), 191–197.

Eiholzer, U., Gisin, R., Weinmann, C., Kriemler, S., Steinert, H., Torresani, T., … Prader, A. (1998). Treatment with human growth hormone in patients with Prader-Labhart-Willi syndrome reduces body fat and increases muscle mass and physical performance. *European Journal of Pediatrics*, *157*(5), 368–377.

Gillessen-Kaesbach, G., Robinson, W., Lohmann, D., Kaya-Westerloh, S., Passarge, E., & Horsthemke, B. (1995). Genotype-phenotype correlation in a series of 167 deletion and non-deletion patients with Prader-Willi syndrome. *Human Genetics*, *96*(6), 638–643.

Gunay-Aygun, M., Heeger, S., Schwartz, S., & Cassidy, S. B. (1997). Delayed diagnosis in patients with Prader-Willi syndrome due to maternal uniparental disomy 15. *American Journal of Medical Genetics*, *71*(1), 106–110.

Heksch, R., Kamboj, M., Anglin, K., & Obrynba, K. (2017). Review of Prader-Willi syndrome: The endocrine approach. *Translational Pediatrics*, *6*(4), 274–285.

Ledbetter, D. H., Riccardi, V. M., Airhart, S. D., Strobel, R. J., Keenan, B. S., & Crawford, J. D. (1981). Deletions of chromosome 15 as a cause of the Prader-Willi syndrome. *The New England Journal of Medicine*, *304*(6), 325–329.

Lin, H. Y., Lin, S. P., Chuang, C. K., Chen, M. R., Yen, J. L., Lee, Y. J. … Kuo, P. L. (2007). Genotype and phenotype in patients with Prader-Willi syndrome in Taiwan. *Acta Paediatrica*, *96*(6), 902–905.

Lindgren, A. C., Hagenas, L., Muller, J., Blichfeldt, S., Rosenborg, M., Brismar, T., & Ritzen, E. M. (1997). Effects of growth hormone treatment on growth and body composition in Prader-Willi syndrome: A preliminary report. The Swedish National Growth Hormone Advisory Group. *Acta Paediatrica. Supplement*, *423*, 60–62.

Monk, M. (1988). Genomic imprinting. *Genes & Development*, *2*(8), 921–925.

Muscogiuri, G., Formoso, G., Pugliese, G., Ruggeri, R. M., Scarano, E., Colao, A., & Restare. (2019). Prader-Willi syndrome: An uptodate on endocrine and metabolic complications. *Reviews in Endocrine & Metabolic Disorders*, *20*(2), 239–250.

Nicholls, R. D., Knoll, J. H., Butler, M. G., Karam, S., & Lalande, M. (1989). Genetic imprinting suggested by maternal heterodisomy in non-deletion Prader-Willi syndrome. *Nature*, *342*(6247), 281–285.

Prader, A., Labhart, A., & Willi, H. (1956a). Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus, und Oligophrnie Nach Myatonieartigem Zustand im Neugerborenenalter. *Schweizerische Med Wochenschr*, *8*, 1260–1261.

Prader, A., Labhart, H., & Willi, H. (1956b). Ein Syndrom von Adipositas, Kryptorchismus und Oligophrenie nach myatonieartigem Zustand in Neugeborenenamter. *Schweiz Med Wochenschr*, *86*, 1260–1261.

Reik, W. (1989). Genomic imprinting and genetic disorders in man. *Trends in Genetics*, *5*(10), 331–336.

Roth, J., Glick, S. M., Yalow, R. S., & Berson, S. A. (1963). Secretion of human growth hormone: Physiologic and experimental modification. *Metabolism*, *12*, 577–579.

Whitman, B. Y., Myers, S., Carrel, A., & Allen, D. (2002). The behavioral impact of growth hormone treatment for children and adolescents with Prader-Willi syndrome: A 2-year, controlled study. *Pediatrics*, *109*(2), E35.

Whittington, J. E., Holland, A. J., Webb, T., Butler, J., Clarke, D., & Boer, H. (2001). Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UKhealth region. *Journal of Medical Genetics*, *38*(11), 792–798.

Wollmann, H. A., Schultz, U., Grauer, M. L., & Ranke, M. B. (1998). Reference values for height and weight in Prader-Willi syndrome based on 315 patients. *European Journal of Pediatrics*, *157*(8), 634–642.

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