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ORIGINAL ARTICLE

Short stature and growth hormone deficiency in a subset of patients with Potocki–Lupski syndrome: Expanding the phenotype of PTLS

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Abstract

Potocki–Lupski Syndrome (PTLS, MIM 610883), or duplication of chromosome 17p11.2, is a clinically recognizable condition characterized by infantile hypotonia, failure to thrive, developmental delay, intellectual disability, and congenital anomalies. Short stature, classified as greater than two standard deviations below the mean, has not previously been considered a major feature of PTLS. Retrospective chart review on a cohort of 37 individuals with PTLS was performed to investigate the etiology of short stature. Relevant data included anthropometric measurements, insulin growth factor-1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3), growth hormone (GH) stimulation testing, blood glucose levels, brain MRI, and bone age. Approximately 25% (9/37) of individuals with PTLS had short stature. Growth hormone deficiency (GHD) was definitively identified in two individuals. These two PTLS patients with growth hormone deficiency, as well as three others with short stature and no documented GHD, received growth hormone and obtained improvement in linear growth. One individual was identified to have pituitary abnormalities on MRI and had complications of hypoglycemia due to unrecognized GHD. Individuals with PTLS can benefit from undergoing evaluation for GHD should they present with short stature or hypoglycemia. Early identification of GHD could facilitate potential therapeutic benefit for individuals with PTLS, including linear growth, musculoskeletal, and in cases of hypoglycemia, potentially cognitive development as well.

KEYWORDS

growth hormone, hypoglycemia, Potocki–Lupski syndrome, short stature

1 | INTRODUCTION

Potocki–Lupski syndrome (PTLS, MIM 610883) is a clinically recognizable chromosomal microduplication condition characterized by infantile hypotonia, developmental delay, intellectual disability, and congenital anomalies (Potocki et al., 2007). The disorder is caused by heterozygous duplication at 17p11.2, which includes the *RAI1* gene. This duplication is the reciprocal recombination product of the 17p11.2 deletion, which causes Smith–Magenis syndrome (SMS) (Potocki, Chen, et al., 2000). While PTLS and SMS share the same genomic region, their clinical manifestations are distinct. In fact, some parallel traits may be on opposite ends of a given phenotypic spectrum representing mirror traits (Lupski, 2019; Neira-Fresneda & Potocki, 2015; Ricard et al., 2010). Historically, SMS has been viewed as a more severe syndrome with characteristic dysmorphic features, destructive and self-injurious behaviors, congenital malformations, and disrupted sleep associated with an aberration of the circadian rhythm of melatonin (Potocki, Glaze, et al., 2000). Since the initial

recognition of PTLS, the routine use of array comparative genomic hybridization (aCGH), or "chromosomal microarray analysis (CMA)" allows rapid detection of the microduplication associated with PTLS, accelerating further phenotypic delineation and recognition of unidentified clinical features (Martin & Ledbetter, 2017; Sansovic, Ivankov, Bobinec, Kero, & Barisic, 2017).

Since early studies delineating the cardinal clinical characteristics of PTLS (Potocki et al., 2007), and owing in great part the broad availability of aCGH, knowledge of the phenotypic spectrum of the microduplication has expanded considerably. There is now a better understanding of the variable physical features, congenital malformations, and neurocognitive profiles in PTLS patients. However, there is clinical variability amongst those with the recurrent duplication, and individuals with non-recurrent duplications are not distinguishable by phenotype, with the exception of those with a larger duplication that encompasses the *PMP22* gene and manifest neuropathy (Yuan et al., 2015; Zhang et al., 2010). An illustrative example of this variability relates to the cardiovascular phenotype. Whereas the majority (~60%) of persons with PTLS do not have a congenital cardiovascular malformation, the malformations observed in the remaining 40% can be as severe as hypoplastic left heart (HLHS) or relatively minor left ventricular outflow tract (LVOT) anomalies (such as bicuspid aortic valve) and/or atrial septal defects (Bravo, Gamez, Perez, Aguaron, & De Leon-Luis, 2013; Jefferies et al., 2012; Sanchez-Valle, Pierpont, & Potocki, 2011; Yusupov, Roberts, Lacro, Sandstrom, & Ligon, 2011).

Another example of the variability of clinical features in PTLS relates to linear growth. Most newborns with PTLS are appropriate for gestational age across all growth parameters. However, 71% of infants exhibit a pattern of gradual weight deceleration, with failure to thrive, oropharyngeal dysphagia, and gastroesophageal reflux (Soler-Alfonso et al., 2011). Deficient linear growth has been reported in a subset of older children and adults with PTLS (Potocki et al., 2007; Potocki, Chen, et al., 2000). Yet, unlike SMS where 50–75% of persons have short stature (Smith et al., 2019), short stature has not previously been appreciated as a common feature in PTLS. When present, short stature in individuals with PTLS persists despite interventions such as gastrostomy feedings to treat growth failure attributed to oropharyngeal dysphagia, gastroesophageal reflux, failure to thrive, and hypotonia. The etiology of short stature in SMS and PTLS has not been systematically investigated to date.

Non-syndromic growth hormone deficiency (GHD) is identified in children and adolescents without a chromosomal disorder or genetic condition following a period of decreased growth velocity, which may result in short stature, or a height standard deviation score (SDS) below the expected range around the sex-adjusted mid-parental height ("target height"). Short stature is defined as a height of two standard deviations (*SD*) below the mean ($Z < -2$). This short stature or sub-optimal growth velocity prompts further evaluation (Collett-Solberg, 2019). Certain chromosomal syndromes, such as Down syndrome or Turner syndrome, are associated with short stature that is not due to disturbances in growth hormone production, thus GHD is not frequently assessed in these patients. Concurrent manifestations of unrecognized GHD such as hypoglycemia may be a presenting symptom as growth hormone acts as a counter-regulatory hormone needed to maintain normal serum glucose levels (Antoniazzi, Cavarzere, & Gaudino, 2015). Hypoglycemia due to growth hormone deficiency occurs most commonly in patients with severe congenital growth hormone deficiency, and often in conjunction with a deficiency in adrenocorticotropic hormone (ACTH) leading to inadequate cortisol production (Laron, 1998). The identification of previously unrecognized hypoglycemia can be a distinct biomarker in the clinical evaluation for short stature related to GHD. Individuals with PTLS who have short stature have not previously been reported to have GHD or other pituitary abnormalities. Recurrent hypoglycemia is not a recognized phenotypic feature in the PTLS population.

Comprehensive, retrospective chart review of clinical records from 37 individuals with PTLS indicate that GHD may represent the severe end of the spectrum with regards to linear growth. We present a case series of nine individuals with PTLS and short stature who underwent evaluation for GHD. Our data suggest short stature may be more common in PTLS than previously ascertained, with GHD representing the most severe end of the spectrum.

2 | METHODS

Informed consent to retrospectively review, analyze, and publish clinical data was obtained on all PTLS subjects under protocol H-9171 approved by the Institutional Review Board at Baylor College of Medicine in Houston, Texas.

Comprehensive, retrospective chart review of clinical records from 37 subjects (20 males; 17 females; Age range 5 months – 38 years) with PTLS who were evaluated or whose external clinical records were reviewed at the Texas Children's Hospital from 2003–2018 was performed. Nine (9/37) subjects (age range: infancy –12 years 11 months; 5 males) had short stature and their clinical data were tabulated (Table 1). Detailed clinical information of these nine subjects (9/37) is provided in the case series below.

3 | RETROSPECTIVE CHART REVIEW

Clinical results were collected as follows: Insulin growth factor-1 (IGF-1) and insulin like growth factor binding protein 3 (IGFBP-3) measured to evaluate for the possibility of GHD. Bone age was done to evaluate the degree of skeletal maturation (Greulich & Pyle, 1959). GH stimulation tests were performed and GH replacement was initiated if clinically indicated with peak GH values recorded and growth velocity measured before and during treatment with GH. GHD was diagnosed if the peak GH level on stimulation testing was below 10 ng/ml (GH Research Society, 2000). Treatments were provided to patients prior to the updated recommendations in 2019 which propose that a new cut-off of below 7 ng/ml be used to diagnose GHD (Collett-Solberg, 2019). Individuals who were started on GH treatment were monitored every 6 months to determine if there was improvement in linear growth. Additional brain imaging was reviewed when available to assess for the presence of a brain abnormality that could contribute to GHD.

TABLE 1 Evaluation of short stature in individuals with PTLS

	Subject								
Phenotypic information	**1**	**2**	**3**	**4 [BAB 1913]**	**5 [BAB1671]**	**6 [BAB 504]**	**7**	**8 [BAB1006]**	**9**
Age at diagnosis	15 Mos	7 years	14 Mos	12 years	Infancy	6 years	3 years	14 years	3 years
Current age	7 years	11 years	7 years	29 years	20 years	37 years	7 years	37 years	4 years
Gender	F	F	M	F	F	M	M	F	M
Stature (*SD*) at diagnosis	-2.4	-4.47	-4.26	-4.4	-4.2	-6.44	-3.09	-2.23	–2.86
Deletion size in Mb	3.375	3.375	4.793	3.7	3.7	3.7	3.376	3.7	3.376
Minimum breakpoint interval (hg19)	16,842,295-20,217,777	16,842,347-20,217,777	15,754,173-20,547,669	‡	‡	‡	16,842,067-20,217,777	‡	16,842,163-20,217,777
Brain MRI findings	Normal	Small pituitary gland, ectopic posterior pituitary tissue, absent pituitary stalk	Not performed	Normal	Paucity of cerebral white matter, small corpus callosum, borderline cerebellar tonsillar ectopia	Not performed	Normal	Normal	Normal
Delayed bone age (defined by >2 *SD* below mean for age and sex)	Study unable to be read	+	–	+	–	+	+	+	+
Growth velocity prior to evaluation (defined as height velocity in cm/yr)	N/A	0.4	N/A	3.2	0	2	0.2	3.4	3.8
IGF-1[a] (ng/ml)	139 (32–179)	<16 (99–483)	79 (31–214)	66 (123–330)	216 (208–619)	103 (55–331)	100 (30–155)	59 (117–771)	30 (16–134)
IGFBP-3[b] (mg/L)	2.84 (2.17–4.79)	0.3 (1.4–6.1)	3.0 (1.1–5.2)	1.9 (2.0–4.8)	3.3 (3.4–9.5)	3.9 (3.4–7.0)	3.6 (0.9–4.3)	1.5 (1.5–4.3)	1.3 (0.7–3.6)
Peak GH value following GH stim test (ng/ml)	N/A	0.4	N/A	21	8.1	Records unavailable	14.3	9.4	N/A
Growth hormone treatment initiated	–	+	–	+	–	+	–	+	§
Growth response following treatment (defined as height velocity in cm/yr)	N/A	6.7	N/A	7.7	N/A	Records unavailable; final adult height: -1.47 SD	N/A	12	8.2

Note: ‡Breakpoint defined in Potocki et al. (2007). §Received GH for SGA with failure of catch up growth indication.

Abbreviations: N/A, not applicable; SD, standard deviation.

[a]Insulin-like growth factor 1.

[b]IGF Binding Protein 3.

4 | CASE SERIES

4.1 | Subject 1

Subject 1 was diagnosed with PTLS by clinical CMA at 15 months due to a history of failure to thrive, hypotonia, and developmental delay. CMA identified a de novo duplication spanning a minimum of 3.375 Mb and a maximum of 3.684 Mb on chromosome 17p11.2. At the time of diagnosis, subject 1 was at the eighth percentile for height (Z = −1.38) with a mid-parental height of 159.9 cm (29th percentile; Z = −0.5). However, at a follow up visit at 29 months, she was below the first percentile for height (Z = −2.4) and at 36 months continued to remain below the first percentile for height (Z = −2.62). Brain MRI was normal. Bone age was non- diagnostic due to movement during the examination. IGF-1 and IGFBP-3 were within normal limits. Further evaluation for GHD was not done.

4.2 | Subject 2

Subject 2 was diagnosed with PTLS by clinical CMA at 7 years 7 months due to a history of previously recognized growth hormone deficiency, failure to thrive, developmental delay, and a history of club foot. CMA identified a duplication spanning a minimum of 3.375 Mb and a maximum of 3.860 Mb on chromosome 17p11.2. Despite normal growth parameters at birth, she presented to pediatric endocrine clinic with poor weight gain and growth deceleration with length persisting below the third percentile through infancy and childhood (Z = −4.47 *SD*). Her mid-parental height was calculated to be 165.6 cm (63rd percentile, Z = 0.3). Hypoglycemia was first documented when she was found unresponsive at age 3 years and subsequently occurred intermittently through early childhood. Compliance to recommended medical therapy was suboptimal. Brain MRI showed a small pituitary gland, ectopic posterior pituitary tissue, and an absent pituitary stalk. Bone age at chronological age 7 years, 6 months was delayed at 5 years per the standards of Greulich and Pyle. Eventually, she was diagnosed with adrenal insufficiency at 7 years by a 1 mcg ACTH stimulation test that showed a peak cortisol of 11.4 ug/dl (normal ≥ 18 ug/dl). In addition, her growth hormone stimulation test showed a peak GH value of 0.4 ng/ml, consistent with GH deficiency. Her height velocity prior to beginning growth hormone was 0.4 cm/year with a height SDS of −5.31. She was treated with growth hormone therapy starting at 7 years 9 months with subsequent, subtle improvement of linear growth (Z = −4.97 at age 8 years 5 months) and resolution of hypoglycemia, with an estimated height velocity of 6.7 cm/year. Compliance issues impacted first year height velocity evaluations.

4.3 | Subject 3

Subject 3 was diagnosed with PTLS by clinical CMA at 14 months old due to a history of hypotonia and failure to thrive. CMA identified a de novo 4.8 Mb duplication on chromosome 17p11.2. At the time of diagnosis, subject 3 was below the first percentile for height (Z = −4.26). He had normal growth parameters at birth and his mid-parental height was 167.8 cm (10th percentile; Z = −1.3). A brain MRI was not performed. Bone age was concordant with chronological age at 5 years 4 months. IGF-1 and IGFBP-3 were within normal limits. Further evaluation for GHD was not done.

4.4 | Subject 4

Subject 4, previously published as BAB 1913 (Potocki et al., 2007; Potocki et al., 1999; Potocki, Chen, et al., 2000), was initially diagnosed with PTLS by G-banded chromosome and then later confirmed to have a de novo 3.7 Mb duplication at chromosome 17p11.2 by research array. On our exam at age 12 years, she had short stature (Z = −4.43), speech delay and dysmorphic features. Her mid-parental height was calculated to be 165.5 cm (62nd percentile; Z = 0.4). During infancy, she had a history of poor feeding, poor suck, and hypotonia that subsequently required G-tube feedings to correct failure to thrive. Bone age performed at chronological age of 11 years 6 months was delayed at 8 years 10 months by the Gruelich and Pyle standards. Low IGF-1 (66 ng/ml; ref range: 123–330) and IGFBP-3 (1.9 mg/L; ref range: 2–4.8) levels prompted a GH stimulation test which showed a peak growth hormone level of 21 ng/ml, which is considered normal by current criteria, however, her height velocity at that time was sub-optimal at 3.2 cm/year. Despite normal GH stimulation test, she received GH therapy under the diagnostic label of idiopathic short stature with improvement after treatment, achieving a first year height velocity of 7.65 cm/year.

4.5 | Subject 5

Subject 5, previously published as BAB 1671 (Potocki et al., 2007), was initially diagnosed with PTLS in infancy by G-banded chromosome analysis due to failure to thrive and dysmorphic features and later confirmed to have a de novo 3.7 Mb duplication by research array. She had always had a height that measured below the growth curve, however, at 14 years old, she was well below the first percentile for height (Z = −4.2). Her mid-parental height was calculated as 148.5 cm (first percentile; Z = −2.3). Brain MRI showed paucity of cerebral white matter, small corpus callosum, and borderline cerebellar tonsillar hypoplasia. Bone age was concordant with chronological age at 16 years 6 months when it was performed. IGF-1 and IGFBP-3 levels were borderline low normal so a GH stimulation test was pursued for further evaluation. The peak GH value was 8.1 ng/ml following stimulation test, however, GH was not initiated due to closure of the growth plates. She may have benefited from growth hormone therapy given her sub-optimal response to GH stimulation testing had this been recognized earlier.

4.6 | Subject 6

Subject 6, previously published at BAB 504 (Potocki et al., 2007), was diagnosed with PTLS by high resolution G-banded chromosome

analysis at 6 years old due to global developmental delays, hypotonia, feeding difficulties, and failure to thrive. A research array confirmed a de novo 3.7 Mb duplication on chromosome 17p11.2. At his initial evaluation at 6 years 6 months old, he was well below the first percentile for height (Z = −6.44). Records are not available to review for his mid-parental height. A brain MRI was not performed. Bone age was delayed (2 *SD* below the mean for age and sex). His height velocity prior to his evaluation was 2 cm/year. IGF-1 and IGFBP-3 were within normal limits, however, he received GH therapy under the diagnostic label of idiopathic short stature and achieved a final adult height of 166 cm (Z = −1.47).

4.7 | Subject 7

Subject 7 was diagnosed with PTLS by clinical CMA at 3 years old due to developmental delay and failure to thrive. CMA identified a duplication spanning a minimum of 3.375 Mb and a maximum of 3.860 Mb on chromosome 17p11.2. At his initial evaluation, he was below the first percentile for height (Z = −3.09). His mid-parental height was calculated as 168 cm (11th percentile; Z = −1.2). Brain MRI was normal. Bone age was delayed reading at 2 years 8 months old at chronological age 4 years 3 months old. His growth velocity prior to evaluation for GHD was 0.22 cm/year. IGF-1 and IGFBP-3 levels were within normal limits. GH stimulation test was performed with a peak GH value of 14.3 ng/ml, which is not consistent with classic GHD. Growth hormone was not initiated and he continues to remain well below the first percentile for height at 7 years (Z = −3.17).

4.8 | Subject 8

Subject 8, previously published as BAB 1006 (Potocki et al., 1999, 2007; Potocki, Chen, et al., 2000), initially presented to the genetics clinic at 12 years and 11 months old due to peripheral neuropathy, growth hormone deficiency, and mild intellectual disability (Potocki et al., 1999). Diagnosis of duplication 17p11.2 was established by cytogenetic methods (Potocki et al., 1999) and the common de novo 3.7 Mb duplication was identified by research array (Potocki et al., 2007). At initial evaluation, she was at the first percentile (Z = −2.23) for height. Her mid-parental height was calculated to be 164.5 cm (57th percentile; Z = 0.2). Short stature had previously been appreciated beginning at 10–11 years old after growth velocity slowed down and height plotted below the fifth percentile on the growth chart. Her evaluation at 11 years old was consistent with growth hormone deficiency and growth hormone was initiated. She had a peak GH value of 9.4 ng/ml on GH stimulation testing and an IGF-1 level of 59 ng/ml (ref range: 117–771) and IGFBP-3 level 1.5 mg/L (ref range: 1.5–4.3). Bone age was 1 *SD* below the mean for age, however, this was performed after she had already been receiving growth hormone treatment so may not be representative of her initial bone age delay. Her treatment with growth hormone therapy demonstrated improvement in linear growth, with an ultimate adult height of 161.8 cm (Z = −0.22).

4.9 | Subject 9

Subject 9 was diagnosed with PTLS by clinical CMA at 2 years 9 months due to failure to thrive, developmental delay, dysmorphic features, and linear growth deficiency (−2.86 *SD*). CMA identified a duplication spanning a minimum of 3.376 Mb and a maximum of 4.151 Mb of chromosome 17p11.2. His mid-parental height was 174.1 cm (35th percentile; = − 0.4). IGF-1 and IGFBP-3 levels were at the lower limits of normal. Bone age was concordant with the chronological age. Subject 9 met criteria for growth hormone therapy based on a history of being small for gestational age (SGA) and failure of catch up growth. A growth hormone stimulation test was not performed due to normal IGF-1 and IGFBP-3 level. He showed improvement in linear growth from a height velocity of 3.8 cm/year to 8.2 cm/year after GH replacement, however, due to insurance barriers is currently off of GH. He received growth hormone for 9 months.

5 | RESULTS

In our cohort, short stature is a feature in 9 of 37 (25%) of individuals with PTLS (Table 1). Five of these (Subjects 2, 4, 6, 8, 9) were treated with growth hormone with improvement of linear growth. All of the untreated subjects have remained below −2 *SD* in stature. Only two of the five individuals treated (Subjects 2 and 8) have documented evidence for meeting diagnostic criteria for classic GHD, and one of these (Subject 2) had structural pituitary anomalies and hypoglycemia. Results of a GH stimulation assay performed in childhood for Subject 6 (age 37 years) are not available, yet could have also met diagnostic criteria. Likewise, although Subject 5 was not treated with GH due to closure of growth plates, and not tallied in this report as GHD, the GH peak following stimulation was only 8.1 ng/ml, thus below the 10 ng/ml level stipulated by the GH Research Society, 2000. Despite a normal GH stimulation test, Subject 4 (who had delayed bone age and abnormal growth factor studies) was treated with GH and demonstrated marked increase in height velocity. Subject 9 had normal bone age and growth factor studies and did not undergo GH stimulation testing. However, Subject 9 was treated with GH based on history of SGA and lack of catch up growth.

6 | DISCUSSION

In the general population, growth deficiency occurs in 2.5% of children making it a relatively common reason for referral to the medical genetics clinic (Graber & Rapaport, 2012; Teran, Chesner, & Rapaport, 2016). In daily clinical practice, the question of growth deficiency predictably arises in children with common chromosomal disorders such as Turner syndrome and Down syndrome (Lindsay, Feldkamp, Harris, Robertson, & Rallison, 1994). The diagnosis of growth deficiency due to growth hormone deficiency (GHD) in children with other chromosomal disorders, is challenging, partly due to the lack of a true gold standard, and the relatively poor correlation of

growth and the genes residing in the critical chromosomal locus. In the last decade, the expanded use of CMA has enhanced rapid identification of rare copy number variants (CNV) increasing the number of recognized patients with syndromic chromosomal disorders. With the increased use of CMA, clinicians are able to follow larger cohorts of identified patients with rare chromosomal CNVs to further delineate detailed phenotypic information and expand the recognizable features (Berg, Potocki, & Bacino, 2010; Mannik et al., 2015). Such is the case of Potocki-Lupski Syndrome (PTLS), a multisystem disorder that results from an interstitial duplication of chromosome 17 at band p11.2 [dup(17) (p11.2p11.2)] (Potocki, Chen, et al., 2000).

Fewer than 100 individuals with PTLS have been reported in the medical literature (Pratico et al., 2018). Common clinical manifestations of PTLS are growth deficiency, infantile hypotonia, congenital heart disease, sleep disordered breathing, developmental delay, intellectual disability, and autism (Potocki et al., 2007; Sanchez-Valle et al., 2011; Treadwell-Deering, Powell, & Potocki, 2010). The underlying mechanism responsible for growth deficiency in PTLS has not been fully elucidated. Initial assessment of growth failure in children with PTLS suggest poor feeding, failure to thrive, and gastroesophageal reflux as the most likely contributors of growth deficiency. However, as the current data shows, there are individuals with growth deficiency that cannot be explained by these features and require further investigation to elucidate a potentially treatable etiology. Based on the data presented here, at least 25% (9/37) of individuals with PTLS have short stature despite adequate nutrition and in at least two of these individuals (subject 2 and subject 8), the short stature was confirmed to be due to GHD. And while Subjects 5 and 6 cannot be strictly proven to have GHD by current standards, we believe that the clinical data is sufficiently compelling to warrant suspicion of an underlying disturbance in the hypothalamic–pituitary axis in these individuals as well. We have identified that GH therapy has improved linear growth in all 5 individuals who were treated, despite three of them not meeting strict criteria for GH deficiency. This aligns with the hypothesis that GH therapy can provide improvement of linear growth in a similar manner as other genetic conditions, such as Noonan syndrome, Turner syndrome (due to *SHOX* deficiency) and Prader-Willi syndrome (Aycan, Z. &Baş, V.N., 2014; Pasquino, AM, et al., 1996; Seo,GH & Yoo, HW., 2018). We observed poor growth in those individuals who did not receive growth hormone therapy. Our study indicates that short stature is a relatively common feature of PTLS and that GHD represents the severe end of the spectrum with regards to poor linear growth in these patients and that consideration should be given to providing GH therapy to individuals with PTLS who do not meet criteria for classic GH deficiency. We also recommend that proper consideration is given to the appropriate risks and benefits to GH therapy for each case.

We identified 1 individual with documented GHD that had a history of hypoglycemia with pituitary insufficiency that had either gone unrecognized or was the main clinical manifestation prior to their diagnosis of PTLS. This individual represents the most severe end of the growth spectrum with pituitary insufficiency and hypoglycemia as the main presenting features suggestive of GHD. GHD and hypoglycemia—in a child with or without other features of PTLS—should prompt clinical testing with CMA. Further studies need to be completed to understand the relationship between unrecognized hypoglycemic episodes and the impact on cognitive skills in those with PTLS and GHD, which is beyond the scope of the present study.

Overall, GHD is a newly recognized clinical feature of PTLS and can present with or without hypoglycemia and other pituitary hormone insufficiency. As short stature emerges as a more defined feature of PTLS, we recommend that clinicians consider endocrinology evaluation to evaluate for the presence of GHD in those individuals with PTLS that have short stature and growth deficiency that is not otherwise attributable to poor feeding, gastroesophageal reflux and/or hypotonia. Based on the data presented here, we also consider that GH therapy is an effective treatment for individuals with short stature and PTLS, and should be considered even if the strict criteria for classical GH deficiency are not met. Finally, we recognize that this is a small cohort of individuals with PTLS and further systematic investigation to evaluate the efficacy of GH therapy in PTLS is needed.

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CONFLICT OF INTERESTS

R. F.: The Department of Molecular and Human Genetics at Baylor College of Medicine derives revenue from molecular genetic testing offered in the Baylor Genetics Laboratories. C. S.-A.: The Department of Molecular and Human Genetics at Baylor College of Medicine derives salary support from molecular genetic testing offered in the Baylor Genetics Laboratories. J. N.-F.: No conflicts of interest. B. M.-C.: No conflicts of interest. J. R. L.: Baylor College of Medicine (BCM) and Miraca Holdings have formed a joint venture with shared ownership and governance of the Baylor Genetics (BG), which performs clinical microarray analysis and clinical exome sequencing. J. R. L. serves on the Scientific Advisory Board of the BG. J. R. L. has stock ownership in 23andMe, is a paid consultant for Regeneron pharmaceuticals, and is a co-inventor on multiple United States and European patents related to molecular diagnostics for inherited neuropathies, eye diseases, and bacterial genomic fingerprinting. The Department of Molecular and Human Genetics at Baylor College of Medicine derives revenue from molecular genetic testing offered in the Baylor Genetics Laboratories. L. P.: The Department of

Molecular and Human Genetics at Baylor College of Medicine derives revenue from molecular genetic testing offered in the Baylor Genetics Laboratories.

AUTHOR CONTRIBUTIONS

Lorraine Potocki and James R. Lupski contributed to protocol design, data collection, data interpretation, redaction and revision of the manuscript. Rachel Franciskovich, Claudia Soler-Alfonso, Juanita Neira-Fresneda, and Bonnie McCann-Crosby contributed to data collection, data interpretation, redaction, and revision of the manuscript. All authors have seen and approved the final version.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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