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Cognitive and Behavioral Phenotype of Children with Pseudohypoparathyroidism Type 1A

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Abstract

Context—Pseudohypoparathyroidism 1A (PHP1A) is a rare, genetic disorder. Most patients with PHP1A have cognitive impairment but this has not been systematically studied.

Objective—To evaluate cognition and behavior in children with PHP1A.

Design—We prospectively enrolled children with PHP1A, one unaffected sibling (when available) and controls matched on BMI/age/gender/race. Evaluations included cognitive and executive function testing. Parents completed questionnaires on behavior and executive function.

Main Outcome Measure—We hypothesized that children with PHP1A would have lower intelligent quotient (IQ) scores than controls.

Results—We enrolled 16 patients with PHP1A, 8 unaffected siblings and 15 controls. Results are presented as mean (SD). The PHP1A group had a composite IQ of 85.9 (17.2); 25% had a composite IQ <-2SD. The PHP1A group had significantly lower IQs than matched controls (composite IQ -17.3, 95%CI -28.1 to -6.5, $p< 0.01$) and unaffected siblings (composite IQ -21.5, 95%CI -33.9 to -9.1, $p< 0.01$). Special education services were utilized for 93% of the patients with PHP1A. Deficits were observed in executive function and parents reported delayed adaptive behavior skills and increased rates of attention deficit hyperactivity disorder.

Conclusions—Children with PHP1A have lower intelligence quotient scores, poorer executive function, delayed adaptive behavior skills and increased behavior problems. The majority required special education services.

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Keywords

Pseudohypoparathyroidism; Albright Hereditary Osteodystrophy; cognition

Introduction

Pseudohypoparathyroidism (PHP) is a rare, genetic disorder caused by heterozygous inactivating mutations involving *GNAS* exons that encode the alpha-subunit of the stimulatory G-protein (Gαs), which mediates the actions of numerous G protein-coupled receptors. The Albright Hereditary Osteodystrophy (AHO) phenotype, which is associated with several forms of PHP, consists of short adult stature, brachydactyly and subcutaneous ossifications. AHO caused by maternally inherited, inactivating mutations involving *GNAS* also results in multi-hormone resistance, early-onset obesity and cognitive impairment. This disorder is termed PHP type 1a (PHP1A). Conversely, AHO caused by paternally inherited, inactivating mutations affecting the same GNAS exons does not cause hormone resistance, obesity or cognitive impairment, and is therefore termed pseudopseudohypoparathyroidism (PPHP). More recently, imprinting defects at the *GNAS* locus (PHP type 1b; PHP1B) were found to account for ~25% of patients with AHO and multi-hormonal resistance [Elli et al., 2016].

Cognitive impairment was recognized in the original description of PHP by Fuller Albright in 1942 [Albright, Smith & Parson, 1942], but further studies characterizing these clinical features have been limited. In a study of a single kindred, family members affected by PHP1A had a significantly lower full scale intelligence quotient (IQ) than family members affected by PPHP (87.5 vs. 117.2, $p<0.01$) [Mouallem et al., 2008]. A literature review showed cognitive impairment reported as a diagnosis in 78% of patients with PHP1A and 10% of patients with PPHP, but there is no information available on severity or specific areas of deficit [Mouallem et al., 2008].

This lack of knowledge impedes adequate care of patients with PHP as physicians are unable to counsel families on developmental expectations or provide appropriate early intervention and educational resources in a timely manner. To address this problem, we undertook the first systematic evaluation of cognitive function, executive function and adaptive behavior in children with PHP1A.

Materials and Methods

Study Design and Setting

This was a prospective study of children with PHP1A. As controls, we enrolled unaffected siblings and unrelated individuals matched on race, gender, age and BMI. Patients with PHP and their siblings were recruited from the Vanderbilt Pediatric Endocrinology Clinics and throughout the United States and Canada using online advertisements. Matched controls were recruited from Vanderbilt Pediatric and Pediatric Subspecialty Clinics. All study visits were conducted at the Vanderbilt Clinical Research Center (Nashville, TN). The study was

approved by the Vanderbilt Institutional Review Board and parental consent/age appropriate assent was obtained prior to study enrollment.

Participants

Patients were recruited from the Monroe Carell Jr. Children's Hospital at Vanderbilt and through online advertisements. We enrolled patients 6 to 18 years old into one of the following four groups: 1) children with a clinical diagnosis of PHP with multi-hormone resistance, 2) one unaffected sibling (when available) and 3) matched controls. Controls were matched on gender, race, age (±2 years) and BMI (±2 kg/m^2 at last clinic visit). A diagnosis of PHP1A was confirmed based on clinical phenotype and genetic testing. Exclusion criteria for the sibling and matched control groups included obesity due to a genetic syndrome or untreated endocrinopathy, parent-reported diagnosis of autism or significant learning disorder and other significant medical conditions.

Cognitive Assessment

Cognitive assessments were performed by trained study personnel and supervised by a developmental psychologist.

General Cognitive Ability—The Kaufman Brief Intelligence Test, Second Edition (KBIT-2) [Kaufman, 2004], assessed general cognitive ability. There were 2 domains, verbal and nonverbal, as well as a composite IQ. All scales yield standard scores with a mean of 100 (SD= 15); higher scores indicate better function. We also collected data on repeated grades, school settings, use of special education resources and treatment with speech, occupational and physical therapies.

Adaptive Behavior—Parents completed the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) [Sparrow & Balla, 2005], resulting in an adaptive behavior composite and 3 domain scores, each with a mean of 100 (SD=15); higher scores indicate better function.

Behavior Problems—Parents completed the Child Behavior Checklist for ages 6 to 18 years (CBCL) [Achenbach, 2009]. The raw scores were converted to DSM-IV oriented scales for the following domains; affective, anxiety, somatic, attention deficit/hyperactivity (ADHD), oppositional defiant and conduct. The scales yield T scores with a mean of 50 (SD=10); higher scores indicate greater problems.

Executive Function—Executive function was assessed in children >8 years old using the following performance based measures from the Delis-Kaplan Executive Function System (DKEFS) [Homack, Lee & Riccio, 2005]: trail-making test (flexibility of thinking on a visual-motor task), verbal fluency test (fluent productivity in the verbal domain), color-word interference test (inhibitory control) and design fluency test (fluent productivity in the spatial domain). Raw scores were converted to scaled scores with a mean of 10 (SD=3); lower scores indicate poorer performance.

We also used a parent-reported questionnaire, the Behavior Rating Inventory of Executive Function (BRIEF) [Gioia, Isquith, Guy & Kenworthy, 2000]. Parents were asked whether the

child “had problems with these behaviors over the last 6 months” and were given response options of “never” (1), “sometimes” (2), or “often” (3). There were two composite scores, the behavioral regulation index (BRI) and metacognition index (MI). The general executive composite (GEC) is calculated based on these composite scores; if the BRI and MI differed by ≥13, GEC was not reported. The BRI, MI and GEC produce T scores with a mean of 50 (SD=10); higher scores indicate greater problems.

Covariates

Data were obtained on potential confounding variables. We collected parent reported race and ethnicity, education level and family yearly income. Height was measured using a wall-mounted stadiometer. Weight was measured using a digital scale while participants were lightly clothed without shoes. BMI z-scores were calculated using gender and age specific Centers for Disease Control growth charts.

Genetic testing

DNA samples were collected from participants with PHP if they did not have a known genetic diagnosis. *GNAS* exons 2-13 (NM001077488.3) were sequenced by GENEWIZ (South Plainfield, NJ). If a pathogenic mutation was not detected, we next evaluated the DNA samples for the 3-kb *STX16* deletion that frequently causes AD-PHP1B, for other deletions within *STX16* or *GNAS*, and for *GNAS* methylation changes (Bastepe et al., 2003). For analysis of *GNAS* exon 1, primer sequences (forward: 5′-CGCGCTCCTTGCCGAGGAG-3′ and reverse: 5′-CTGCGGGGCGCCCTTCGAG-3′) and PCR amplification conditions (94C 5 min; 94C 45 seconds; 65C 45 seconds, 72C 45 seconds, times 40, final extension 10 min. at 72C; in 10% DMSO) were kindly provided Dr. Guiomar Perez de Nanclares, Vitoria-Gasteiz, Spain. Nucleotide sequence analysis was performed at the MGH Sequencing Core Facility and the mutation identified in patient 33 (exon 1, c.C91T) was confirmed by incubating the PCR product with endonuclease *Pst*I with subsequent separation of digested amplicons by agarose gel electrophoresis.

Statistical Methods

Continuous variables were analyzed with the Student's t-test. If Levene's test for equality of variances was significant, equal variances were not assumed. For categorical variables, Chi-squared test was used unless multiple cells have an expected cell count <5 and then an exact unconditional test was used. When the PHP1A and sibling groups were compared, a paired t-test was used. Data are presented as mean (SD) unless otherwise specified.

Results

Patient Characteristics

A total of 19 patients with PHP and multi-hormonal resistance from 16 unrelated families were enrolled in the study, along with 9 unaffected siblings and 15 controls. A family with 4 siblings (3 affected, 1 unaffected) was found to have the 3-kb *STX16* deletion that is known to cause PHP1B and were excluded from this study. This left 16 patients with PHP1A and 8 unaffected siblings.

All patients were white. The baseline characteristics of the three groups are provided in table 1. There were no significant differences between the PHP1A and matched control group's demographic or socioeconomic characteristics. Three children in the PHP1A group were taking medication for ADHD (lisdexamfetamine dimesylate, atomoxetine and methylphenidate transdermal). No patients in the control groups were treated for ADHD.

Genetic Testing—All patients in the PHP group had resistance to parathyroid hormone and thyroid stimulating hormone. All patients had thyrotropin levels <5 μunits/mL (range 0.949 - 4.572) at the time of testing. Table 2 details the genetic diagnosis, family history and clinical features of each patient. Nine patients had previous clinical genetic testing through a CLIA-approved laboratory and tested positive for heterozygous inactivating mutations in *GNAS*; two of these mutations are novel. We identified a heterozygous inactivating *GNAS* mutation in 5 additional patients. The 14 patients with an identified *GNAS* inactivating mutation and 2 patients with subcutaneous ossifications but without a genetic diagnosis (one did not provide a DNA sample) are included in the PHP1A subgroup.

General Cognitive Ability—The PHP1A group (n=16) had an average composite IQ of 85.9 (17.2), range 60 –116 and 25% had a composite IQ <70 (2SD below the mean) which was significantly lower than the matched control group (mean differences: composite IQ -17.3, 95%CI -28.1 to -6.5, p< 0.01; verbal IQ -15.6, 95% CI -23.5 to -7.8, p< 0.001; nonverbal IQ -14.4, 95%CI -27.3 to -1.6, p= 0.03). The PHP1A group also had significantly lower IQs than their unaffected sibling (Figure 1, n=8, composite IQ -21.5, 95%CI -33.9 to -9.1, p< 0.01; verbal IQ -17.9, 95%CI -26.7 to -9.1, p< 0.01; nonverbal IQ -19.1, 95%CI -35.3 to -2.9, p= 0.03). In the PHP1A group, there was not a significant association between IQ and parent education or family income.

In the PHP1A group, 2 children were homeschooled; both had a composite IQ of 62. Of the remaining 14 children, 8 (57%) had a history of placement in a self-contained, special education classroom and 7 (43%) had repeated a grade. Only 1 child (7%) had not received special education services. The most common special education services were a one-on-one classroom aide and special testing accommodations. Many children also received occupational therapy (43%), physical therapy (57%) and speech therapy (36%). In contrast, no children in the sibling and matched control groups were receiving any type of special education services. One child in the matched control group (7%) had repeated a grade. There was not a significant difference in composite IQ between the children with PHP1A who had been placed in a special education classroom and those in a mainstream classroom (IQ 83.3, 95%CI 70.5 to 96.0, range 60-99 vs. IQ 94.8, 95% CI 86.0 to 103.6, range 81 to 116, p=0.10).

Adaptive Behavior—Two mothers, one in the matched control group and one in the PHP1A/sibling group, did not complete the VABS-II and one in the PHP1A/sibling group did not complete the CBCL. The PHP1A group had significantly lower adaptive behavior composite scores compared with the matched control group (Table 3) and compared with their unaffected sibling (mean difference -27.0, 95%CI -36.5 to -17.5, p<0.001, n=7). The PHP1A group had uniformly lower scores in the communication, daily living skills and socialization domains.

Behavior Problems—The PHP1A group had significantly more affective problems and ADHD problems on the CBCL compared with the matched control group (Table 3) and compared with their sibling (mean difference: affective 13.1, 95%CI 2.5 to 23.8, p= 0.02 ; ADHD 8.0, 95%CI 1.5 to 14.5, p= 0.02, n=7). The PHP1A group also had more anxiety problems and somatic problems compared with their sibling (somatic: 14.0, 95%CI 18.8 to 9.2, p<0.001; affective 13.9, 95%CI 4.8 to 23.0, p<0.01). There were no differences in oppositional defiant or conduct problems.

Executive Function—The PHP1A group had significantly poorer performance than matched controls in 2 or more scores in all DKEFS subsets (trail making, verbal fluency, design fluency and color-word interference, Table 3). The PHP1A group had poorer performance than their siblings in all DKEFs subsets (supplementary figure 1) with significantly lower scores in the trail making test (mean difference: number-letter sequencing -6.7, 95%CI -12.4 to -1.0, p= 0.03; number-letter switching -5.0, 95%CI -9.9 to -0.1, p= 0.05), the verbal fluency test (mean difference: letter fluency -2.7, 95%CI -5.3 to -0.04, p=0.05; category fluency -5.3, 95%CI -9.9 to -0.8, p= 0.03) and the design fluency test (mean difference: design fluency -4.3, 95%CI -8.1 to -0.6, p=0.03).

Two mothers, one in the matched control group and one in the PHP1A/sibling group, did not complete the BRIEF questionnaire. GEC scores were not included in the analysis if the MI and BRI scores differed by 13 or more points (7 PHP1A subjects, 2 siblings and no controls). The PHP1A group had significantly higher MI scores but there was no difference in BRI or GEC scores compared with matched controls (Table 3). Compared with their sibling, patients with PHP1A had significantly higher scores in BRI and GEC (mean difference: BRI 19.9, 95%CI 8.4 to 31.3, p<0.01, n=7 pairs; MI 12.1, 95%CI -3.8 to 28.1, p=0.11, n= 7 pairs; GEC 18.3, 95%CI 8.3 to 28.2, p= 0.01, n=4 pairs). The PHP1A group had the highest mean scores in the areas of working memory (67.1 (13.1), 6 of 15 (40%) patients scored >70) and initiate (68.9 (11.6), 6 of 15 (40%) patients scored >70).

Discussion

This is the first study to systematically evaluate cognition, adaptive behavior, behavior problems and executive function in children with PHP1A. We found that children with PHP1A have a wide range of composite IQ scores but show a consistent deficit of more than one standard deviation (-21.5, 95%CI -33.9 to -9.1) compared with their unaffected sibling. This deficit was present in both the verbal and nonverbal IQ scores. Overall, children with PHP have higher mean IQ scores than patients affected by other imprinting disorders, such as Prader-Willi syndrome (IQ 63.5 (11.7), range 30-103) [Whittington, 2004].

While 25% of the PHP1A group had an IQ >2SD below the mean (composite IQ <70), 93% received special education services. The mother of the child who did not receive additional services reported that her child “didn't do well in school” and her teachers “asked for an evaluation but it wasn't done.” Our cohort included a wide range of family income and parental education, increasing the generalizability of the findings. In addition, many children repeated a grade (43%), highlighting the need for earlier learning evaluations and interventions.

Most children with PHP1A demonstrated impairments in executive function based on data from both child performance (DKEFS) and parental report (BRIEF). Children with PHP1A had a particular deficit in the area of metacognition. The BRIEF MI represents the ability to self-manage tasks and monitor performance. It includes the subdomains initiate, plan, organize, monitor and working memory, that provide insight into problem solving ability. In our cohort, children with PHP1A had the greatest parent-reported executive function deficits in the subdomains working memory and initiate. Consistent with these findings, children with PHP1A also had difficulty with DKEFS performance-based tasks measuring working memory (trail making test) and the ability to initiate and sustain effort (design fluency and verbal fluency tests). These findings suggest that children with PHP1A may exhibit deficits in executive function ability, which was captured by performance-based measures. Difficulty in the successful application of executive function skills towards goal attainment was exemplified by rating scale measures [Toplak, West & Stanovich, 2013]. These children may benefit from interventions addressing task organization, problem-solving skills and efforts to increase sustained attention. Special education resources such as one-on-one aides may assist these children with keeping track of multi-step directions, refocusing when they lose track of the class discussion, and sticking with a task until completion.

Unlike ADHD-combined type or hyperactive type, children with ADHD-inattentive type have a deficit in working memory, rather than decreased inhibition [Diamond, 2005]. In our study, 40% of the PHP1A group had working memory scores >70 on the BRIEF, an indicator of ADHD – inattentive type [Gioia et al., 2000]. The same subjects all had clinically significant scores (>65) on the CBCL ADHD domain, despite ongoing treatment for ADHD in two subjects. In the general population, prevalence of ADHD is approximately 5-7% [Willcutt, 2012]. The inattentive subtype is most common subtype but these patients are less likely to be referred for clinical services [Willcutt, 2012].

In addition to the elevated scores in the CBCL ADHD domain, children with PHP1A had clinically significant elevations in the affective domains. The elevation in somatic problems and anxiety problems was not significant when compared with matched controls and further studies are needed to understand the effects of PHP1A on quality of life. Consistent with the lower IQ scores, children with PHP1A scored significantly lower on all adaptive behavior subdomains (VABS-II) compared with controls and siblings. The deficits did not indicate severe impairments as most patients scored in the moderately low to adequate range.

Strengths of this study include a relatively large sample size for this rare disease and the use of both performance testing and validated parent questionnaires. Our inclusion of a sibling comparison group allowed for us to control for both genetic and environmental factors that may influence cognition and behavior. Our PHP cohort was composed of patients with PHP1A and we cannot generalize to PHP1B or PPHP. The one kindred with PHP1B due to the 3-kb *STX16* deletion had similar results to this PHP1A group (unpublished data) but further studies are needed. Longitudinal data are needed to better understand the natural history of development and cognition in PHP.

In summary, children with PHP1A have significant deficits in cognition, adaptive behavior and executive function, as well as behavior problems. Children with PHP1A may also be at

higher risk of ADHD-inattentive type and behavioral and pharmacotherapy should be considered when appropriate. It is clear that children with PHP1A typically require additional education services and we recommend that all children with PHP1A receive evaluation by early intervention specialists.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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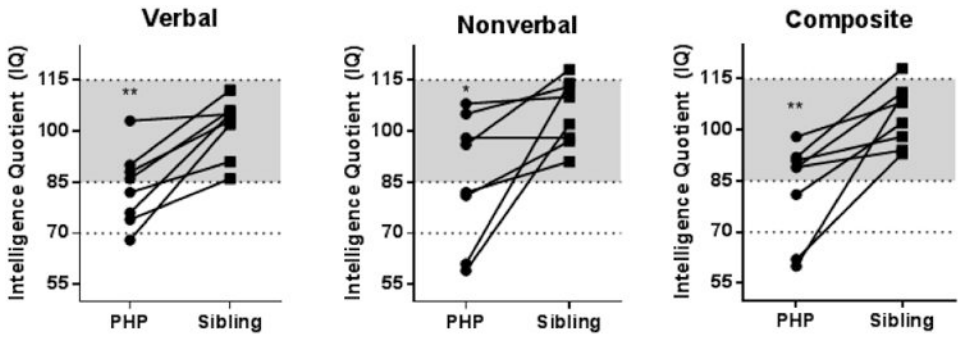

Figure 1.

Intelligence quotient scores from children with PHP1A vs. an unaffected sibling, measured by the Kaufman Brief Intelligence Test, 2nd edition. Shaded area represents the normal range; dotted line at 70 represents 2SD below the mean. * $p<0.05$, ** $p<0.01$

Table 1

Demographics and Baseline Characteristics, presented as % (n) unless otherwise specified. P-value compares PHP1A and matched control groups (continuous variables – Student's t-test, education – Chi-squared test, ethnicity – exact unconditional test).

	PHP1A (n=16)	Unaffected Siblings (n=8)	Matched controls (n=15)	P value
Age in years, mean (SD)	12.6 (2.6)	14 (3.2)	12.5 (2.3)	0.97
Female gender (%)	58 (11)	63 (5)	67 (10)	0.60
BMI z-score, mean (SD)	2.27 (0.47)	1.07 (0.76)	2.22 (0.35)	0.76
Hispanic ethnicity	6 (1)	0	13 (2)	0.47
Mother's education				
1. <High School	6 (1)	12.5 (1)	7 (1)	0.62
2. High School or Some College	44 (7)	50 (4)	47 (7)	
3. ≥ College degree	50 (8)	37.5 (3)	53 (8)	
Father's education				
1. <High School	13 (2)	12.5 (1)	27 (4)	0.44
2. High School or Some College	50 (8)	50 (4)	53 (8)	
3. ≥ College degree	38 (6)	37.5 (3)	20 (3)	
Family income				
<$50,000	38 (6)	25 (2)	53 (8)	0.38
$50,000-100,000	38 (6)	37.5 (3)	13 (2)	
>$100,000	25 (4)	37.5 (3)	33 (5)	

Table 2

Genotype and phenotype of participants with pseudohypoparathyroidism (*GNAS* NM 001077488.3)

ID	Diagnosis	Mutation	Clinical Features[a]	Age	Gender	Family members affected?	Unaffected sibling for analysis?
1	PHP1A	No mutation in *GNAS* exons 1-13, no *GNAS* methylation changes; no deletion detected in *STX16/GNAS*	so, ob[b], br, ss, PTH, TSH	16	Female	Mother unaffected	Yes
2	PHP1A	p.W234X	ob, br, PTH, TSH, GH	10	Male	Mother (PPHP)	Yes
3	PHP1A	c.C1024T/p.R342X [Lemos & Thakker, 2015]	so, ob, br, PTH, TSH	13	Female	Mother (PPHP) and 1 of 1 sibling (PHP1A)	No
4	PHP1A	c.565_568delGACT/p.DY190fs [Lemos & Thakker, 2015]	so, ob, br, ss, PTH, TSH	18	Female	Unknown	Yes
5	PHP1A	c.1100_1101insA [Lubell, Garzon, Anyane-Yeboa & Shah, 2009]	so, br, ob[b], PTH, TSH, GH	10	Male	Mother (PPHP) and 2 of 2 siblings (PHP1A)	No
6	PHP1A	c.TTC1166del/p.LR389del [Thiele et al., 2011]	ob, br, ss, PTH, TSH, GH	9	Male	Unknown	No
7	PHP1A	c.CTGA187del [Lemos & Thakker, 2015]	so, ob[b], br, PTH, TSH	14	Female	Unknown	Yes
8[c]	PHP1A	c.C728T/p.A243V	ob, br, PTH, TSH	14	Female	Mother (PPHP) and 1 of 1 sibling (PHP1A)	No
9[c]	PHP1A	c.C728T/p.A243V	ob, br, PTH, TSH	12	Male	Mother (PPHP) and 1 of 1 sibling (PHP1A)	No
10	PHP1A	c.GACT568del/p.DY190fs [Lemos & Thakker, 2015]	so, ob, br, PTH, TSH, GH	11	Female	No	Yes
11	PHP1A	c.G125A/p.R42H [Lemos & Thakker, 2015]	ob, br, PTH, TSH	8	Female	Mother (PPHP) and 1 of 1 sibling (PHP1A)	No
12	PHP1A	Intron 5 c.846+1G>T [Wilson, Oude Luttikhuis, Clayton, Fraser & Trembath, 1994]	so, ob, br, PTH, TSH	14	Male	Unknown	No
13	PHP1A	DNA sample unavailable	so, ob, br, PTH, TSH	14	Female	Mother unaffected	Yes
14	PHP1A	c.C91T/p.Q31X [Lemos & Thakker, 2015]	ob, br, PTH, TSH, GH	12	Female	Mother unaffected	No
15	PHP1A	Intron 4 IVS4+5G>C [Lietman, Goldfarb, Desai & Levine, 2008]	ob[b], PTH, TSH, GH	12	Male	Unknown	Yes
16	PHP1A	c.TG1107del [Lemos & Thakker, 2015]	so, ob, br, ss, PTH, TSH	14	Female	Mother unaffected	Yes

[a] so - subcutaneous ossifications, ob – obesity, br – brachydactyly, ss – short stature, PTH – parathyroid hormone resistance, TSH – hypothyroidism, GH – growth hormone deficiency.

[b] Currently overweight with a history of early childhood obesity.

[c] Siblings

Table 3

Adaptive functioning and executive functioning, presented as mean (SD).

	PHP1A	Matched controls	Mean Difference (95% CI)	P value
Vineland-II Adaptive Behavior Scales, second edition				
Adaptive behavior composite	81.9 (9.9) n=15	112.7 (10.1) n=14	-30.8 (-38.4 to -23.2)	<0.001
Child Behavior Checklist for Ages 6 to 18, DSM-IV oriented scales				
	n=15	n=15		
Affective	64.8 (9.1)	57.5 (7.3)	7.3 (1.1 to 13.5)	0.02
Anxiety	62.1 (9.5)	56.2 (6.7)	5.9 (-0.3 to 12.1)	0.06
Somatic	62.5 (8.4)	61.3 (6.8)	1.2 (-4.5 to 6.9)	0.67
Attention deficit/hyperactive	62.1 (8.2)	52.0 (3.0)	10.1 (5.4 to 14.9)	<0.001
Oppositional Defiant	58.1 (9.7)	54.9 (7.7)	3.2 (-3.3 to 9.7)	0.33
Conduct	56.2 (7.9);	52.3 (5.5)	3.9 (-1.3 to 9.0)	0.13
Delis Kaplan Executive Function System				
Trail making test	n=13	n=13		
Visual scanning	7.6 (3.1)	9.1 (2.9)	-1.5 (-3.9 to 1.0)	0.23
Number-letter sequencing	6.5 (3.6)	10.6 (2.7)	-4.2 (-6.7 to -1.6)	<0.01
Number-letter switching	3.9 (2.9)	8.5 (2.2)	-4.6 (-6.7 to -2.5)	<0.01
Motor speed	6.6 (3.9)	9.7 (2.3) n = 12	-3.1 (-5.7 to - 0.4)	0.03
Verbal fluency test	n=14	n=13		
Letter fluency	5.5 (1.9)	7.5 (2.8)	-2.0 (-3.9 to -0.2)	0.03
Category fluency	5.4 (2.3)	9.3 (2.9)	-3.9 (-5.9 to -1.8)	<0.01
Category switching	7.4 (3.2)	8.5 (3.5)	-1.2 (-3.8 to 1.5)	0.37
Design fluency test	n=13	n=13		
Design fluency	6.2 (1.7)	10.5 (2.6)	-4.4 (-6.2 to -2.6)	<0.001
Switching	7.3 (2.8)	10.8 (2.7)	-3.5 (-5.7 to -1.3)	<0.01
Color-word interference test	n=13	n=12		
Color naming	5.3 (3.3)	9.3 (2.0)	-4.0 (-6.3 to -1.8)	<0.01
Word reading	7.6 (2.2)	9.9 (2.5)	-2.3 (-4.2 to -0.4)	0.02
Inhibition	7.4 (2.9)	9.3 (3.1)	-1.9 (-4.4 to 0.6)	0.13
Inhibition-switching	6.8 (3.6)	9.7 (2.0)	-2.8 (-5.2 to -0.4)	0.02
Behavior Rating Inventory of Executive Function, second edition				
Behavioral regulation index	57.9 (12.2) n=15	52.1 (10.4) n=14	5.8 (-2.9 to 14.5)	0.18
Metacognition index	65.5 (12.3) n=15	50.9 (10.1) n=14	14.6 (5.9 to 23.2)	<0.01
General executive composite	58.6 (11.6) n=8	50.6 (11.0) n=14	7.9 (-2.4 to 18.4)	0.13