Title: Specificity of Early Childhood Hyperphagia Profiles in Neurogenetic Conditions

Abstract:

Hyperphagia is highly penetrant in Prader-Willi syndrome (PWS) and has increasingly been reported in other neurogenetic conditions (NGC). The Hyperphagia Questionnaire (HQ) was completed for 99 4-8-year-olds with PWS, Angelman syndrome (AS), Williams syndrome (WS), or low-risk controls (LRC). All NGC groups were significantly elevated in HQ Total and Behavior scores compared to LRC. Only AS and WS were significantly elevated in the Drive domain, and only PWS in the Severity domain. After controlling for externalizing behavior, HQ Total scores were higher for PWS relative to other groups. Hyperphagic symptoms may not differentiate PWS from other NGCs in early childhood. However, hyperphagic phenotypes may be most severe in PWS. Further investigation of these profiles may inform etiology and syndrome-specific treatments.

Keywords: Hyperphagia; Neurogenetic conditions; Prader-Willi syndrome; Angelman syndrome; Williams syndrome

INTRODUCTION

Hyperphagia, defined as an extreme unsatisfied drive to consume food, is a concerning cause of childhood obesity associated with disruptive food-related thoughts and behaviors (Heymsfield et al., 2014; Malhotra et al., 2021). Hyperphagia is the cardinal feature of Prader-Willi Syndrome (PWS), a neurogenetic condition (NGC) caused by lack of expression on the paternal copy of chromosome 15 through one of three mechanisms: paternal deletion, maternal uniparental disomy (UPD), or imprinting defect (Bittel & Butler, 2005). PWS is characterized by hypotonia and feeding difficulties in infancy followed by the emergence in childhood of mild to moderate intellectual disability (ID), challenging behaviors, hyperphagia, and obesity (Butler et al., 2016; Cassidy et al., 2012; Dykens, 2004). While there are some reports of differing phenotypic profiles based on sex or genetic subtype of PWS, the developmental phenotype generally involves the onset and worsening of both hyperphagia and challenging behaviors between childhood and early adulthood (Dykens, 2004; Dykens & Roof, 2008).

Despite hyperphagia being a hallmark feature of PWS, the relationship of hyperphagia to other clinical and behavioral symptoms of PWS is complex. Even young children with PWS are at risk of cardiovascular sequelae of obesity, including obstructive sleep apnea, type 2 diabetes, pulmonary issues, and hypertension (Bellis et al., 2022; Butler et al., 2016). However, although unrestrained hyperphagia contributes to obesity in PWS, it may not be the sole cause, particularly in young children. There are also biological factors associated with the syndrome that may cause or worsen weight gain, including reduced resting energy expenditure and the potential side effects of psychiatric medications (Butler et al., 2007, 2016; Kotler et al., 2016). Longitudinal observational studies have shown that children with PWS begin to gain weight in early childhood without significant increase in calories and before the onset of hyperphagia (Miller et al., 2011). Additionally, the relationship between hyperphagia and challenging behaviors in PWS is not well-understood. While hyperphagia is the presumed driver of atypical food-related behaviors such as seeking and hoarding food, eating inedibles, repetitive requests for food, and food-related tantrums, the behavioral phenotype of PWS also includes non-food-related atypical behaviors (Dimitropoulos et al., 2006; Dykens et al., 1996; Whittington & Holland, 2010). These include hoarding non-food items, ordering and arranging objects, repeating rituals, and skin-picking. There is conflicting literature about whether this spectrum of challenging behaviors in PWS develops independently from hyperphagia (Dimitropoulos et al., 2006; Whittington & Holland, 2010).

This lack of specificity about the role of hyperphagia in clinical and behavioral profiles of PWS is further complicated by an incomplete understanding of how and when hyperphagia emerges in childhood. Hyperphagia and weight gain in PWS are now widely characterized by a model of five "nutritional phases," in which hyperphagia and food-seeking behaviors emerge and intensify in "Phase 3" at around age 8 (Butler et al., 2016; Cassidy et al., 2012; Miller et al., 2011). However, some researchers have reported varied phenotypic profiles that do not fit neatly into this model. Researchers from one clinic who had difficulty assigning their patients to nutritional phases using information in clinical records stated that the transition to hyperphagia between birth and Phase 3 is "a continuum without explicit criteria of where to draw lines between phases" (Kotler et al., 2016, pg 3). They further reported that about 30% of children and adults in their cohort were described by caregivers as "picky eaters," with children aged 1-3 years exhibiting sensory sensitivity or aversion to different textures (Kotler et al., 2016). Thus, even in a syndrome characterized by development of hyperphagia, there is a need to further characterize its manifestation, particularly in early childhood.

In addition, there is a need to understand how hyperphagia in PWS compares to other NGCs. As late as 2007, hyperphagia was thought to be the feature that differentiated PWS from other NGCs (Hodapp & Dykens, 2007). However, increasingly, hyperphagic symptoms are reported in subsets of children with other NGCs such as fragile X syndrome (FXS) (de Vries et al., 1993; Nowicki et al., 2007; Raspa et al., 2010) and Angelman syndrome (AS), with some studies reporting similar rates of features in AS and PWS (Mertz et al., 2014; Welham et al., 2015). Indeed, a number of atypical food-related behaviors have been reported across multiple NGCs; for example, sensory sensitivity, rigidity, and/or obsessiveness, which can manifest as food selectivity (Bozzini et al., 2019; Zickgraf et al., 2020), are common in PWS, FXS, and Williams syndrome (WS) (Aguilar et al., 2020; Huston et al., 2021; Kotler et al., 2016; Raspa et al., 2010). In addition, many NGCs have a high prevalence of symptoms or comorbid diagnoses of autism spectrum disorder (ASD) (Dykens et al., 2011; Richards et al., 2015), which is associated with both food-related and non-food related challenging behaviors and increased prevalence of overweight and obesity (Cermak et al., 2010; Flygare Wallén et al., 2018; Hill et al., 2015). These shared phenotypic features may relate more broadly to co-occurring ID, which is common in many of the same NGCs with higher prevalence of ASD (Hodapp & Dykens, 2007; Richards et al., 2015) and is independently associated with higher rates of disordered eating (Flygare Wallén et al., 2018; Gravestock, 2000).

Together, these studies underscore a continued need for evidence to inform hyperphagia profiles across NGCs, particularly in the early childhood period, a period of development during which hyperphagia is less understood even in PWS. Developing this specificity surrounding hyperphagia and atypical food-related behaviors in NGCs can elucidate how the genetic architecture of each syndrome maps onto clinical outcomes, informing the development of therapeutics and preventative approaches (Hodapp & Dykens, 2007).

To address this gap, the present study aimed to characterize hyperphagia and examine its associations with other phenotypic characteristics in young children with an NGC (PWS, AS, and WS) and without an NGC (i.e., a group of age-matched low-risk controls). PWS and AS are both caused by mutations in Chromosome 15, although distinct genetic mechanisms produce different phenotypes across the two conditions (Cassidy et al., 2000). AS is characterized by lack of speech, seizures, fine and gross motor delays, and a behavioral profile that includes happy demeanor, frequent laughter, and often an affinity for water (Bird, 2014; Wheeler et al., 2017). WS is caused by a microdeletion on chromosome

7q11.23 that results in symptoms such as cardiovascular disease and a behavioral profile that includes hypersociability (Kozel et al., 2021). While genetically and phenotypically distinct, PWS, AS, and WS share core features such as ID and elevated behavioral symptoms related to anxiety, attention, and ASD (Neo & Tonnsen, 2019). Contrasting these NGCs enables us to identify any hyperphagic symptoms that are specific to one syndrome, versus those shared across NGCs associated with ID or common co-occurring behavioral symptoms. Our research questions (RQ) were as follows:

(RQ1) How do hyperphagic symptoms differ in early childhood across NGC groups (PWS, AS, WS) and non-NGC controls?

(RQ2) How do hyperphagic symptoms relate to other clinical and developmental features in early childhood?

MATERIALS AND METHODS

Study Design

We conducted a cross-sectional examination of early childhood hyperphagia and other clinical features in 4-8-year-old children with and without an NGC. Data were collected through the [MASKED FOR REVIEW], an ongoing longitudinal caregiver-reported survey study of children with rare NGCs and a comparison group of low-risk controls (LRC). Caregivers enter the study when their child is as young as three months of age and complete surveys with age-appropriate questionnaires at 6-month or 12-month intervals, depending on child age. Starting when their child is 4 years old, caregivers are asked to complete a hyperphagia measure annually.

Participants and Recruitment

Families for both the NGC and LRC groups were recruited for the longitudinal study nationally through web-based parent support groups, paid web advertisements and social networks. Syndrome-specific research registries were also used to recruit families of children with NGCs. Children were excluded from the NGC group if they were adopted; if English was not the primary language spoken in their home or if they were living outside the United States; or, if they experienced any medical conditions *not associated with their syndrome* that could impact development (e.g., traumatic brain injury). Children were excluded from the LRC group if they were born at less than 37 weeks gestation; if they were adopted; if English was not the primary language spoken in their home or if they were living outside the United States; if any developmental concerns or medical conditions that could impact development were noted by caregivers, pediatricians, or other providers; or if they had an immediate family member diagnosed with autism, ID, or other genetic syndrome.

From [MASKED], inclusion in this sub-study was limited to subjects who had at least one datapoint for the hyperphagia measure. For subjects with more than one available datapoint, we selected the most recent observation. Subjects of the analyses described herein (N = 99) were part of the LRC group (n = 35) or had one of three NGCs: PWS (n = 17), AS (n = 22), or WS (n = 25). While children with Down syndrome and FXS are part of the longitudinal study, they were not included in this analysis due to insufficient sample sizes in this age range. For those in an NGC group, submitting confirmation of genetic diagnosis was not required to participate in the study; however, the diagnoses of 84% (54/64) of the participants in this sub-study were verified via genetic report (15/17 with PWS; 19/22 with AS; 20/25 with WS). Genetic subtypes were reported for a subset of children with PWS (n = 12 with paternal deletion; n = 5 with maternal UPD) and AS (n = 18 with maternal deletion; n = 2 with *UBE3A* mutation; n = 1 with paternal UPD).

Families were compensated approximately $10/hour for completing the broader set of study forms. Study procedures were reviewed and approved by the [MASKED] Institutional Review Board, and families provided written consent for participation.

Measures

Outcome Measure

Hyperphagia Questionnaire (HQ). The HQ (Dykens et al., 2007) is an 11-item caregiver-reported measure that scores three domains of hyperphagia: (1) hyperphagic Behavior (5 items) addresses actions one takes to obtain food; (2) hyperphagic Drive (4 items) describes the degree to which one is focused on food; and (3) hyperphagic Severity (2 items) describes the degree to which thoughts and behaviors associated with food interfere with functioning and daily routines. This three-factor structure (i.e., Behavior, Drive, Severity) has been shown to have good internal consistency in children and adults with PWS in both English and a 10-item Italian translation (Dykens et al., 2007; Licenziati et al, 2022). Items on the HQ are rated on a 5-point scale where 5 indicates the most severe and/or frequent. We analyzed the total raw score and the raw score for each domain of the 11-item English version of the HQ.

Other Clinical and Developmental Measures

Social Communication Questionnaire (SCQ). The SCQ (Rutter et al., 2003) is a caregiver-reported 40-item screening tool for ASD that evaluates communication skills and social functioning. We analyzed the total raw score for the SCQ, with higher scores representing more social communication impairment.

Social Responsiveness Scale, Second Edition (SRS-2). The SRS-2 (Constantino & Gruber, 2012) is a 65-item caregiver-reported tool for identifying ASD-related social impairment and its severity. We analyzed the total T-score for the SRS-2, where higher scores reflect more autism symptomatology.

Sensory Experiences Questionnaire (SEQ). The SEQ (Baranek et al., 2006) is a caregiver-reported 105-item questionnaire that measures sensory behaviors and interests among children with ASD and/or developmental disabilities. We analyzed the total raw score for the SEQ. Higher SEQ scores reflect the presence of more sensory features.

Child Behavior Checklist (CBCL). The CBCL 1.5-5 (Achenbach & Rescorla, 2000) measures caregiver-perceived problem behaviors and competencies of the child. Specifically, we examined raw

Internalizing and Externalizing behavior scores, where higher scores indicate higher rates and/or severity of problem behaviors. Internalizing scores reflect behaviors related to anxiety, depression, withdrawal, and somatic complaints, while Externalizing scores reflect non-compliant and aggressive behaviors. All parents were given CBCL 1.5-5 regardless of their child's age, as this version is most developmentally appropriate for children with NGCs.

Vineland Adaptive Behavior Scales – Third Edition (VABS-3). The VABS-3 (Sparrow et al., 2016) is a standardized, semi-structured interview tool that measures caregiver-reported adaptive behavior. Specifically, we included standard scores from the Expressive Communication, Receptive Communication, Gross Motor, and Fine Motor scales, where higher scores indicate higher levels of adaptive skills. We also included the Adaptive Behavior Composite (ABC), a standard composite score that encompasses adaptive behavior in the domains of communication, daily living skills, and socialization, where a higher ABC score indicates higher adaptive functioning. Because families are asked to complete the VABS-3 about their child during their second study visit, VABS-3 data is not available on the subset of the analysis cohort who have not completed more than one visit.

Data Analysis Plan

To examine whether there were any differences in descriptive characteristics between groups, comparisons were made using (1) chi-squared tests for binary and categorical variables, or (2) Wilcoxon rank sum tests for continuous variables. The variables included age, sex, race, ethnicity, BMI, maternal education, and household income.

Seven participants were missing at least one item on the main outcome measure (See Table 2): One participant with AS was missing 4 items (#2, #7, #8, #9); six participants were missing 1 item (#8 missing by one with AS, two with WS, and two LRC; #10 missing by one LRC). Missing items were scored using mean imputation of items in the same domain.

To address how hyperphagic symptoms differ in early childhood across NGC groups and controls (RQ1), the Wilcoxon rank sum test was used to compare the HQ Total and domain scores across groups. Next, we used Wilcoxon sum rank tests with Holm-Bonferroni corrections to account for multiple comparisons were used to compare domain and item-level symptoms for each NGC group relative to the LRC group.

To address how hyperphagic symptoms relate to other clinical and developmental features in early childhood (RQ2), multiple linear regression analysis was used to develop and compare a series of fitted models for predicting HQ Total scores from clinical and developmental measures as well as diagnostic status. Prior to conducting the regression analyses, measures of central tendency and variability were computed and reported for the HQ Total score and the clinical and developmental measures. For the LRC group, we ensured that scores on standardized clinical measures (VABS-3, SRS-2) were within normal limits. Then, Spearman's rank-order correlations were computed to examine the relationships between the outcome and the clinical and developmental measures for each group and for the sample overall. Bivariate scatterplots of the outcome versus the clinical measures were also examined.

Based on the correlation analysis as well as previous studies that have established associations between hyperphagia and problem behaviors in PWS (Dimitropoulos et al., 2006; Dykens et al., 2007), three clinical and developmental predictors were selected for the stepwise regression analysis: CBCL Externalizing raw score, SEQ Total raw score, and VABS-3 ABC score. We did not include any other clinical or developmental measures to predict HQ Total scores due to concerns about multicollinearity and power. First, a univariate model was fit with CBCL Externalizing raw scores predicting HQ Total scores (Model 1). Then, SEQ Total raw scores and VABS-3 ABC score were added to this initial model in a stepwise fashion (Models 2 and 3, respectively). Then, dummy variables were created for the diagnostic groups, with the LRC group as the reference group, to examine the extent to which diagnostic group predicted HQ Total scores after controlling for these clinical and developmental features. Finally, a model was fit that included the clinical and developmental measures and the diagnostic group dummy variables predicting HQ Total scores (Model 4). Model fit was evaluated by comparing the R^2 values across the four models.

Possible violations of the assumptions of ordinary least squares regression were checked for in the final selected model by examining scatterplots of studentized residuals against each predictor and y-hat as well as scatterplots of Cook's D statistic against each predictor. These plots were also checked for any atypical data points that could be influencing the final model. In the case of atypical data points, sensitivity analyses were conducted with the unusual observation(s) eliminated from the data set to compare these fitted models to the original models.

RESULTS

Participant characteristics

There were no differences between groups in age, sex, maternal education, or household income (Table 1). However, BMI of children with PWS was significantly higher than LRC and WS, and BMI of children with WS was significantly lower than LRC. BMI of children with AS was not significantly different from the other three groups.

RQ1: How do hyperphagic symptoms differ in early childhood across NGC groups and non-NGC controls?

Group Comparisons of HQ Domain Scores

Compared to the LRC group, all NGC groups exhibited significant elevations in both HQ Total and HQ Behavior scores (Figure 1). Additionally, children with AS and WS exhibited significantly elevated HQ Drive scores relative to the LRC group, whereas those with PWS trended towards elevation in this domain (p = .05), and children with PWS exhibited significantly elevated HQ Severity. When comparing NGC groups to each other, no significant differences were observed in either HQ Total or HQ Behavior scores. However, the PWS group exhibited significantly elevated HQ Severity scores relative to the AS and WS groups (Figure 1), which did not differ from each other.

HQ Domain and Item-level Comparisons for NGC Groups Relative to the LRC Group

Item-level analyses of hyperphagic symptoms (Table 2) indicated that, compared to the LRC group, children with PWS and AS were significantly elevated for two of the same HQ Behavior items ("Foraging through the trash for food"; "Being clever or fast in obtaining food"); however, only children with PWS were significantly elevated in endorsement of the HQ Behavior item "Trying to steal food". The PWS and AS groups were also significantly elevated for the same HQ Drive item ("Distress when told to stop food-related talk/behavior"). Only the PWS group showed elevated endorsement of the two items that assess HQ Severity ("Time spent talking about food"; "Interference with daily activities from food-related talk or behavior"). Despite elevation in total HQ Behavior and Drive scores relative to the LRC group, the WS group was not significantly elevated in endorsement of any single item when correcting for multiple comparisons.

RQ2: How do hyperphagic symptoms relate to other clinical and developmental features in early childhood?

Table 3 presents descriptive summaries of the clinical and developmental measures for each group. As expected, descriptive analyses revealed atypical clinical features and adaptive behaviors in NGC groups relative to the LRC group with three exceptions: SEQ Total scores (PWS group), CBCL Internalizing scores (PWS and AS groups), and CBCL Externalizing scores (PWS group).

Table 4 presents Spearman's correlation coefficients for hyperphagia symptoms and each clinical feature. Across the sample, higher levels of hyperphagia were associated with higher levels of symptoms across all clinical measures (SCQ, SRS-2, CBCL, SEQ) and lower levels of adaptive functioning (VABS-3). These results were partially maintained in the LRC and NGC subgroups. For the LRC group, higher levels of hyperphagia (HQ Total) were associated with more autism symptomology (SCQ, SRS-2), sensory features (SEQ), and internalizing and externalizing challenging behaviors (CBCL). For the PWS group, higher levels of hyperphagia were associated with more externalizing behavior (CBCL) and lower levels of receptive communication, fine motor skills, and overall adaptive behavior (VABS-3). For the WS group, higher levels of hyperphagia were associated with higher expressive communication skills (VABS-3). There were no significant associations between hyperphagia symptoms and other clinical and developmental measures for the AS group.

Table 5 presents a series of fitted regression models predicting HQ Total scores from clinical and developmental measures and diagnostic group, with LRC as the reference group. The best fitting model was Model 4, which had the following predictors: CBCL Externalizing raw score, SEQ Total raw score, VABS-3 ABC score, and dummy variables representing the NGC groups. The final model explained 34% of variability in HQ Total Scores. Within this model, HQ scores were significantly predicted by CBCL Externalizing raw score and PWS group status. Post-estimation comparisons between groups indicated that the estimated HQ Total score for the PWS group was also significantly elevated relative to the AS and WS groups, and that there was not a significant difference between estimated HQ Total scores in the AS and WS groups. Figure 2 presents a scatterplot showing HQ Total scores versus CBCL Externalizing raw scores with fitted lines for each diagnostic group.

DISCUSSION

Although hyperphagia has been explored among NGC groups in older children (Foerste et al., 2016; Welham et al., 2015), the present study is the first to examine hyperphagic symptoms (e.g., hyperphagic behavior, drive, and severity) across multiple NGCs in early childhood. Our findings among children aged 4-8 years suggest that the presence of any hyperphagic symptoms is not unique to PWS in early childhood, however profiles differ across groups and are most severe in PWS.

Specificity of hyperphagic symptoms across NGCs

Regarding PWS, our findings converge with prior reports of the presence of hyperphagic symptoms in early childhood (Dykens et al., 2007; Miller et al., 2011). We also replicated prior reports that hyperphagia symptoms correlate with other challenging behaviors; for example, Dykens et al. (2007) found HQ Drive and Severity positively correlated with CBCL Internalizing and Externalizing behaviors in individuals with PWS of all ages, including a group of 4–10-year-olds. Using different measures, another study found severity of hyperphagia to be positively correlated with displaying more ritualistic non-food behaviors (Dimitropoulos et al., 2006). The strong association we found between VABS-3 Receptive Communication scores and HQ Total scores in these young children is striking and warrants additional exploration.

In AS, we found no significant correlations between hyperphagic symptoms and other clinical and developmental features assessed. However, we did find that children with AS showed elevations in HQ Behavior and Drive domains and items compared to controls, overlapping with PWS in endorsement of several symptoms. This work aligns with previous studies that have shown hyperphagic symptoms among a third or more of children with AS (Berry et al., 2005; Bindels-de Heus et al., 2020; Welham et al., 2015). One study that examined food-related behavior among older children (8-14 years) with AS, PWS, and other NGCs using the Food-Related Problems Questionnaire reported similar findings to ours regarding similarities and differences in hyperphagic symptoms between PWS and AS (Welham et al., 2015c). Specifically, they found that the AS group scored significantly higher than at least one other NGC group on several domains, and that there were not significant differences between AS and PWS in a negative behavior composite that included “inappropriate negative behavior in response to food restriction” and “eating inedible items”. This aligns with our findings about similarities in hyperphagic symptoms that were elevated in PWS and AS in the same HQ Behavior and Drive items (e.g., “Foraging through the trash for food” and “Distress when told to stop food-related talk/behavior”), and adds to growing evidence that hyperphagia may be a prevalent clinical feature for AS.

Our findings are particularly interesting regarding WS, in which the presence of hyperphagia has not previously been reported. Relative to children in the LRC group, children with WS were uniquely elevated in the HQ Drive domain, which includes items such as “Distress when told to stop food-related talk/behavior”. Our correlation analysis for WS also showed that overall hyperphagic symptoms were associated with higher expressive communication skills. Individuals with WS can be excessively verbal and exhibit repetitive thoughts and behaviors (Huston et al., 2021; Jones et al., 2000). Given the positive correlation between hyperphagic symptoms and expressive communication, it is possible that parental endorsement of HQ items assessing hyperphagic drive are more reflective of a general perseverance on the topic at hand. It is also notable that despite the presence of elevations relative to LRC, we did not assess whether elevations in symptoms are clinically meaningful; studies with larger sample sizes and/or qualitative studies including children with WS are warranted to confirm and expand on these findings.

Our regression models further contributed to the specificity of childhood hyperphagia profiles by examining relationships between hyperphagia and three clinical/developmental features: externalizing challenging behavior, sensory behaviors and interests, and overall adaptive functioning. Ultimately, we found that externalizing behavior was the only significant clinical/developmental predictor of hyperphagia. The relationship between challenging behaviors and hyperphagia is intuitive; although lack of satiety underlies hyperphagia, the manifestation of hyperphagia is behavioral, including non-compliance when food or food-related talk is restricted. Although we found elevations in hyperphagia in young children with PWS, AS, and WS compared to controls, only a diagnosis of PWS was predictive of elevations in hyperphagia after controlling for challenging behavior.

Limitations

Although our sample represents the youngest known cross-NGC comparison to date, a key limitation of this study is small sample sizes. Larger studies are needed to confirm cross-group findings and allow for more sophisticated within-group analyses of associated symptoms. For example, prior AS research points to potentially greater hyperphagic behavior among individuals with the paternal UPD genotype compared to those who are deletion positive or have a *UBE3A* mutation (Mertz et al., 2014); however, we were not powered to examine differences by subtype in this study.

Another limitation of the present study is that although the three factor HQ measure has been found to have acceptable internal consistency for individuals 3-54 years of age with PWS, other metrics of reliability, such as inter-rater or test-retest reliability, have not been assessed (Dykens et al., 2007; Licenziati et al., 2022). Additionally, since the HQ was specifically designed based on research and clinical programs for individuals with PWS, it may not optimally capture atypical behaviors in other groups. Although the HQ has been used to assess hyperphagia in other syndromes associated with obesity (Foerste et al., 2016; Sherafat-Kazemzadeh et al., 2013; Wang & Shoemaker, 2014), we observed missing item-level data in non-PWS groups only. Out of seven participants with missing data, six lacked the Behavior item that assesses how often the child tries to steal food, where the least frequent answer choice is “a few times a year.” Parents may have skipped this item because the available answer choices did not accurately characterize their child (e.g., if the child never tries to steal food). It is also important to consider that individuals with AS often present with more severe cognitive and communication challenges than the other groups studied here. This may have influenced how parents responded to items differently for AS. For example, one AS parent presumably skipped three items that implied verbal communication (e.g., “Time spent talking about food”). For parents of children with AS who endorsed such items, it is unclear how they interpreted them (e.g., if they were considering the child’s gestures or sounds instead of words).

An adaptation of the HQ, the HQ for Clinical Trials (HQ-CT), specified a recall period of two weeks for all items and removed items that did not address observable behaviors (Fehnel et al., 2015). The 9-item HQ-CT, which uses a single composite score, has been used to assess hyperphagia in phase 3 clinical trials for PWS and may be more suitable for use in other NGCs (Fehnel et al., 2015; Roof et al., 2023). Additionally, qualitative studies are needed to further contextualize the hyperphagic phenotypes exhibited by non-PWS comparison groups to inform the development or refinement of measurement tools.

Future Directions

This study providing preliminary data on the specificity of hyperphagia profiles across NGCs in early childhood is an important step towards identifying predictors of symptoms and outcomes and improving treatment approaches.

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Figure 1

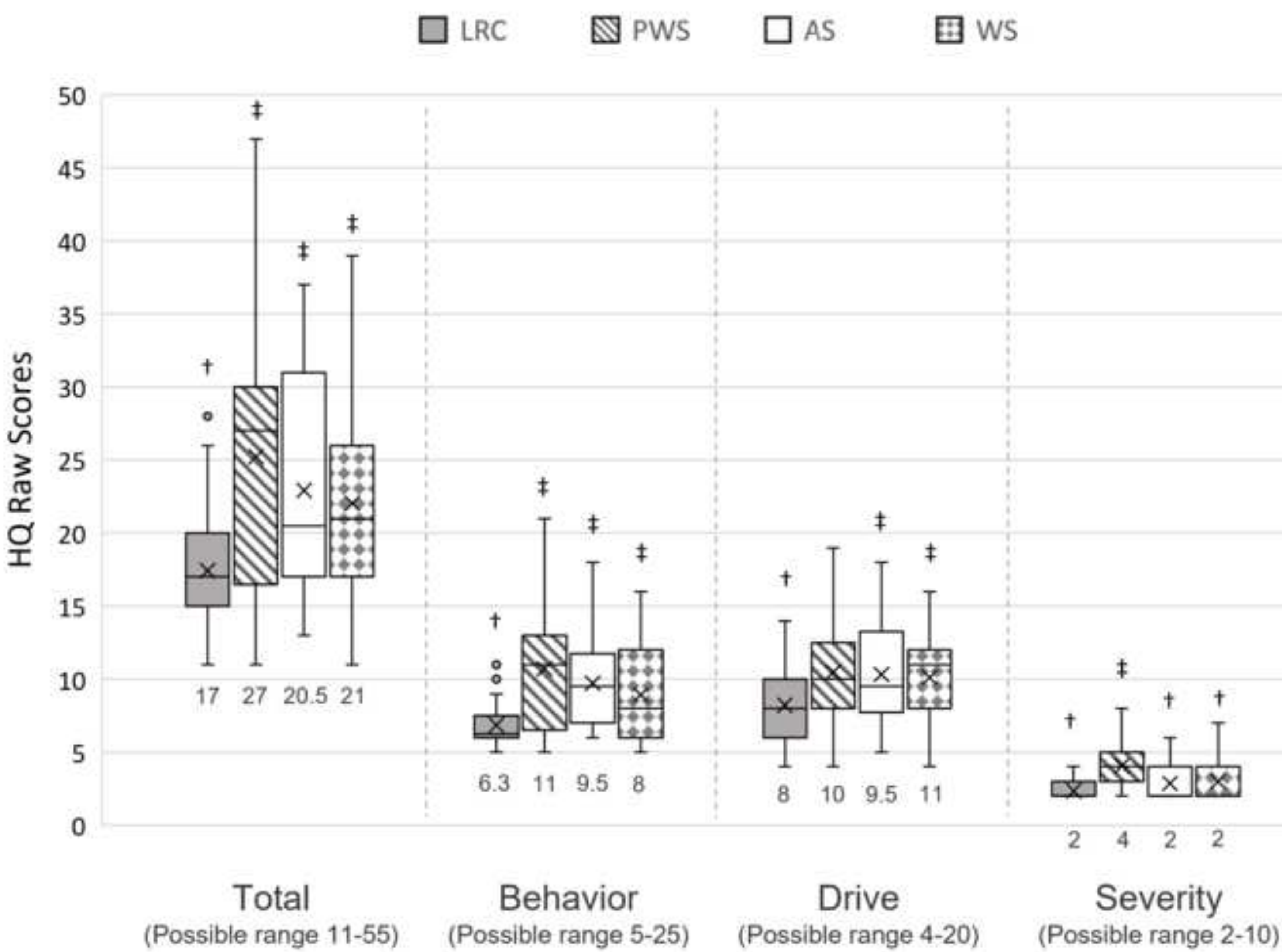
LRC
PWS
AS
WS
HQ Raw Scores
50
45
40
35
30
25
20
15
10
5
0
17 27 20.5 21
6.3 11 9.5 8
8 10 9.5 11
2 4 2 2
Total
(Possible range 11-55)
Behavior
(Possible range 5-25)
Drive
(Possible range 4-20)
Severity
(Possible range 2-10)

Figure 2

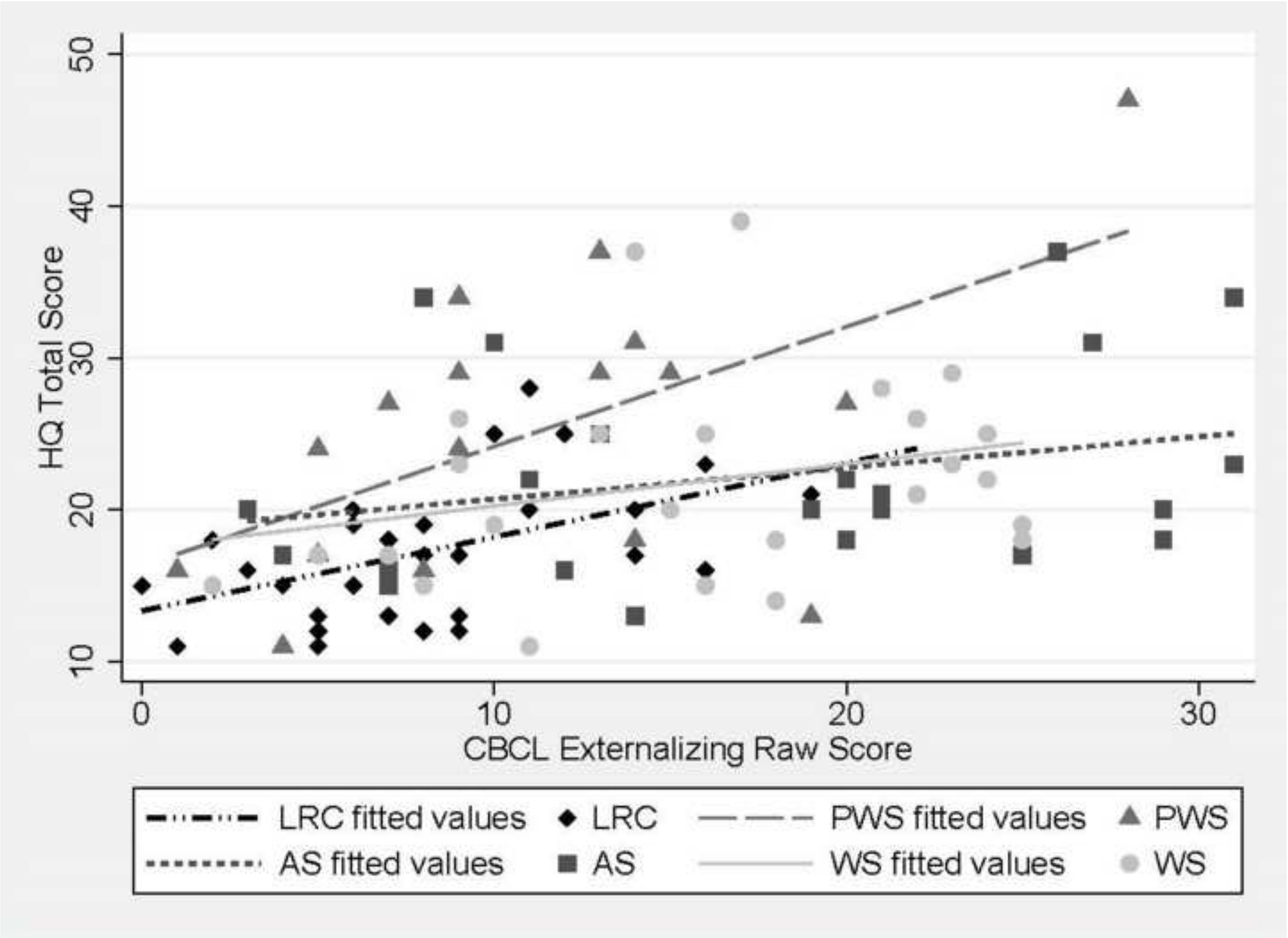
HQ Total Score
10
20
30
40
50
0
10
20
30
CBCL Externalizing Raw Score
LRC fitted values
LRC
PWS fitted values
PWS
AS fitted values
AS
WS fitted values
WS

Table 1

*Descriptive Characteristics of Participants with and without Neurogenetic Conditions (*N *= 99)*

Characteristic	LRC (*n* = 35)	PWS (*n* = 17)	AS (*n* = 22)	WS (*n* = 25)	Total
Age (months), mean (*SD*)	65.7 (11.0)	66.2 (9.4)	64.2 (12.1)	68.7 (11.2)	66.2 (11.0)
Sex (Male), *n* (%)	22 (63%)	7 (41%)	12 (55%)	11 (44%)	52 (53%)
Race (White), n (%)†	33 (97%)	15 (88%)	20 (95%)	22 (92%)	90 (94%)
Ethnicity (non-Hispanic), *n* (%)†	33 (97%)	15 (88%)	21 (100%)	21 (88%)	90 (94%)
BMI (kg/m^2), mean (*SD*)†	16.4 (1.7)	18.8 (2.6)‡	16.5 (2.6)	15.7 (2.6)§	16.5 (2.4)
Mother's Education, *n* (%)†					
High school diploma or less	1 (3%)	0 (0%)	1 (5%)	0 (0%)	2 (2%)
Some college/Associate's degree	2 (6%)	3 (18%)	6 (29%)	3 (14%)	14 (15%)
Bachelor's degree	12 (35%)	7 (41%)	4 (19%)	10 (48%)	33 (36%)
Advanced degree	19 (56%)	7 (41%)	10 (48%)	8 (38%)	44 (47%)
Mean Family Income ($1,000), mean (*SD*)†	124.2 (51.7)	118.9 (72.4)	117.3 (73.1)	137.2 (77.7)	125.7 (63.5)

Note. LRC = low-risk control, PWS = Prader-Willi syndrome, AS = Angelman syndrome, WS = Williams syndrome, BMI = Body mass Index. Individual percentage values were rounded and may not total 100%. †*n* = 96 for Race and Ethnicity; *n* = 65 for BMI; *n* = 93 for Mother's Education; *n* = 61 for Mean Family Income. ‡$p < .05$ compared to LRC using Wilcoxon rank sum test. §$p < .05$ compared to LRC and PWS using Wilcoxon rank sum test.

Table 2

Hyperphagia Questionnaire Domains and Items: Neurogenetic Condition Groups Compared to Low-Risk Controls

HQ Items by Domain	PWS (*n* = 17) vs LRC (*n* = 35)			AS (*n* = 22) vs LRC (*n* = 35)			WS (*n* = 25) vs LRC (*n* = 35)		
Scale	Z	p	r_{pb}	Z	p	r_{pb}	Z	p	r_{pb}
Behavior (total)	3.04	**.002**	0.54	3.78	**<.001**	0.51	2.19	**.03**	0.37
2. Try to bargain or manipulate	1.63	.10	0.30	0.72	.47	0.09	1.46	.14	0.23
4. Forage through trash for food	4.03	**<.001**	0.48	2.92	**<.01**	0.35	-	-	-
5. Get up at night to food seek	1.82	.07	0.20	1.02	.31	0.13	-0.85	.40	-0.11
8. Try to steal food	3.50	**<.001**	0.51	2.05	.04	0.34	2.06	.04	0.34
10. Clever or fast in obtaining food	2.89	**<.01**	0.44	4.51	**<.001**	0.59	2.36	.02	0.36
Drive (total)	1.92	.05	0.31	1.97	**.049**	0.31	2.52	**.01**	0.33
1. Upset when denied food	0.98	.33	0.12	0.85	.40	0.14	0.94	.35	0.12
3. Effort required to redirect	2.39	.02	0.35	2.29	.02	0.34	2.14	.03	0.29
6. Persistence after being told no more	1.50	.13	0.24	1.12	.26	0.18	1.85	.06	0.26
9. Distress when told to stop food-related talk/behavior	2.65	**<.01**	0.43	2.94	**<.01**	0.44	2.41	.02	0.35
Severity (total)	4.53	**<.001**	0.60	1.26	.21	0.26	1.79	.07	0.29
7. Time spent talking about food	3.79	**<.001**	0.51	1.24	.21	0.17	1.75	.08	0.26
11. Interference with daily activities from food-related thoughts, talk, or behavior	4.01	**<.001**	0.52	1.71	.09	0.26	1.95	.05	0.25

Note. LRC = low-risk control, PWS = Prader-Willi syndrome, AS = Angelman syndrome, WS = Williams syndrome, r_{pb} = point biserial rho. All *p*-values reflect uncorrected values; bolded *p*-values significant after Holm-Bonferroni correction; *p*-values for the total scales are not corrected but also bolded if significant at the α < 0.05 level.

Table 3

*Descriptive Statistics of Clinical and Developmental Measures (*N *= 99)*

	Mean (*SD*) Range			
Characteristic or Scale	**LRC (*n* = 35)†**	**PWS (*n* = 17)‡**	**AS (*n* = 22)§**	**WS (*n* = 25)¶**
HQ Total	17.44 (4.31) 11-28	25.24 (9.41) 11-47	22.92 (7.34) 13-37	22.04 (6.79) 11-39
SCQ Total	3.80 (3.19) 0-15	8.18 (6.65) 1-27	14.32 (5.67) 5-27	10.36 (5.71) 2-29
SRS-2 Total	47.17 (4.51) 40-58	63.00 (9.90) 47-87	72.64 (8.70) 53-87	65.64 (10.50) 47.97
SEQ Total	52.54 (10.08) 39-83	57.29 (12.28) 39-94	73.59 (13.36) 48-99	71.40 (13.34) 44-101
CBCL Internalizing	6.20 (5.07) 0-25	8.00 (5.58) 2-22	8.73 (6.03) 2-21	10.96 (5.65) 3-25
CBCL Externalizing	8.17 (4.99) 0-22	11.35 (6.76) 1-28	17.64 (9.13) 3-31	15.88 (6.86) 2-25
VABS-3 Receptive Communication	14.61 (2.45) 11-20	9.46 (2.82) 4-13	4.05 (2.68) 1-9	9.86 (3.07) 1-15
VABS-3 Expressive Communication	15.14 (2.69) 8-22	9.38 (3.45) 1-14	1.25 (0.64) 1-3	8.38 (4.09) 1-15
VABS-3 Gross Motor	14.75 (2.85) 7-22	5.62 (3.10) 1-11	5.05 (2.72) 1-9	8.52 (1.78) 4-11
VABS-3 Fine Motor	14.64 (2.26) 10-20	10.69 (2.59) 7-16	5.80 (1.91) 1-10	9.67 (2.82) 4-15
VABS-3 ABC	93.89 (10.49) 79-116	72.77 (8.99) 54-84	51.80 (6.61) 36-62	70.48 (9.64) 50-88

Note. LRC = Low-risk control, PWS = Prader Willi Syndrome, AS = Angelman syndrome, WS = Williams Syndrome, HQ = Hyperphagia Questionnaire, SCQ = Social Communication Questionnaire, SRS-2 = Social Responsiveness Scale, SEQ = Sensory Experiences Questionnaire, CBCL = Child Behavior Checklist, VABS-3 = Vineland-3, ABC = Adaptive Behavior Composite. †VABS-3 data: *n* = 28. ‡VABS-3 data: *n* = 13. §VABS-3 data: *n* = 20. ¶VABS-3 data: *n* = 22.

Table 4

Spearman's Correlation Coefficients for Hyperphagia Questionnaire Total Raw Score with Clinical and Developmental Measures

	HQ Total				
Characteristic or Scale	**LRC (n = 35)†**	**PWS (n = 17)‡**	**AS (n = 22)§**	**WS (n = 25)¶**	**Overall (N = 99)**
SCQ Total	**0.55*****	0.001	0.31	-0.21	**0.38*****
SRS-2 Total	**0.39***	-0.27	0.14	-0.04	**0.32****
SEQ Total	**0.51****	-0.31	0.13	-0.18	**0.26****
CBCL Internalizing	**0.37***	0.39	0.21	-0.15	**0.27****
CBCL Externalizing	**0.51****	**0.49***	0.33	0.29	**0.50*****
VABS-3 Receptive Communication	0.02	**-0.86*****	-0.37	0.37	**-0.36****
VABS-3 Expressive Communication	0.06	-0.32	-0.02	**0.49***	**-0.25***
VABS-3 Gross Motor	-0.11	-0.11	0.33	0.28	**-0.30****
VABS-3 Fine Motor	0.27	**-0.55***	-0.05	0.09	**-0.30****
VABS-3 ABC	-0.01	**-0.64***	-0.28	0.41	**-0.34****

Note. LRC = Low-risk control, PWS = Prader Willi Syndrome, AS = Angelman syndrome, WS = Williams Syndrome, HQ = Hyperphagia Questionnaire, BMI = body mass index, SCQ = Social Communication Questionnaire, SRS-2 = Social Responsiveness Scale, SEQ = Sensory Experiences Questionnaire, CBCL = Child Behavior Checklist, VABS-3 = Vineland-3, ABC = Adaptive Behavior Composite. †VABS-3 data: n = 28. ‡VABS-3 data: n = 13. §VABS-3 data: n = 20. ¶VABS-3 data: n = 22.

*p < .05, **p < .01, ***p < .001. Bolded values also indicate significant values.

Table 5

Comparison of Fitted Regression Models Predicting Hyperphagia Questionnaire Total Raw Score

Predictors	Estimate	Model 1	Model 2	Model 3	Model 4
CBCL Externalizing	β	**0.42**	**0.41**	**0.38**	**0.39**
	se	**0.08**	**0.09**	**0.10**	**0.10**
	t	**5.03*****	**4.33*****	**3.69*****	**3.94*****
SEQ Total	β		0.02	-0.01	0.03
	se		0.05	0.05	0.06
	t		0.35	-0.19	0.44
VAB-3 ABC	β			-0.06	-0.003
	se			0.05	0.08
	t			-1.18	-0.04
Prader-Willi Syndrome	β				**7.18**
	se				**2.62**
	t				**2.78****
Angelman Syndrome	β				1.64
	se				3.67
	t				0.45
Williams Syndrome	β				1.41
	se				2.58
	t				0.55
Constant	β	**21.16**	**21.16**	**20.91**	**18.98**
	se	**0.65**	**0.65**	**0.71**	**1.89**
	t	**32.47*****	**32.33*****	**29.27*****	**10.05*****
Summary Statistics					
R^2		0.2070	0.2080	0.2429	0.3399
F-Statistic (df)		25.32 (1, 97)	12.61 (2, 96)	8.34 (3, 78)	6.44 (6, 75)
p of F		<.0001	<.0001	.0001	<.0001

Note. CBCL = Child Behavior Checklist, SEQ = Sensory Experiences Questionnaire, VABS-3 = Vineland-3, ABC = Adaptive Behavior Composite. CBCL, SEQ, and VABS-3 scores were mean-centered.
$^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$. Bolded values also indicate significant values.

Figure Titles and Captions

Figure 1

Title: Median Hyperphagia Questionnaire Total and Domain Scores Among Neurogenetic Condition Groups Compared to Low-Risk Controls

Caption: *Note*. LRC = low-risk control, PWS = Prader-Willi syndrome, AS = Angelman syndrome, WS = Williams syndrome. Numbers and x's represent medians. Tops and bottoms of each box represent the interquartile range, and error bars represent minimums and maximums, except in the case of outliers denoted by circles. For HQ Total score and for each domain, significant differences ($p < .05$) were present between two bars if their symbols are different (i.e., bars labeled with "‡" are significantly different than bars labeled with "†" within each set of 4 bars

Figure 2

Title: Fitted Hyperphagia Questionnaire Total Scores Versus CBCL Externalizing Raw Scores by Diagnostic Group

Caption: (none)