# American Journal on Intellectual and Developmental Disabilities Specificity of Early Childhood Hyperphagia Profiles in Neurogenetic Conditions --Manuscript Draft--

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Corresponding Author:	Sara Andrews, MPH RTI International Research Triangle Park, North Carolina UNITED STATES
First Author:	Sara M Andrews, MPH
Order of Authors:	Sara M Andrews, MPH
	Anita A Panjwani, PhD
	Sarah Nelson Potter, PhD
	Lisa R Hamrick, MS
	Anne C Wheeler, PhD
	Bridgette L Kelleher, PhD
Manuscript Region of Origin:	UNITED STATES
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.

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15 Williams syndrome

# INTRODUCTION

17	Hyperphagia, defined as an extreme unsatisfied drive to consume food, is a concerning cause of
18	childhood obesity associated with disruptive food-related thoughts and behaviors (Heymsfield et al.,
19	2014; Malhotra et al., 2021). Hyperphagia is the cardinal feature of Prader-Willi Syndrome (PWS), a
20	neurogenetic condition (NGC) caused by lack of expression on the paternal copy of chromosome 15
21	through one of three mechanisms: paternal deletion, maternal uniparental disomy (UPD), or imprinting
22	defect (Bittel & Butler, 2005). PWS is characterized by hypotonia and feeding difficulties in infancy
23	followed by the emergence in childhood of mild to moderate intellectual disability (ID), challenging
24	behaviors, hyperphagia, and obesity (Butler et al., 2016; Cassidy et al., 2012; Dykens, 2004). While there
25	are some reports of differing phenotypic profiles based on sex or genetic subtype of PWS, the
26	developmental phenotype generally involves the onset and worsening of both hyperphagia and
27	challenging behaviors between childhood and early adulthood (Dykens, 2004; Dykens & Roof, 2008).
28	Despite hyperphagia being a hallmark feature of PWS, the relationship of hyperphagia to other
29	clinical and behavioral symptoms of PWS is complex. Even young children with PWS are at risk of
30	cardiovascular sequelae of obesity, including obstructive sleep apnea, type 2 diabetes, pulmonary
31	issues, and hypertension (Bellis et al., 2022; Butler et al., 2016). However, although unrestrained
32	hyperphagia contributes to obesity in PWS, it may not be the sole cause, particularly in young children.
33	There are also biological factors associated with the syndrome that may cause or worsen weight gain,
34	including reduced resting energy expenditure and the potential side effects of psychiatric medications
35	(Butler et al., 2007, 2016; Kotler et al., 2016). Longitudinal observational studies have shown that
36	children with PWS begin to gain weight in early childhood without significant increase in calories and
37	before the onset of hyperphagia (Miller et al., 2011). Additionally, the relationship between hyperphagia
38	and challenging behaviors in PWS is not well-understood. While hyperphagia is the presumed driver of
39	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).

45 This lack of specificity about the role of hyperphagia in clinical and behavioral profiles of PWS is 46 further complicated by an incomplete understanding of how and when hyperphagia emerges in 47 childhood. Hyperphagia and weight gain in PWS are now widely characterized by a model of five 48 "nutritional phases," in which hyperphagia and food-seeking behaviors emerge and intensify in "Phase 49 3" at around age 8 (Butler et al., 2016; Cassidy et al., 2012; Miller et al., 2011). However, some 50 researchers have reported varied phenotypic profiles that do not fit neatly into this model. Researchers 51 from one clinic who had difficulty assigning their patients to nutritional phases using information in 52 clinical records stated that the transition to hyperphagia between birth and Phase 3 is "a continuum 53 without explicit criteria of where to draw lines between phases" (Kotler et al., 2016, pg 3). They further 54 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 55 56 (Kotler et al., 2016). Thus, even in a syndrome characterized by development of hyperphagia, there is a 57 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

64 behaviors have been reported across multiple NGCs; for example, sensory sensitivity, rigidity, and/or 65 obsessiveness, which can manifest as food selectivity (Bozzini et al., 2019; Zickgraf et al., 2020), are 66 common in PWS, FXS, and Williams syndrome (WS) (Aguilar et al., 2020; Huston et al., 2021; Kotler et al., 67 2016; Raspa et al., 2010). In addition, many NGCs have a high prevalence of symptoms or comorbid 68 diagnoses of autism spectrum disorder (ASD) (Dykens et al., 2011; Richards et al., 2015), which is 69 associated with both food-related and non-food related challenging behaviors and increased prevalence 70 of overweight and obesity (Cermak et al., 2010; Flygare Wallén et al., 2018; Hill et al., 2015). These 71 shared phenotypic features may relate more broadly to co-occurring ID, which is common in many of 72 the same NGCs with higher prevalence of ASD (Hodapp & Dykens, 2007; Richards et al., 2015) and is 73 independently associated with higher rates of disordered eating (Flygare Wallén et al., 2018; 74 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

88	7q11.23 that results in symptoms such as cardiovascular disease and a behavioral profile that includes
89	hypersociability (Kozel et al., 2021). While genetically and phenotypically distinct, PWS, AS, and WS
90	share core features such as ID and elevated behavioral symptoms related to anxiety, attention, and ASD
91	(Neo & Tonnsen, 2019). Contrasting these NGCs enables us to identify any hyperphagic symptoms that
92	are specific to one syndrome, versus those shared across NGCs associated with ID or common co-
93	occurring behavioral symptoms. Our research questions (RQ) were as follows:
94	(RQ1) How do hyperphagic symptoms differ in early childhood across NGC groups (PWS, AS, WS)
95	and non-NGC controls?
96	(RQ2) How do hyperphagic symptoms relate to other clinical and developmental features in
97	early childhood?
98	MATERIALS AND METHODS
99	Study Design
100	We conducted a cross-sectional examination of early childhood hyperphagia and other clinical
101	features in 4-8-year-old children with and without an NGC. Data were collected through the [MASKED
102	FOR REVIEW], an ongoing longitudinal caregiver-reported survey study of children with rare NGCs and a
103	comparison group of low-risk controls (LRC). Caregivers enter the study when their child is as young as
104	three months of age and complete surveys with age-appropriate questionnaires at 6-month or 12-
105	month intervals, depending on child age. Starting when their child is 4 years old, caregivers are asked to
106	complete a hyperphagia measure annually.
107	Participants and Recruitment
108	Families for both the NGC and LRC groups were recruited for the longitudinal study nationally
109	through web-based parent support groups, paid web advertisements and social networks. Syndrome-
110	specific research registries were also used to recruit families of children with NGCs. Children were
111	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.

119 From [MASKED], inclusion in this sub-study was limited to subjects who had at least one 120 datapoint for the hyperphagia measure. For subjects with more than one available datapoint, we 121 selected the most recent observation. Subjects of the analyses described herein (N = 99) were part of 122 the LRC group (n = 35) or had one of three NGCs: PWS (n = 17), AS (n = 22), or WS (n = 25). While 123 children with Down syndrome and FXS are part of the longitudinal study, they were not included in this 124 analysis due to insufficient sample sizes in this age range. For those in an NGC group, submitting 125 confirmation of genetic diagnosis was not required to participate in the study; however, the diagnoses 126 of 84% (54/64) of the participants in this sub-study were verified via genetic report (15/17 with PWS; 127 19/22 with AS; 20/25 with WS). Genetic subtypes were reported for a subset of children with PWS (n =128 12 with paternal deletion; n = 5 with maternal UPD) and AS (n = 18 with maternal deletion; n = 2 with 129 *UBE3A* mutation; n = 1 with paternal UPD). 130 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, andfamilies provided written consent for participation.

133 Measures

134 Outcome Measure

135 Hyperphagia Questionnaire (HQ). The HQ (Dykens et al., 2007) is an 11-item caregiver-reported 136 measure that scores three domains of hyperphagia: (1) hyperphagic Behavior (5 items) addresses 137 actions one takes to obtain food; (2) hyperphagic Drive (4 items) describes the degree to which one is 138 focused on food; and (3) hyperphagic Severity (2 items) describes the degree to which thoughts and 139 behaviors associated with food interfere with functioning and daily routines. This three-factor structure 140 (i.e., Behavior, Drive, Severity) has been shown to have good internal consistency in children and adults 141 with PWS in both English and a 10-item Italian translation (Dykens et al., 2007; Licenziati et al, 2022). 142 Items on the HQ are rated on a 5-point scale where 5 indicates the most severe and/or frequent. We 143 analyzed the total raw score and the raw score for each domain of the 11-item English version of the 144 HQ. 145 **Other Clinical and Developmental Measures** 146 Social Communication Questionnaire (SCQ). The SCQ (Rutter et al., 2003) is a caregiver-147 reported 40-item screening tool for ASD that evaluates communication skills and social functioning. We 148 analyzed the total raw score for the SCQ, with higher scores representing more social communication 149 impairment. 150 Social Responsiveness Scale, Second Edition (SRS-2). The SRS-2 (Constantino & Gruber, 2012) is 151 a 65-item caregiver-reported tool for identifying ASD-related social impairment and its severity. We 152 analyzed the total T-score for the SRS-2, where higher scores reflect more autism symptomatology. 153 Sensory Experiences Questionnaire (SEQ). The SEQ (Baranek et al., 2006) is a caregiver-154 reported 105-item questionnaire that measures sensory behaviors and interests among children with 155 ASD and/or developmental disabilities. We analyzed the total raw score for the SEQ. Higher SEQ scores 156 reflect the presence of more sensory features. 157 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

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159 Internalizing and Externalizing behavior scores, where higher scores indicate higher rates and/or severity 160 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 161 162 parents were given CBCL 1.5-5 regardless of their child's age, as this version is most developmentally 163 appropriate for children with NGCs. 164 Vineland Adaptive Behavior Scales – Third Edition (VABS-3). The VABS-3 (Sparrow et al., 2016) 165 is a standardized, semi-structured interview tool that measures caregiver-reported adaptive behavior. 166 Specifically, we included standard scores from the Expressive Communication, Receptive

167 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

169 that encompasses adaptive behavior in the domains of communication, daily living skills, and

170 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.

#### 173 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.

187 To address how hyperphagic symptoms relate to other clinical and developmental features in 188 early childhood (RQ2), multiple linear regression analysis was used to develop and compare a series of 189 fitted models for predicting HQ Total scores from clinical and developmental measures as well as 190 diagnostic status. Prior to conducting the regression analyses, measures of central tendency and 191 variability were computed and reported for the HQ Total score and the clinical and developmental 192 measures. For the LRC group, we ensured that scores on standardized clinical measures (VABS-3, SRS-2) 193 were within normal limits. Then, Spearman's rank-order correlations were computed to examine the 194 relationships between the outcome and the clinical and developmental measures for each group and for 195 the sample overall. Bivariate scatterplots of the outcome versus the clinical measures were also 196 examined.

197 Based on the correlation analysis as well as previous studies that have established associations 198 between hyperphagia and problem behaviors in PWS (Dimitropoulos et al., 2006; Dykens et al., 2007), 199 three clinical and developmental predictors were selected for the stepwise regression analysis: CBCL 200 Externalizing raw score, SEQ Total raw score, and VABS-3 ABC score. We did not include any other clinical 201 or developmental measures to predict HQ Total scores due to concerns about multicollinearity and 202 power. First, a univariate model was fit with CBCL Externalizing raw scores predicting HQ Total scores 203 (Model 1). Then, SEQ Total raw scores and VABS-3 ABC score were added to this initial model in a 204 stepwise fashion (Models 2 and 3, respectively). Then, dummy variables were created for the diagnostic 205 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<sup>2</sup> 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 yhat 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** 

#### 217 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

221 different from the other three groups.

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

223 controls?

#### 224 Group Comparisons of HQ Domain Scores

225 Compared to the LRC group, all NGC groups exhibited significant elevations in both HQ Total and 226 HQ Behavior scores (Figure 1). Additionally, children with AS and WS exhibited significantly elevated HQ 227 Drive scores relative to the LRC group, whereas those with PWS trended towards elevation in this 228 domain (*p* = .05), and children with PWS exhibited significantly elevated HQ Severity. When comparing 229 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.

Item-level analyses of hyperphagic symptoms (Table 2) indicated that, compared to the LRC

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

234 group, children with PWS and AS were significantly elevated for two of the same HQ Behavior items 235 ("Foraging through the trash for food"; "Being clever or fast in obtaining food"); however, only children 236 with PWS were significantly elevated in endorsement of the HQ Behavior item "Trying to steal food". 237 The PWS and AS groups were also significantly elevated for the same HQ Drive item ("Distress when told 238 to stop food-related talk/behavior"). Only the PWS group showed elevated endorsement of the two 239 items that assess HQ Severity ("Time spent talking about food"; "Interference with daily activities from 240 food-related talk or behavior"). Despite elevation in total HQ Behavior and Drive scores relative to the 241 LRC group, the WS group was not significantly elevated in endorsement of any single item when 242 correcting for multiple comparisons. 243 RQ2: How do hyperphagic symptoms relate to other clinical and developmental features in early childhood? 244 245 Table 3 presents descriptive summaries of the clinical and developmental measures for each 246 group. As expected, descriptive analyses revealed atypical clinical features and adaptive behaviors in 247 NGC groups relative to the LRC group with three exceptions: SEQ Total scores (PWS group), CBCL 248 Internalizing scores (PWS and AS groups), and CBCL Externalizing scores (PWS group). 249 Table 4 presents Spearman's correlation coefficients for hyperphagia symptoms and each 250 clinical feature. Across the sample, higher levels of hyperphagia were associated with higher levels of 251 symptoms across all clinical measures (SCQ, SRS-2, CBCL, SEQ) and lower levels of adaptive functioning 252 (VABS-3). These results were partially maintained in the LRC and NGC subgroups. For the LRC group, 253 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 (VABS3). There were no significant associations between hyperphagia symptoms and other clinical and
developmental measures for the AS group.

260 Table 5 presents a series of fitted regression models predicting HQ Total scores from clinical and 261 developmental measures and diagnostic group, with LRC as the reference group. The best fitting model 262 was Model 4, which had the following predictors: CBCL Externalizing raw score, SEQ Total raw score, 263 VABS-3 ABC score, and dummy variables representing the NGC groups. The final model explained 34% of 264 variability in HQ Total Scores. Within this model, HQ scores were significantly predicted by CBCL 265 Externalizing raw score and PWS group status. Post-estimation comparisons between groups indicated 266 that the estimated HQ Total score for the PWS group was also significantly elevated relative to the AS 267 and WS groups, and that there was not a significant difference between estimated HQ Total scores in 268 the AS and WS groups. Figure 2 presents a scatterplot showing HQ Total scores versus CBCL Externalizing 269 raw scores with fitted lines for each diagnostic group.

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#### DISCUSSION

271 Although hyperphagia has been explored among NGC groups in older children (Foerste et al.,

272 2016; Welham et al., 2015), the present study is the first to examine hyperphagic symptoms (e.g.,

273 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.

276 Specificity of hyperphagic symptoms across NGCs

277 Regarding PWS, our findings converge with prior reports of the presence of hyperphagic 278 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. 279 280 (2007) found HQ Drive and Severity positively correlated with CBCL Internalizing and Externalizing 281 behaviors in individuals with PWS of all ages, including a group of 4–10-year-olds. Using different 282 measures, another study found severity of hyperphagia to be positively correlated with displaying more 283 ritualistic non-food behaviors (Dimitropoulos et al., 2006). The strong association we found between 284 VABS-3 Receptive Communication scores and HQ Total scores in these young children is striking and 285 warrants additional exploration.

286 In AS, we found no significant correlations between hyperphagic symptoms and other clinical 287 and developmental features assessed. However, we did find that children with AS showed elevations in 288 HQ Behavior and Drive domains and items compared to controls, overlapping with PWS in endorsement 289 of several symptoms. This work aligns with previous studies that have shown hyperphagic symptoms 290 among a third or more of children with AS (Berry et al., 2005; Bindels-de Heus et al., 2020; Welham et 291 al., 2015). One study that examined food-related behavior among older children (8-14 years) with AS, 292 PWS, and other NGCs using the Food-Related Problems Questionnaire reported similar findings to ours 293 regarding similarities and differences in hyperphagic symptoms between PWS and AS (Welham et al., 294 2015c). Specifically, they found that the AS group scored significantly higher than at least one other NGC 295 group on several domains, and that there were not significant differences between AS and PWS in a 296 negative behavior composite that included "inappropriate negative behavior in response to food 297 restriction" and "eating inedible items". This aligns with our findings about similarities in hyperphagic 298 symptoms that were elevated in PWS and AS in the same HQ Behavior and Drive items (e.g., "Foraging 299 through the trash for food" and "Distress when told to stop food-related talk/behavior"), and adds to 300 growing evidence that hyperphagia may be a prevalent clinical feature for AS.

301 Our findings are particularly interesting regarding WS, in which the presence of hyperphagia has 302 not previously been reported. Relative to children in the LRC group, children with WS were uniquely 303 elevated in the HQ Drive domain, which includes items such as "Distress when told to stop food-related 304 talk/behavior". Our correlation analysis for WS also showed that overall hyperphagic symptoms were 305 associated with higher expressive communication skills. Individuals with WS can be excessively verbal 306 and exhibit repetitive thoughts and behaviors (Huston et al., 2021; Jones et al., 2000). Given the positive 307 correlation between hyperphagic symptoms and expressive communication, it is possible that parental 308 endorsement of HQ items assessing hyperphagic drive are more reflective of a general perseverance on 309 the topic at hand. It is also notable that despite the presence of elevations relative to LRC, we did not 310 assess whether elevations in symptoms are clinically meaningful; studies with larger sample sizes and/or 311 qualitative studies including children with WS are warranted to confirm and expand on these findings. 312 Our regression models further contributed to the specificity of childhood hyperphagia profiles 313 by examining relationships between hyperphagia and three clinical/developmental features: 314 externalizing challenging behavior, sensory behaviors and interests, and overall adaptive functioning. 315 Ultimately, we found that externalizing behavior was the only significant clinical/developmental 316 predictor of hyperphagia. The relationship between challenging behaviors and hyperphagia is intuitive; 317 although lack of satiety underlies hyperphagia, the manifestation of hyperphagia is behavioral, including 318 non-compliance when food or food-related talk is restricted. Although we found elevations in 319 hyperphagia in young children with PWS, AS, and WS compared to controls, only a diagnosis of PWS was 320 predictive of elevations in hyperphagia after controlling for challenging behavior. 321 Limitations 322 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.

328 Another limitation of the present study is that although the three factor HQ measure has been 329 found to have acceptable internal consistency for individuals 3-54 years of age with PWS, other metrics 330 of reliability, such as inter-rater or test-retest reliability, have not been assessed (Dykens et al., 2007; 331 Licenziati et al., 2022). Additionally, since the HQ was specifically designed based on research and 332 clinical programs for individuals with PWS, it may not optimally capture atypical behaviors in other 333 groups. Although the HQ has been used to assess hyperphagia in other syndromes associated with 334 obesity (Foerste et al., 2016; Sherafat-Kazemzadeh et al., 2013; Wang & Shoemaker, 2014), we observed 335 missing item-level data in non-PWS groups only. Out of seven participants with missing data, six lacked 336 the Behavior item that assesses how often the child tries to steal food, where the least frequent answer 337 choice is "a few times a year." Parents may have skipped this item because the available answer choices 338 did not accurately characterize their child (e.g., if the child never tries to steal food). It is also important 339 to consider that individuals with AS often present with more severe cognitive and communication 340 challenges than the other groups studied here. This may have influenced how parents responded to 341 items differently for AS. For example, one AS parent presumably skipped three items that implied verbal 342 communication (e.g., "Time spent talking about food"). For parents of children with AS who endorsed 343 such items, it is unclear how they interpreted them (e.g., if they were considering the child's gestures or 344 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.,

349	2023). Additionally, qualitative studies are needed to further contextualize the hyperphagic phenotypes
350	exhibited by non-PWS comparison groups to inform the development or refinement of measurement
351	tools.
352	Future Directions
353	This study providing preliminary data on the specificity of hyperphagia profiles across NGCs in
354	early childhood is an important step towards identifying predictors of symptoms and outcomes and
355	improving treatment approaches.

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

Characteristic	LRC ( <i>n</i> = 35)	PWS ( <i>n</i> = 17)	AS ( <i>n</i> = 22)	WS ( <i>n</i> = 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) <i>, n</i> (%)	22 (63%)	7 (41%)	12 (55%)	11 (44%)	52 (53%)
Race (White), n (%) $^{\dagger}$	33 (97%)	15 (88%)	20 (95%)	22 (92%)	90 (94%)
Ethnicity (non-Hispanic), $n$ (%) <sup>+</sup>	33 (97%)	15 (88%)	21 (100%)	21 (88%)	90 (94%)
BMI (kg/m²), mean (SD) <sup>+</sup>	16.4 (1.7)	18.8 (2.6) <sup>‡</sup>	16.5 (2.6)	15.7 (2.6) <sup>§</sup>	16.5 (2.4)
Mother's Education, $n (\%)^{\dagger}$					
High school diploma or less	1 (3%)	0 (0%)	1 (5%)	0 (0%)	2 (2%)
Some college/Associate's	2 (6%)	3 (18%)	6 (29%)	3 (14%)	14 (15%)
degree					
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),	124.2 (51.7)	118.9 (72.4)	117.3 (73.1)	137.2 (77.7)	125.7 (63.5)
mean (SD) $^{\dagger}$					

*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%. <sup>†</sup>*n* = 96 for Race and Ethnicity; *n* = 65 for BMI; *n* = 93 for Mother's Education; *n* = 61 for Mean Family Income. <sup>‡</sup>*p* < .05 compared to LRC using Wilcoxon rank sum test. <sup>§</sup>*p* < .05 compared to LRC and PWS using Wilcoxon rank sum test.

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

HQ Items by Domain	PWS $(n = 17)$ vs		AS $(n = 22)$ vs			WS $(n = 25)$ vs			
Scale	7	nc (n = 5.	r <sub>ah</sub>	7	$\frac{1}{7} \qquad p \qquad r_{\perp}$		$7$ n $r_{\rm sh}$		r <sub>ah</sub>
Behavior (total)	3.04	.002	0.54	3.78	<u>ب</u> <.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  $\alpha < 0.05$  level.

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

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

			HQ Total		
Characteristic or Scale	LRC ( <i>n</i> = 35) <sup>†</sup>	PWS ( <i>n</i> = 17) <sup>‡</sup>	AS (n = 22) <sup>§</sup>	WS ( <i>n</i> = 25) <sup>¶</sup>	Overall ( <i>N</i> = 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 <sup>*</sup>	-0.05	0.09	-0.30**
VABS-3 ABC	-0.01	-0.64*	-0.28	0.41	-0.34**

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

*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. <sup>†</sup>VABS-3 data: n = 28. <sup>‡</sup>VABS-3 data: n = 13. <sup>§</sup>VABS-3 data: n = 20. <sup>¶</sup>VABS-3 data: n = 22.

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

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***	<b>4.33</b> <sup>***</sup>	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	β				7.18
Syndrome	se				2.62
	t				2.78**
Angelman	β				1.64
Syndrome	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 <sup>2</sup>		0.2070	0.2080	0.2429	0.3399
F-Statistic (df)		25.32 (1, 97)	12.61 (2, 96)	8.34 (3 <i>,</i> 78)	6.44 (6 <i>,</i> 75)
p of F		<.0001	<.0001	.0001	<.0001

Comparison of Fitted Regression Models Predicting Hyperphagia Questionnaire Total Raw Score

*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 "<sup>‡</sup>" are significantly different than bars labeled with "<sup>†</sup>" within each set of 4 bars

# Figure 2

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

Caption: (none)