Hyperphagia and the Identification of Genetic Variants in Patients With Early-Onset Obesity

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Introduction

- Genetic variants that disrupt key central energy and appetite regulatory signaling pathways, such as the melanocortin-4 receptor (MC4R) pathway, can lead to hyperphagia and early-onset obesity[1]
- Early identification of children with pathogenic (P) or likely pathogenic (LP) variants can allow for tailored care and targeted drug therapy.[2,3] A finding of a variant of uncertain significance (VUS) has been shown to help in reducing stigma and self-blame and advance clinician understanding of obesity-related causes[4-6]
- Fit-for-purpose hyperphagia screening tools can aid in identifying patients with early-onset obesity who should undergo genetic testing[2,3]

Objective

- To assess the ability of novel hyperphagia questionnaires to identify candidates for MC4R pathway–related genetic testing
- To determine the proportion of patients with early-onset obesity who present to pediatric obesity clinics and possess ≥1 of 79 MC4R pathway gene variants

Methods

- Inclusion criteria
  - Had early-onset obesity (body mass index [BMI] ≥97th percentile before the age of 6 years)
  - Were 6 to 26 years of age at study enrollment (6-18 years at POWER enrollment)
- Exclusion criteria
  - Had prior testing for MC4R variants
  - Had causes of secondary obesity (eg, endocrine or neurologic diagnoses; medication-induced weight gain)
- This was a prospective observational study at 3 Pediatric Obesity Weight Evaluation Registry (POWER) sites between November 29, 2022, and May 31, 2024
- Two novel questionnaires were administered
  - The Symptoms of Hyperphagia (SoH) assessed the frequency of hunger-related symptoms in a 24-hour recall period (4 items; range 0-2). If the participant was <12 years of age or unable to self-report, the caregiver version was used (5 items)
  - The Impacts of Hyperphagia (IoH) assessed the extent to which hyperphagia negatively affects the participant's life (6 items; range 0-3). If the participant was <12 years of age or unable to self-report, the caregiver version was used (10 items)
- A stand-alone hyperphagia (self/caregiver reported) question was administered: "Does your child have hard-to-control or excessive hunger?"
- Genetic testing was performed for variants in 79 genes
  - Variant findings were P, LP, or a VUS

- **The prevalence of MC4R VUS was high in children with early-onset obesity**
- **Self-reported hyperphagia was associated with higher scores on the SoH, but the SoH was unable to predict the presence of a genetic variant in this study population with a high prevalence of VUS**

Table 1. Patient Characteristics at Study Enrollment

Characteristic	n (%)
Age group at study enrollment	
6-11 y	93 (46)
12-19 y	111 (54)
Sex	
Male	94 (46)
Female	110 (54)
Race	
White	98 (48)
Black	70 (34)
Other/Mixed	36 (18)
Health insurance	
Private	54 (26)
Public	56 (27)
Self-Pay/None	6 (3)
Not reported/missing	88 (43)
Weight status	
Overweight	2 (1)
Obesity class 1	6 (3)
Severe obesity class 2	59 (29)
Severe obesity class 3	137 (67)
Hyperphagia (self-/caregiver-reported)	
Yes	104 (51)
No	100 (49)

Table 2. Patient Characteristics by Presence of Gene Variant

Characteristic	With any gene, n (%)*	*P*-value
Age group		0.16
6-11 y	65 (70)	
12-19 y	87 (78)	
Sex		0.53
Male	72 (77)	
Female	80 (73)	
Race		0.21
White	68 (69)	
Black	57 (81)	
Other/Mixed	27 (75)	
Health insurance		0.83
Private	38 (70)	
Public	43 (77)	
Self-Pay/None	5 (83)	
Missing	66 (75)	
Weight status		*0.02 (comparing class 2 vs class 3 only)*
Overweight	1 (50)	
Obesity class 1	4 (67)	
Severe obesity class 2	51 (86)	
Severe obesity class 3	96 (70)	
Hyperphagia (self-/caregiver-reported)		0.26
Yes	81 (78)	
No	71 (71)	

*Percentage of patients with versus without ≥1 gene variant.

Results

Study population

- 212 patients enrolled
- 204 had genetic data and were included in the analytic data set
- For demographics, see Table 1

Obesity-related gene variants

- 74.5% (n=152) had ≥1 P, LP, or VUS finding in the 79 genes
- 64 patients had ≥2 variants
- Most variants (92%) were classified as a VUS

Hyperphagia

- Higher scores on SoH and IoH scores were not associated with an MC4R pathway gene variant finding
- 51% (104/204) of patients self-reported having hyperphagia
  - This was 53% (81/152) among patients with ≥1 gene variant
- A positive response on the self-reported hyperphagia question was associated with higher scores on the SoH and IoH questionnaires

Patient phenotypes

The presence of a variant did not vary by age, sex, race, insurance type, or self-reported hyperphagia (Table 2)

Limitations

- The high prevalence of VUS findings limited the understanding of the predictive ability of the SoH questionnaire; therefore, it is unknown if the results would be similar in a population with prevalent LP or P findings

References: 1. Huvenne et al. *Obes Facts*. 2016;9(3):158-173. **2.** Heymsfield et al. *Curr Obes Rep*. 2025;14:13. **3.** Abuzzahab et al. *Obesity (Silver Spring)*. 2025;33:1217-1231. **4.** Ko et al. *Obes Endocrinol*. 2025;1:wjaf001. **5.** Meisel and Wardle. *J Genet Couns*. 2014;23:179-186. **6.** Conrad et al. *J Psychosom Res*. 2009;66:287-295.