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Utility of Genetic Testing in Youth with Early Onset Obesity

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ABSTRACT

Background: Monogenic obesity syndromes are likely underdiagnosed and overall incidence in childhood obesity is poorly defined.

Objectives: 1) Describe genetic variants detected among youth with early onset obesity; 2) Compare clinical features of children with variants in monogenic obesity genes with those without; and 3) Evaluate family experiences with genetic testing for obesity.

Methods: Records of patients with early onset obesity with monogenic obesity testing (Uncovering Rare Obesity Program, Rhythm Pharmaceuticals) between 07/21-06/24 were reviewed. Demographic, weight, and metabolic data were abstracted. A survey was distributed via email to families.

Results: Of 102 children tested, 82 patients had genetic variants, with 43% having more than 1 variant. Most were variants of uncertain significance (VUS) (89%). 16 pathogenic or risk variants were detected; 3 patients had a recognized diagnosis. There was no difference in age of obesity onset, BMI z-score, or clinical features in patients with pathogenic or risk variants compared to those with only VUS or negative testing (all $p>0.05$).

Survey responses reported 41% thought genetic testing helped them understand their child's weight and increased their motivation to implement lifestyle changes in 48%. Nearly all were glad they had genetic testing done.

Conclusions: Monogenic obesity testing for early onset obesity has limited diagnostic yield with current understanding, but families recommend genetic testing be offered. Degree of obesity does not appear to predict pathogenic variants.

Keywords: Monogenic obesity, Genetic testing, Family experience.

INTRODUCTION

Obesity is a chronic disease that affects over 160 million children and adolescents worldwide with significant impacts on morbidity and mortality. The etiology of childhood obesity is complex and multifactorial with influences from socioecological systems, environment, and genetics. It is important to identify and understand the risk factors for each individual patient to provide the most comprehensive approach to management [1-3].

Heritability studies report a range of 40% to 75% genetic influence on individual obesity risk [3-6]. Monogenic obesity syndromes are likely underdiagnosed and overall incidence in childhood obesity is poorly defined, with the most common gene change in melanocortin 4 receptor (MC4R) accounting for 5-7% of early onset obesity alone [7,8]. The suggested criteria for considering a genetic obesity syndrome include early onset severe obesity with BMI>120% of the 95th percentile before the age of 5 years and hyperphagia [2,9]. However, as the obesity epidemic worsens, more young children are fulfilling this first criteria. Hyperphagia is difficult to objectively quantify by caregiver history and symptomatology [10]. Furthermore, while some genetic obesity syndromes present with additional clinical clues such as developmental delay and dysmorphic features, polygenic mutations that contribute to obesity may be more subtle [3,4].

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As recognition of genetic obesity syndromes increases, use of genetic testing for obesity is expanding and providers without specific training in genetics will be required to answer patients' questions and concerns regarding results [11]. Little is known about families' perception of genetic testing for obesity.

In this study, the aims were to 1) describe genetic variants detected among youth with early onset obesity; 2) compare clinical features of children with variants in monogenic obesity genes with those without detected changes; and 3) evaluate patient experiences with genetic testing for obesity.

METHODS

A retrospective chart review was completed of 102 patients with early onset obesity who were seen by an endocrinologist at Cincinnati Children's Hospital Medical Center and had monogenic obesity testing through the Uncovering Rare Obesity Program from July 2021 through June 2024. Rhythm Pharmaceuticals sponsors this program for individuals under 18 years of age with a BMI ≥97th percentile to receive free genetic testing through Prevention Genetics. During the period of study, the panel included 79 genes and the 16p11.2 chromosomal region known to be associated with obesity risk [12] [**Supplement 1**].

The electronic medical record was reviewed and demographic, anthropomorphic, and metabolic lab data were abstracted. Not all patients had laboratory studies completed, especially the youngest children. Given missing data, we could not appropriately analyze laboratory evidence of comorbidities (data not shown). Patients were classified by BMI z-scores from CDC growth charts [13] except if the child was under 2 years of age since no CDC data exists for that population. WHO growth chart z-scores were used for children under 2 years of age [14]. Clinic notes were reviewed for provider documentation of reported eating behaviors characteristic of hyperphagia such as sneaking food, binge eating, tantrums related to eating, or eating to the point of vomiting [10].

Patients' genetic test results were reviewed. Patients were categorized in three groups based on results: 1) negative; 2) variant(s) of unknown significance (VUS); or 3) pathogenic/risk variants. For patients with multiple variants, they were included in the pathogenic/risk group if any such variants existed, while patients with only VUS(s) were categorized in the VUS group. Statistical analysis included Chi-Square or Fisher's exact tests for categorical variables and ANOVA test for continuous variables.

A REDCap survey was distributed via email to family members or patients if they were now ≥18 years old who had monogenic obesity testing through the Uncovering Rare Obesity Program. Surveys were distributed 6 to 36 months after genetic testing was conducted. Surveys were sent to all emails listed in each patient's chart to give all caregivers an opportunity to respond. Survey questions focused on family perception of genetic testing and its impact on their child's weight management [**Supplement 2**].

This study was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center.

RESULTS

During the study period, 102 children had genetic testing for early onset obesity completed through the Uncovering Rare Obesity Program. Characteristics of the study population are shown in **Table 1**. Most children had severe obesity [**Figure 1**]. Almost all children had early onset of obesity prior to 5 years of age (92%), with 44% with onset prior to 2 years of age. No subjects had syndromic findings on physical exam except two children who had known Trisomy 21 prior to testing.

Table 1: Characteristics of the Study Cohort (n=102).

Average Age When Testing Sent	**8.0 ± 4.9 years (Range 0.8-19.7)**
Sex	
Female	60 (59%)
Race	
White	76 (75%)
Black	16 (16%)
Hispanic	2 (2%)
Asian	2 (2%)
Bi-racial (white/black)	6 (6%)
Ethnicity	
Non-Hispanic	95 (93%)
Hispanic	7 (7%)

Figure 1.

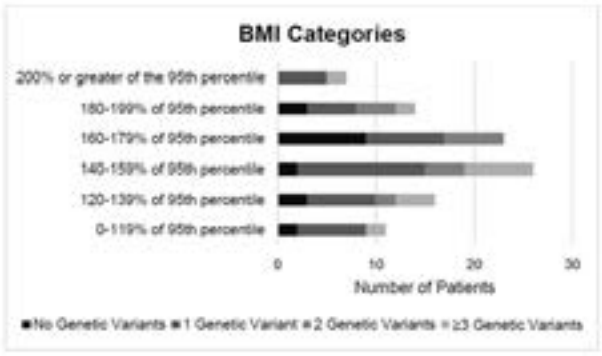

Figure 1: BMI Categories.

20% of patients had negative genetic obesity panels. The number and type of genetic variants detected on patient testing is summarized in **Table 2**, with the majority classified as VUS (89%). Sixteen pathogenic or risk variants were detected [**Table 3**]. Three patients had a confirmed diagnosis by genetic testing, including one GNAS mutation for pseudohypoparathyroidism type 1a and two MC4R deficiency variants. One patient had two deleterious changes: one pathogenic change in BBS10 and a risk variant in PCSK1. Of the 15 patients with pathogenic or risk variants, 6 reported hyperphagia symptoms, 7 had documented developmental delay, and 1 had documented onset of obesity after 5 years of age.

Table 2: Genetic Changes Identified in the Cohort (n=102)

Patients with Any Genetic Change Detected	82
# of Genetic Changes Detected	145
Number of Genetic Changes	
1	47 (57%)
2	17 (21%)
3	10 (12%)
More than 3	8 (10%)

Type of Mutation	
Pathogenic	9 (6%)
Risk	7 (5%)
Variant of Unknown Significance	129 (89%)
Mode of Inheritance	
Autosomal Recessive	81 (56%)
Autosomal Dominant	34 (23%)
X-Linked	3 (2%)
Unknown	27 (19%)
Ciliopathy Gene Mutation	59 (41%)
* Percentages out of 145 total genetic changes	

Table 3: Pathogenic or Risk Mutations Detected

Gene	Inheritance	Clinical Syndrome
GNAS* n=1	AD	Pseudohypoparathyroidism
MC4R* n=2	AD	MC4R Deficiency
Deletion of TRIM32 n=1	Unknown	Bardet-Biedl Syndrome 11 Limb-girdle muscular dystrophy
Deletion of PCNT n=1	Unknown	Microcephalic osteodysplastic primordial dwarfism, type II
RPGRIP1L n=1	AR	Joubert Syndrome
BBS10 n=1	AR	Bardet-Biedl Syndrome 10
BBS1 n=1	AR	Bardet-Biedl Syndrome 1
SDCCAG8 n=1	AR	Bardet-Biedl Syndrome 16 Senior-Loken syndrome-7
PCSK1 c.661A>G n=7	AR	Endocrinopathy due to proprotein convertase 1/3 deficiency
*Confirmed diagnosis AD=Autosomal dominant AR=Autosomal recessive		

There was no difference in BMI z-score or age of obesity onset in patients with pathogenic or risk variants compared to those with only VUS or negative testing, and no correlation between the number of genetic variants and BMI Z-score (all p>0.05). Genetic changes were observed equally in males and females. Almost all patients with pathogenic/risk variants were white (14/15), and 1 was Hispanic. There was no difference in family history of obesity, reported hyperphagia, or developmental delay between groups (all p>0.05).

Clinical characteristics showed no significant differences between patients with no genetic changes, only ciliopathy gene changes, or only non-ciliopathy gene changes. However, patients with only ciliopathy changes trended toward a lower average BMI z-score than those with no changes (3.94 vs. 4.84, p=0.05).

Surveys were sent to all patient families who underwent genetic testing (a total of 161 email addresses). The survey questions are included in Supplement 2. 35 responses were received, but 6 were excluded due to respondents claiming they had not received their genetic test results. The remaining 29 responses were reviewed. Most participants were white (86%) and mothers (93%), with 2 patient responses. 12 reported that their child's genetic test was negative. In review of the actual genetic tests of those 12 patients, 6 were truly negative and 6 tests had VUS. 51% reported that genetic testing helped them understand their child's weight and 48% reported that it increased their motivation to implement healthy lifestyle changes. While overall impact on family's understanding and motivation varied, those who perceived their child to have a negative genetic test were more likely to report that genetic testing was unhelpful (10/12) and did not change family's approach to weight management (8/12). However, 97% were glad they had genetic testing done and 93% would recommend it for families who are concerned about their child's weight. Based on the results of genetic testing, 79% felt like their child would be more likely to benefit from weight loss medications or surgery compared to other children.

DISCUSSION

This study describes the findings of genetic testing sent to evaluate patients with early onset obesity by endocrinology providers from a single children's hospital. Of the 102-youth screened, 80% had a genetic change reported, but most were VUS and only 3 patients had a confirmed diagnosis. Many patients had more than 1 genetic change reported on the panel (43%), but obesity phenotype did not worsen with more changes detected nor with pathogenic/risk variants.

It is difficult to clinically identify which patients may have a genetic change contributing to their obesity since traditional indicators such as severity or earlier onset of obesity do not appear to predict pathogenic variants. In this study, less than half of patients with pathogenic/risk variants reported hyperphagia and 47% had documented developmental delay. With obesity rates in youth continuing to worsen, pediatric providers will increasingly need to evaluate children with early onset weight gain and determine appropriate work-up and management [2]. Given that some children with a monogenic obesity syndrome will not have any other clinically concerning features, it is difficult to discern which patients may have an underlying genetic predisposition for obesity without ordering testing [3]. In addition to diagnostic utility, identifying patients with potential genetic changes will become increasingly important for optimal treatment approach as targeted medications are developed for certain obesity-related pathways, such as setmelanotide for genetic changes in the leptin-melanocortin pathway [15]. One recent study by Berra et al. found that patients with BBS and SEMA variants had less average weight decrease while taking a GLP-1 or GIP/GLP-1 receptor agonists compared to those with negative genetic obesity testing [16]. Despite low diagnostic yield with current understanding, genetic testing is an important part of early onset obesity evaluation and could yield important insights for personalized treatment plans that will maximize benefit to a patient's physiology.

Disruption of primary cilia function is associated with syndromic pediatric obesity, such as Bardet-Biedl and Alström syndromes [17]. In this study, patients with only ciliopathy gene changes surprisingly trended towards a lower BMI compared to patients with no detected genetic changes. This could suggest that VUS chang-

es are common in these genes and may be less likely to clinically impact metabolism with a single gene change. However, larger and more diverse population studies are needed. As more clinical data is gathered, it will allow better insight into how certain gene changes may alter hunger signaling and energy metabolism.

Of note, our study reports a higher percentage of patients with reported pathogenic or risk genetic variants (15%) compared to other published studies that utilized smaller gene panels to evaluate children with early onset obesity. Serra-Juhé et al. reported ~5% (23/463) of subjects had a likely pathogenic variant using a 15 gene panel [18], Loid et al. reported 8% (7/92) had a pathogenic or likely pathogenic variant using a 24 gene panel [19], and Roberts et al. reported 7.7% (9/117) had a risk or pathogenic variant using a 40 gene panel [20]. Additionally, in our study testing was done within the context of clinical care by Endocrinologists compared to a general pediatrics or weight management clinic. We suspect Endocrine Society guidelines [9] were used to determine the need of testing (hyperphagia, neurodevelopmental outcomes) and hypothesize this led to a greater pre-test probability versus testing populations with obesity alone. As more genes are recognized as playing an important role in energy homeostasis, it is likely that we will continue to see increasing pathogenic changes identified on expanded genetic testing, giving providers and families more insight into the pathophysiology of early onset weight gain.

Families perceived genetic testing for obesity as a valuable part of the diagnostic workup for early onset obesity in youth. Almost all respondents of our family survey were glad they received genetic testing for obesity and would recommend it for other families. Patients with obesity commonly experience stigma when seeking care, diminishing patient satisfaction with their healthcare. This perception of judgment can also lead to decreased utilization of healthcare, limit adherence with provider recommendations, and decrease success of weight loss efforts [21,22]. Identifying an underlying cause for weight gain can alleviate the burden of societal and self-blame and shame [23]. Genetic testing can serve as a tool to partner with a patient and family to demonstrate thorough consideration of their concerns and can encourage families towards healthy lifestyle changes. Almost half of our survey respondents reported that genetic testing increased their motivation to make healthy diet and exercise changes, including families with positive and negative results. Since much of obesity management relies on patient adherence to daily healthy diet and physical activity, it is crucial to keep patients engaged and motivated.

Our survey responses suggest that many families did not understand their testing results and several respondents were excluded from analysis due to reporting they were never communicated results. Providers who offer this testing need to appropriately counsel families on the high likelihood of finding a VUS and how genetic information might or might not affect clinical care [24]. However, providers who do not have formal genetics training often report difficulty knowing how to best interpret and communicate genetic testing results to patients, especially with VUS [25]. In 2020, the National Human Genome Research Institute sponsored 6 institutions to develop accessible, sustainable online genomics education for healthcare providers [26]. These are currently being piloted at team institutions, but it is expected that these online learning platforms will be a convenient way for non-genetics providers to increase their knowledge and comfort with genetic testing. If a provider does not feel comfortable interpreting a result, families should be referred to appropriately trained genetic counselors to ensure best communication of results [27,28]. Of note, the Uncovering Rare Obesity program offers free consultation with a genetic counselor for their test results [12].

Further study is needed to characterize VUS and elucidate the impact of multiple genetic changes on metabolism. While a single pathogenic change in an autosomal recessive disease may not lead to a full syndromic phenotype, perhaps it still has a clinically relevant impact on metabolism. Or if multiple changes occur in the same metabolic pathway, perhaps there is a cumulative effect that could lead to a more severe obesity phenotype [29]. Future studies should aim to compare metabolic rate and body composition of patients with variants in monogenic obesity genes to objectively quantify impact on energy homeostasis. Additionally, since comorbidities increase with duration of obesity [30], differences may not be apparent in the pediatric population and longer-term data into adulthood should be followed to determine if genetic changes are associated with differential risk for obesity-related complications.

Limitations of this study include the retrospective study design since patient history and laboratory studies were not obtained or recorded in a standardized way, resulting in some missing data from the electronic medical record. Additionally, results may not be applicable to a larger population given that the study population was relatively small, mostly non-Hispanic white, and from a single medical center. The gene panel reviewed in this study is not comprehensive and therefore negative results may miss changes in untested genes that could contribute to a patient's obesity phenotype. Finally, there was no healthy comparison group with genetic testing in this study, so we are unable to comment if the prevalence of VUS is higher or lower than that of the general population.

CONCLUSION

Monogenic obesity testing for youth with early onset obesity has limited diagnostic yield with most tests returning uncertain results. However, it is difficult to clinically distinguish patients who have a genetic change that could contribute to their obesity and testing is useful to identify those who could benefit from specific treatments. Future utility of genetic testing will likely improve as more is understood about the impact of genetics on energy homeostasis and more targeted therapies are developed. Families perceive genetic testing as valuable and testing could improve patient satisfaction with healthcare delivery and motivation for healthy lifestyle change. Further study is needed to determine if a single pathogenic variant in an autosomal recessive gene or if variants in multiple obesogenic genes could impact metabolism and obesity risk.

CONFLICT OF INTEREST DISCLOSURES

The other authors have no conflicts of interest to disclose.

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Drs. Chelsea Murphy, Amy Shah, and Nancy Crimmins conceptualized and designed the study, drafted the initial manuscript, and critically reviewed and revised the manuscript.

Dr. Chelsea Murphy designed the designed the survey, data collection instruments, collected data, carried out the initial analyses.

Dr. Katherine Bowers completed final statistical analysis.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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