ORIGINAL ARTICLE

Obesity Science and Practice **WILEY**

Prevalence of genetic causes of obesity in clinical practice

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Abstract

Background: While obesity is common in the United States, monogenic obesity is
rare, accounting for approximately 5% of individuals with obesity. New targeted
therapies for genetic forms of obesity are available but there is limited guidance on
who requires testing. The aims of this study were to evaluate the prevalence of
potentially clinically significant variants among individuals in Pediatric Endocri-
nology or Medical Weight Center clinics at a single center and to identify clinical
characteristics that may make genetic obesity more likely.

Methods: Children and adults who had a genetic test for obesity, Uncovering Rare
Obesity Gene panel, ordered during routine clinic visits from December 2019 to
March 2021 were identified.

Results: Of the 139 patients with testing ordered, 117 had available results and
clinical data. Over 40% (52/117, 44%) had at least one positive result (variant) with
a variant that is considered pathogenic, likely pathogenic, or a variant of uncertain
significance. No association was detected between age, sex, race, and body mass
index (BMI) or BMI z-score with a variant. Twenty-six individuals (22%) had one or
more variants in genes associated with Bardet Biedl Syndrome, and 8 (6.8%) of them
had pathogenic variants, higher than expected.

Conclusion: Overall, clinical suspicion for genetic obesity is important in determining
who requires genetic testing but no clinical factors were found to predict results.
While obesity is multifactorial, novel medications for genetic forms of obesity indicate
the need for evidence-based guidelines for who requires genetic testing for obesity.

KEYWORDS
body mass index, genetic testing, genetics, obesity, pediatric obesity

1 | INTRODUCTION

Obesity is a common health problem in the United States, affecting
19.3% of children and 42.5% of adults.[1,2] Genetic, epigenetic, and
environmental factors all impact the risk of obesity, and it can be
difficult to identify individuals with genetic obesity syndromes.
Monogenic obesity is rare, accounting for approximately 5% of in-
dividuals with obesity.[3,4] There is significant interest in genetic var-
iants that increase risk of obesity throughout the lifetime[5,6] and
understanding the etiology of a patient's obesity may help clinicians

treat the condition.[7] For example, while exceedingly rare, leptin deficiency can be effectively managed by recombinant human leptin.[8] Additionally, the alpha-melanocyte stimulating hormone (α-MSH) analog setmelanotide was approved by the Food and Drug Administration (FDA) in 2020 for the treatment of obesity due to pathogenic variants (including pathogenic variants, likely pathogenic variants, and variants of uncertain significance) in the genes *LEPR*, *PCSK1* and *POMC* and was approved in 2022 for use in Bardet-Biedl Syndrome (BBS).[9,10] Studies are underway to utilize this medication in other genetic forms of obesity. The emergence of targeted therapies for genetic obesity syndromes highlights the need for expanded genetic testing.

Monogenic forms of obesity may be associated with homozygous (e.g., *LEP*, *LEPR*) or heterozygous (e.g., *BDNF*) variants.[11] Melanocortin 4 receptor (MC4R) deficiency, is the most common cause of monogenic obesity and has co-dominant expression with an obesity phenotype in individuals who are homozygous or heterozygous for a variant in MC4R.[12,13] On the other hand, some syndromic forms of obesity, such as BBS, are thought to have no disease-specific phenotype in individuals who are heterozygous, but there is conflicting available evidence regarding obesity in carriers of BBS variants.[14–16]

The current Endocrine Society guidelines for pediatric obesity recommend genetic testing for patients with onset of obesity prior to 5 years of age with clinical features of genetic obesity syndromes such as neurodevelopmental abnormalities and severe hyperphagia and/or a family history of extreme obesity.[17] The Endocrine Society clinical practice guidelines for management of adult obesity recommend identification of contributing factors such as genetics but there is no guidance on when to pursue genetic testing.[18] In clinical practice, it may be challenging to ascertain a history of early-onset obesity as most patients evaluated in adult clinics, and many in pediatric clinics, do not have body mass index (BMI) data available from early childhood. It is also not clear that an obesity onset cutoff of 5 years old is ideal; the Genetics of Obesity Study used a cutoff of 10 years old and found >5% of patients had clinically significant variants in the *MC4R* gene alone.[19] A recent study completed genetic testing for obesity in children over 2 years old with a BMI over 1.4 times the 95th percentile and adults with a BMI over 40 kg/m^2, both with hyperphagia, and found that 6.2% carried at least one loss of function variant (either from published literature or computationally predicted) in *POMC*, *PCSK1*, or *LEPR*.[20] On review of the literature there were two studies, both in children, where the prevalence of genetic forms of obesity was evaluated. One study of 282 children in a Dutch obesity center found 19% of the cohort had known pathogenic variants, likely pathogenic variants, or VUS that potentially explained the phenotype.[21] Another study, of 117 children in a pediatric weight management clinic, found 61.5% had at least one variant, many of which were of uncertain significance.[22] Differences in genetic testing platforms, location and demographic patterns, and referral patterns to weight management clinics, indicate the need for further understanding of the prevalence of these genetic changes. The authors are not aware of prior reports of genetic testing for obesity in the clinical setting that includes adults in addition to children.

In the authors' experience, barriers to genetic testing for obesity include provider awareness, time required to complete genetic testing paperwork and insurance coverage. A free obesity genetic testing program launched in late 2019 and was quickly utilized by pediatric endocrinologists, weight management clinics, and others managing obesity. A retrospective chart review was completed in order to evaluate the results of obesity genetic testing in routine clinical practice at a tertiary medical center. The aims of this study were to evaluate the prevalence of potentially clinically significant variants and to identify clinical characteristics that differentiate between genetic and multifactorial obesity. The hypothesis was that clinical characteristics, specifically younger age and higher BMI, would be associated with increased risk for genetic forms of obesity.

2 ⎸ MATERIALS AND METHODS

Patients in the Division of Pediatric Endocrinology at Vanderbilt University Medical Center (VUMC) or the Medical Weight Center at VUMC and had the genetic testing for obesity, Uncovering Rare Obesity Gene Panel (UROG) ordered between December 2019 and March 2021, were identified. This genetic panel includes 40 genes. Genes tested (2019 through March 2021) include *ADCY3, ALMS1, ARL6, BBIP1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BDNF, C8orf37, CEP290, CPE, GNAS, IFT172, IFT27, IFT74, KSR2, LEP, LEPR, LZTFL1, MC3R, MC4R, MKKS, MKS1, NCOA1, NTRK2, PCSK1, PHF6, POMC, RAI1, SDCCAG8, SH2B1, SIM1, TRIM32, TTC8, WDPCP*.

Providers were educated on the need for genetic testing, particularly in individuals with early-onset obesity, the comorbidities that increase the risk of genetic forms of obesity (e.g., hyperphagia, family history, developmental delay), and the availability of the UROG panel. No guidelines were created to indicate precisely which patients should have the UROG panel ordered. Providers were not told that this genetic testing would be retrospectively evaluated.

UROG does not detect uniparental disomy or imprinting defects, and therefore will not detect Prader-Willi Syndrome.[23] Patients are eligible for this free testing program if they are 2–18 years of age with a BMI of ≥97th percentile, or 19 years of age or older with a BMI of ≥40 and a history of childhood obesity.[23] Results were considered positive variants if the variant had a classification of pathogenic, likely pathogenic, or variant of uncertain significance (VUS) based on Human Genome Variation Society Category (HGVS).[24] For this analysis, benign or likely benign variants by HGVS were considered negative results. This categorization is based on the initial FDA approval for setmelanotide which includes pathogenic variants (including pathogenic variants, likely pathogenic variants, and variants of uncertain significance) in the genes *LEPR*, *PCSK1* and *POMC*.[25] Throughout this study, pathogenic, likely pathogenic, and VUS variants were included as "positive" variants due to the FDA categorization for setmelanotide.[25]

A chart review was completed for eligible patients. A REDCap database was built using the Clinical Data Interoperability Services (CDIS).[26] This allowed us to import data directly from the EPIC Electronic Medical Record (EMR) system into the REDCap database. Using CDIS: demographics (date of birth, gender, race, ethnicity), problem list, medications, and vital signs (body height, body weight, systolic blood pressure, diastolic blood pressure) were important. The problem lists were reviewed based on ICD-10 diagnoses. Diagnoses associated with BBS, including vision concerns, developmental delay, autism spectrum disorder, seizures, and congenital heart diseases were manually assessed based on CDIS import of problem list. Genetic test results were manually reviewed.

For the primary analysis, the most recent height and weight from the EMR data extraction were used. BMI was computed in kg/m^2, and age was computed from date of weight minus date of birth. To calculate age and gender adjusted BMI z-scores, based on CDC 2000, individuals who were under 2 years old were considered 2 years and adults were considered as 20 years old. To calculate the percent of the 95th percentile BMI for children under 18 years old, based on CDC 2000, individuals who were under 2 years were considered 2 years. For individuals with BMI <25 kg/m^2 or with missing or implausible BMI values, the EMR was manually reviewed. Wilcoxon rank sum tests were used to compare continuous variables and chi squared tests were used to compare categorical variables between groups. Candidate risk factors for the presence of a variant including age, sex, race, and BMI or BMI z-score were evaluated using multivariable logistic regression analysis. All primary statistics were performed in Stata, version 16.1 (StataCorp LLC). A two-sided p-value <0.05 was considered significant. Longitudinal analyses visualizing impact of height, weight, or BMI over time were evaluated for individuals with multiple measurements and were performed in R version 3.6.3. This study was performed under an approved Institutional Review Board protocol from VUMC.

3 | RESULTS

3.1 | Cohort characteristics

Of the 139 patients in who had UROG testing ordered between December 2019 and March 2021, 118 had results available. As tests are often done on home buccal swabs, not all individuals who had the testing ordered ultimately sent samples for analysis. One individual had a restricted EMR chart and thus 117 participants were included. These individuals were majority female ($n = 77$, 66%). Of note, in this same time frame, 77% (3689 of 4796) of patients in the primary Medical Weight Loss Center at VUMC were female. In the overall cohort, individuals had a median age of 15.2 years (IQR 9.8–19.0, range 1–67.7) and 82/117 (70%) were under 18 years old. Based on EMR data report, individuals' race was reported as white ($n = 75$), black ($n = 20$), or other or unknown ($n = 22$). The median BMI, based on most recent height and weight, was 41.7 kg/m^2 (IQR 34.2–49.6) and BMI z-score was 2.68 (IQR 2.38–2.93). Forty-four percent (52/117) of patients had at least one variant (including pathogenic, likely pathogenic, and VUS variants). In total, there were 85 pathogenic, likely pathogenic or VUS genetic variants reported in 52 individuals. There were no differences, by Wilcoxon Rank Sum test for continuous variables or Pearson Chi-square test for categorical variables, between these characteristics in individuals with and without variants (Table 1).

3.2 | Factors that increase risk of positive genetic test

Risk factors for having a variant, including age, sex, race, and BMI, were evaluated, using multivariable logistic regression. None of these parameters significantly increased the risk of having a variant in this

TABLE 1 Characteristics of study participants.

Characteristic	Overall cohort (n = 117)	Individuals with negative genetic testing (n = 65)	Individuals with any variant (n = 52)
Age (year) median (IQR)	15.2 (9.8–19.0) Range: 1–67.7 70% <18 years	15.3 (10.3–18.1)	14.8 (8.9–28.0)
Sex (n, %female)	77 (66%)	47 (72%)	30 (58%)
Race (n, %)	White: 75 (64%) Black: 20 (17%) Unknown/other: 22 (19%)	White: 43 (66%) Black: 11 (17%) Unknown/other: 11 (17%)	White: 32 (62%) Black: 9 (17%) Unknown/other: 11 (21%)
BMI (kg/m^2) median (IQR)	41.7 (34.2–49.6)	41.3 (34.4–49.5)	42.0 (34.1–51.9)
BMI z-score	2.68 (2.38–2.93)	2.62 (2.33–2.92)	2.73 (2.45–3.11)

Note: Variants include results that are pathologic, potentially pathologic, or variants of uncertain significance based on Human Genome Variation Society Category. Descriptive data are presented as median (IQR) for continuous variables and percentage (n) for categorical variables. BMI z-scores were generated based on CDC 2000 values. Individuals less than 2 years were considered as 2 years old and adults were considered as 20 years old to create BMI z-score.

cohort. Similarly, when age, sex, race, and BMI Z-score, instead of BMI, was evaluated, there was no detectable increased risk of having a variant (Table 2). There was a trend toward increased age associating with increased risk of a variant ($p = 0.051$) though BMI z-score is only validated in ages 2–20 years, making this difficult to interpret.

3.3 | Factors that increase risk of positive genetic test in children and adults

Adults age 18 years and older ($n = 35$, %female = 89%, 51.4% with variant) and children ($n = 82$, %female = 56%, 51.5% with variant) were analyzed separately using BMI for adults and BMI z-score for children. Adults had no increased risk of having a variant based on BMI ($p = 0.6$) in univariate analysis. Children had a trend toward an increased risk of a variant with increasing BMI z-score (Wilcoxon rank-sum $p = 0.07$). Those with a negative genetic test had a median BMI z-score 2.7 (IQR: 2.5, 3.0; $n = 48$) and those with a variant had a median BMI z-score 2.8 (IQR 2.7, 3.3; $n = 34$). When adjusted for age, gender, and race this trend was no longer noted, though the sample size is small when separating the cohort into adults and children separately. Evaluating BMI instead by the percent of the 95th percentile, individuals with negative genetic tests had a median of 155% of the 95th%tile (IQR 139, 183, $n = 48$) and those with a variant had a median of 164% of the 95th%tile (IQR 146,181, $n = 34$), which was not different ($p = 0.3$). In pediatrics, either BMI Z-score or BMI percent of the 95th%tile can be utilized to classify body mass more accurately than BMI alone.[27]

3.4 | Genetic variants

Of the 85 variants, there were 33 variants in 26 individuals (22% of cohort) in genes associated with BBS (Figure 1 and Table 3).[14] On review of the participants' problem list, assessing for diagnoses associated with BBS, individuals with BBS related variants had no

vision concerns noted. One of 26 individuals had developmental delay reported (compared to 6/117 with developmental delay or autism spectrum disorder in the overall group) and one of 26 had seizures (compared to 4/117). Finally, one individual with a single BBS variant had congenital heart disease and dextrocardia documented (compared to 0/117). When evaluating for mutations in POMC, PCSK1, or LEPR, seven individuals had pathologic variants, potential pathologic variants, or VUS (6%).

3.5 | Longitudinal assessment of BMI

Longitudinal height, weight, and BMI data was plotted in individuals with multiple data points available to determine if any pattern arose that indicated a specific pattern was more likely to indicate a variant. No patterns or differences in individuals with and without variants emerged based on the available data (Figure S1).

4 | DISCUSSION

In clinical practice, over 40% of patients had at least one genetic variant in a gene associated with obesity (52/117; 44%) including only variants that were pathologic, potentially pathologic, or VUS. Clinical testing was obtained based on provider perspective, following brief education on the need for and availability of genetic testing, without clear guidelines. When evaluating for mutations in POMC, PCSK1, or LEPR, 7 (6%) had variants. This is similar to a prior study by the authors that found 6.2% of individuals had at least one loss of function variant (either from literature or computationally predicted) in these three genes.[20]

Prior studies, with standardized diagnostic approaches, have also attempted to estimate the prevalence of genetic forms of obesity.[21,22] One such study of 282 children in a Dutch obesity center, found 13% had genetic obesity disorders (including known pathogenic variants and likely pathogenic variants where there was

TABLE 2 Multivariable logistic regression assessing factors associated with a variant on genetic testing.

Characteristic	Likelihood of any variant based on age, sex, race, BMI OR (95% CI; p-value)	Likelihood of any variant on age, sex, race, BMI z-score OR (95% CI; p-value)
Age (years)	1.02 (0.98–1.05; 0.31)	1.03 (1.00–1.06; 0.051)
Sex (vs. ref = male)	0.48 (0.21–1.11; 0.086)	0.67 (0.27–1.68; 0.39)
Race (vs. ref: white)		
Black	1.17 (0.41–3.32; 0.77)	1.34 (0.48–3.73; 0.57)
Other/unknown	1.23 (0.45–3.36; 0.68)	1.28 (0.46–3.57; 0.64)
BMI	1.01 (0.97–1.05; 0.68)	—
BMI z-score	—	2.01 (0.92–4.39; 0.082)

Note: Multivariable logistic regression assessing factors associated with a variant on genetic testing. Tested factors include age, sex, race and BMI or BMI z-score.
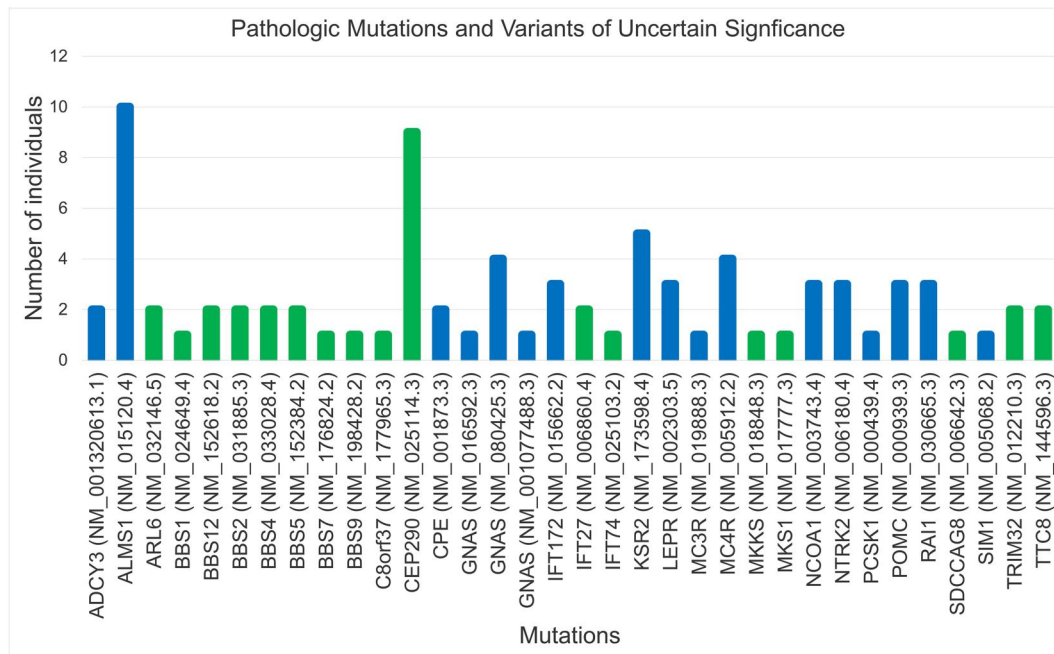
Abbreviation: BMI, body mass index.

FIGURE 1 Genetic variants reported. Genetic tests results that indicated pathologic mutations, potentially pathologic mutations, or variants of uncertain significance based on Human Genome Variation Society Category (HGVS) interpretation. Mutations in green, when homozygous and pathogenic, are implicated in BBS. Mutations in blue are not related to BBS. BBS, Bardet-Biedl Syndrome.

phenotype-genotype correlation).[21] An additional 17 patients (6%) had VUS that potentially explained the phenotype but these individuals were not included in the primary analysis.[21] Features of genetic obesity in their population included early onset (<5 years) and hyperphagia (in individuals without intellectual disability).[21] Similar to this data presented from VUMC, BMI SDS was not significantly associated with genetic obesity.[21] On the other hand, a population of 117 individuals in a pediatric weight management clinic (51.3% male, 53.8% Hispanic) had 72 individuals (61.5%) with at least one variant and 39 (33.3%) had a BBS variant.[22] This study similarly included pathogenic, likely pathogenic, and VUS as variants.[22] The high prevalence found in both this recently published study and the population at VUMC indicate the clear need for additional research into genetic testing in the clinical practice.[22] Both of these recent studies include only children.[21,22] It is critical to consider genetic testing in adults as well as 18/35 adults (51.4%) of adults in this population had at least one variant.

Additionally, 22% (26/117) of individuals had at least one variant in a gene that is associated with BBS. Of these, 8 (6.8% of the cohort or 1/15) were pathogenic variants. This is higher than the expected carrier frequency (of pathogenic variants) in the population of 1/250–1/2200.[28] This cohort was limited by small sample size and retrospective chart review and therefore it was difficult to adequately determine if individuals with BBS gene variants had other features of BBS. At most, only 10 participants had a variant in each gene, making it challenging to evaluate specific variants. In the future, characterizing the phenotype of BBS genetic carriers, and carriers of other forms of monogenic obesity syndrome associated genes, will be critical to better appreciate polygenic risk for obesity, as currently

there is mixed data regarding the risk of obesity in carriers.[15] An understanding of the role of these genes is necessary to guide future management strategies. For example, a novel MC4r agonist, setmelanotide, was recently approved for use in BBS.[10] In the authors' opinion, future studies are needed to evaluate the use of this medication in individuals who have obesity and are heterozygous for a variant implicated in BBS.

While clinical suspicion for genetic obesity is clearly important, there were no detectable patterns that emerged in either cross-sectional or longitudinal analysis that indicated a specific parameter would be helpful in determining who requires genetic testing. A trend toward significance of BMI z-score was noted in the pediatric population and this should be re-evaluated in future studies. One would hypothesize that individuals with higher BMI would be more likely to have genetic variants, but this was not clearly demonstrated in this study.

Limitations to this study include the small sample size, single center cohort, and retrospective data. Longitudinal data was missing in many individuals and the validity of all height and weight measurements at each time point are challenging to confirm. Another limitation, inherent to the genetic testing, is that many genetic results are VUS and it is unknown which of these genetic changes will ultimately be clinically meaningful. Finally, the use of BMI z-score has limitations as this study primarily used a combination of pediatric and adult populations, due to cohort size, and therefore included adult BMI z-scores indexed to an individual who is 20 years old. The phenotyping of individuals with BBS variants was limited by availability of clinical data from patients' problem lists and the small sample size. This is a first step in evaluating the clinical utility of

TABLE 3 Evaluation of pathogenicity of BBS mutations reported.

Gene transcript	DNA variation	Predicted effects	ClinVar ID	Highest allele freq.	Ethnicity of allele freq.	In silico missense predictions	HGVS category
BBS2 (NM_031885.3)	c.1864C>T	p.Arg622*	284737	0.0063	European (non-Finnish)	Not applicable	Pathogenic
TRIM32 (NM_012210.3)	c.134G>A	p.Arg45His	None	0.0065	African	Damaging	VUS
SDCCAG8 (NM_006642.3)	c.1375T>C	p.Tyr459His	940955	0.0018	European (non-Finnish)	Conflicting	VUS
CEP290 (NM_025114.3)	c.942+3del	Intronic	None	Not present	n/a	Not applicable	VUS
CEP290 (NM_025114.3)	c.4962_4963del	p.Glu1656 Asnfs*3	572652	0.0093	Eastern Asian	Not applicable	Pathogenic
BBS2 (NM_031885.3)	c.1527+5G>C	Intronic	972444	0.012	Latino	Not applicable	VUS
CEP290 (NM_025114.3)	c.5813_5817del	p.Thr1938 Asnfs*16	99861	0.0031	Latino	Not applicable	Pathogenic
BBS12 (NM_152618.2)	c.1281A>G	p.Ile427Met	None	Not present	n/a	Tolerated	VUS
TTC8 (NM_144596.3)	c.1327C>T	p.Arg 443Trp	531831	0.18	European (Finnish)	Conflicting	VUS
BBS1 (NM_024649.4)	c.1169T>G	p.Met 390Arg	12143	0.27	European (non-Finnish)	Conflicting	Pathogenic
BBS4 (NM_033028.4)	c.1063G>C	p.Glu 355Gln	rs14784 48702	0.0009	European (non-Finnish)	Conflicting	VUS
BBS7 (NM_176824.2)	c.712_715del	p.Arg238 gluis*59	281526	0.011	European (non-Finnish)	Not applicable	Pathogenic
TRIM32 (NM_012.210.3)	c.125C>T	p.Thr42Ile	None	Not present	n/a	Damaging	VUS
CEP290 (NM_025114.3)	c.7220_7223del	p.Lys2407 Serfs*2	418123	0.012	Latino	Not applicable	Pathogenic
CEP290 (NM_025114.3)	c.4555A>T	p.Ile 1519Leu	241584	0.027	European (non-Finnish)	Conflicting	VUS
IFT74 (NM_025103.2)	c.106C>T	p.Arg36*	None	0.0079	European (non-Finnish)	Not applicable	VUS
ARL6 (NM_032146.5)	c.529C>T	p.Leu177 Phe	None	0.021	Latino	Conflicting	VUS
BBS5 (NM_152384.2)	c.110T>C	p.Ile 37Thr	None	0.0065	African	Conflicting	VUS
BBS5 (NM_152384.2)	c.110T>C	p.Ile 37Thr	None	0.0065	African	Conflicting	VUS
ARL6 (NM_032146.5)	c.529C>T	p.Leu 177Phe	None	0.021	Latino	Conflicting	VUS
TTC8 (NM_144596.3)	c.264+2826G>A	Intronic	None	0.002	European (non-Finnish)	Not applicable	VUS
CEP290 (NM_025114.3)	c.4087C>T	p.Arg 1363Trp	310603	0.94	European (Finnish)	Conflicting	VUS
BBS9 (NM_198428.2)	Duplication of exons 1–2		None	Not present	n/a	Not applicable	VUS
IFT27 (NM_006860.4)	c.319C>T	p.Arg 107Trp	840668	0.18	European (non-Finnish)	Conflicting	VUS
CEP290 (NM_025114.3)	c.523C>A	p.Gln 175Lys	376782	0.026	European (non-Finnish)	Damaging	VUS
BBS4 (NM_033028.4)	c.337C>T	p.Leu 113Phe	846825	0.04	European (Finnish)	Conflicting	VUS
C8orf37 (NM_177965.3)	c.317C>A	p.Pro 106Gln	None	0.00092	European (non-Finnish)	Conflicting	VUS
CEP290 (NM_025114.3)	c.4088G>A	p.Arg 1363Gln	861323	0.035	African	Conflicting	VUS

(Continues)

TABLE 3 (Continued)

Gene transcript	DNA variation	Predicted effects	ClinVar ID	Highest allele freq.	Ethnicity of allele freq.	In silico missense predictions	HGVS category
MKKS (NM_018848.3)	c.1098T>A	p.Asn 366Lys	958862	0.083	African	Conflicting	VUS
BBS12 (NM_152618.2)	c.1092del	p.Glu365 Argfs*18	None	0.00036	European (non-Finnish)	Not applicable	Pathogenic
IFT27 (NM_006860.4)	c.524G>A	p.Arg 175Gln	None	0.016	Eastern Asian	Tolerated	VUS
MKS1 (NM_017777.3)	c.140834_1408-6del	Intronic	188400	0.71	European (Finnish)	Not applicable	Pathogenic
CEP290 (NM_025114.3)	c.2766G>T	p.Leu 922Phe	None	Not present	n/a	Tolerated	VUS

Note: Review of the 33 BBS variants reported and indication of pathogenicity based on genetics report. These 33 variants are from 26 individuals; seven individuals had two variants. All variants reported were heterozygous.

Abbreviations: BBS, Bardet-Biedl syndrome; HGVS, Human Genome Variation Society category; VUS, variant of uncertain significance.

readily available genetic tests for obesity and indicates the need for further assessments, including phenotyping individuals who are carriers for genetic variants associated with BBS or monogenic forms of obesity. Additionally, a future study evaluating the impact of finding these variants, in terms of readiness for change or use of weight loss medications, will further help to delineate the value, and possibly risks, of undertaking this testing in clinical practice.

In conclusion, 44% of patients, in this clinically obtained cohort, had a variant, either pathogenic, likely pathogenic, or a VUS, in clinically obtained genetic testing, in a population of individuals presenting to Pediatric Endocrinology or Medical Weight Center clinics. There were no clear clinical markers that indicated who was more likely to have a variant, beyond clinical suspicion of early-onset obesity. More data is needed to characterize individuals with heterozygous genetic variants associated with monogenic obesity, particularly individuals with genes implicated in BBS. Novel therapeutics are actively being studied and approved for genetic forms of obesity. The use of targeted therapies, and high prevalence of potentially relevant genetic variants in a individuals with obesity, clearly indicate the need for additional studies on who should be undergoing genetic testing and the role different variants play in the risk of obesity. Better understanding the burden of genetic variants associated with polygenic and multifactorial forms of obesity may, in the future, help propel the advent of targeted therapies.

AUTHOR CONTRIBUTIONS

ACKNOWLEDGMENTS

CONFLICT OF INTEREST STATEMENT

Jaclyn Tamaroff, Dylan Williamson, James C. Slaughter and Meng Xu have nothing to disclose. Gitanjali Srivastava has consulted for Rhythm Pharmaceuticals, Novo Nordisk and Eli Lilly. Ashley H. Shoemaker has consulted for Rhythm Pharmaceuticals, Radius Health Inc. and Saniona A/S on studies of obesity and has received research funding from Rhythm Pharmaceuticals, Radius Health Inc., Vivus and Soleno Therapeutics.

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SUPPORTING INFORMATION

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