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Introduction

- Hyperphagia, or pathologic uncontrollable hunger, and early-onset, severe obesity can result from rare genetic variants that disrupt key regulatory pathways of hunger and energy expenditure regardless of environmental factors¹
 - Variants in key genes of the melanocortin-4 receptor (MC4R) pathway, a regulator of energy balance, have been associated with obesity and hyperphagia¹⁻⁴
- The diagnosis of rare genetic diseases may be improved by the expansion of genetic testing, which can allow access to specialized and indicated therapeutic approaches^{1,5-8}
 - Currently, low use of genetic testing may contribute to the underdiagnosis and underreporting of rare genetic causes of obesity^{2,9}
- The goal of the Uncovering Rare Obesity® (URO) program (www.UncoveringRareObesity.com) is to enhance access to genetic testing for individuals with suspected rare genetic causes of obesity in the United States and Canada¹⁰

Objectives

- To investigate the prevalence of gene variants associated with obesity and their relationship to demographic characteristics, obesity, hyperphagia, and family history of genetic disease if earlier testing results are available

Methods

- Eligible consented individuals were tested per physician order for gene variants in a panel of 79 genes and 1 chromosomal region known to be associated with obesity as part of the URO program
- A positive genetic test result was defined as identifying variant(s) classified by the American College of Medical Genetics as pathogenic or likely pathogenic in a manner that is consistent with the mode of inheritance known for causing disease in the respective gene (ie, biallelic variants in a single gene with autosomal recessive inheritance)
- The Phase 3 EMANATE clinical trial (NCT05093634) is assessing the efficacy and safety of the MC4R agonist setmelanotide in patients with obesity due to leptin receptor insufficiency (LEPR heterozygous), proopiomelanocortin insufficiency (POMC or PCSK1 heterozygous), steroid receptor coactivator 1 (SRC1) deficiency, and SH2B adapter protein 1 (SH2B1) deficiency
- Using deidentified data, correlations between detected genetic variants and characteristics of patient obesity, hyperphagia, and family history were assessed using linear regression for continuous variables or chi-square tests for categorical values

Table 1. The Uncovering Rare Obesity® Gene Panel

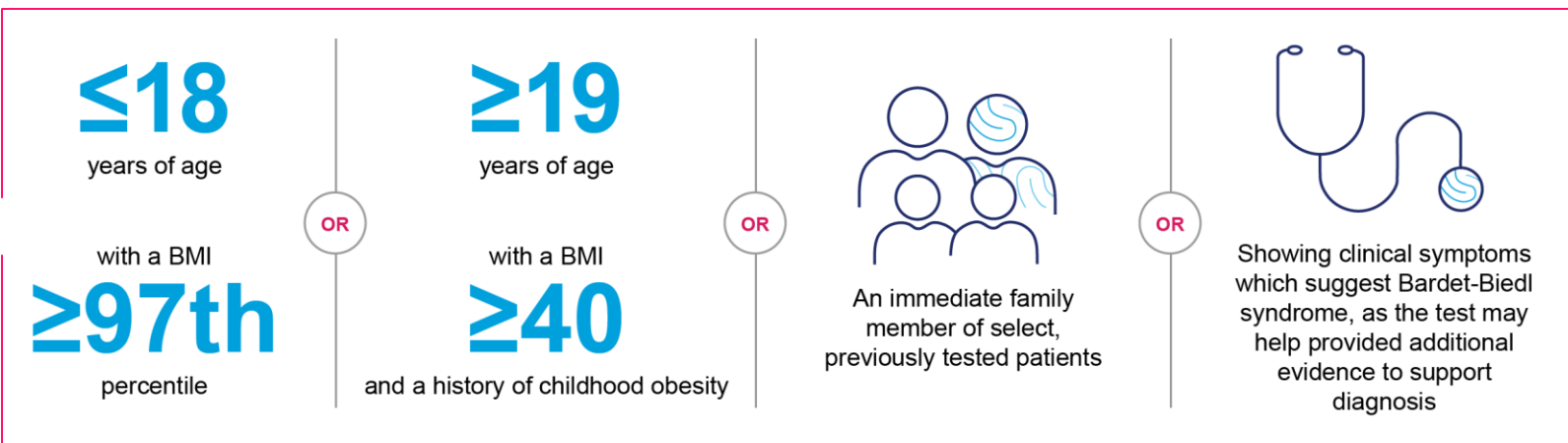
79-gene and 1 chromosomal region panel				
ADCY3	CPE	LEPR	PHF6	SEMA3C
AFF4	CREBBP	LZTFL1 (BBS17)	PHIP	SEMA3D
ALMS1	CUL4B	MAGEL2	PLXNA1	SEMA3E
ARL6 (BBS3)	DNMT3A	MC3R	PLXNA2	SEMA3F
BBIP1 (BBS18)	DYRK1B	MC4R	PLXNA3	SEMA3G
BBS1	EP300	MECP2	PLXNA4	SH2B1
BBS10	GNAS	MKKS (BBS6)	POMC	SIM1
BBS12	HTR2C	MKS1 (BBS13)	PPARG	TBX3
BBS2	IFT172	MRAP2	PROK2	TRIM32 (BBS11)
BBS4	IFT27 (BBS19)	NCOA1 (SRC1)	RAB23	TRPC5
BBS5	IFT74 (BBS20)	NR0B2	RAI1	TTC8 (BBS8)
BBS7	INPP5E	NRP1	RPGRI1L	TUB
BBS9 (PTHb1)	ISL1	NRP2	RPS6KA3	UCP3
BDNF	KIDINS220	NTRK2	SDCCAG8 (BBS16)	VPS13B
C8ORF37 (BBS21)	KSR2	PCNT	SEMA3A	WDPCP (BBS15)
CEP290 (BBS14)	LEP	PCSK1	SEMA3B	16p11.2*

*Assessment for rearrangement of the 16p11.2 chromosomal region.

Design of the URO program

- The URO program gene panel includes 79 genes and 1 chromosomal region of clinical relevance (Table 1)
- Individuals within the United States and Canada were eligible to receive a no-charge genetic test and 2 genetic counseling sessions if they met the eligibility criteria in Figure 1

Figure 1. Eligibility Criteria for the Uncovering Rare Obesity® Program

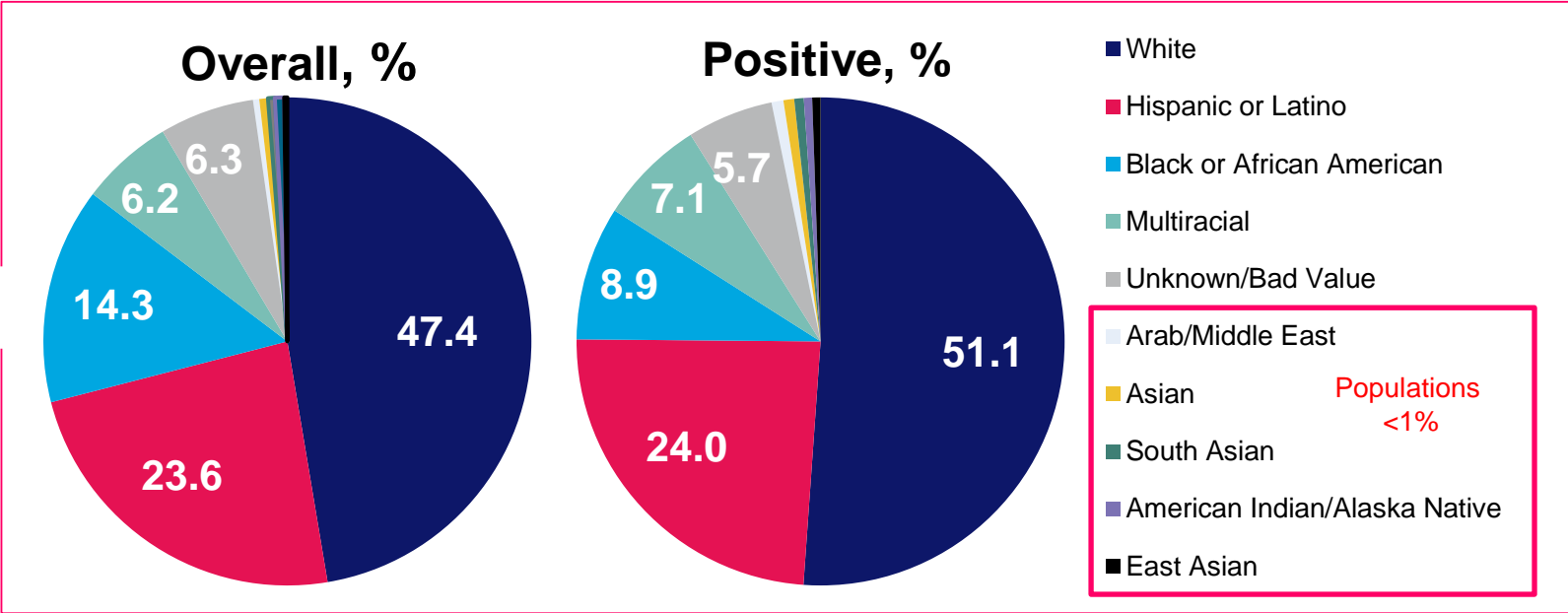


BMI, body mass index.

Results

- At the time of this analysis (June 2024), 43,014 individuals had been tested in the URO program
 - Of these individuals, 30,012 (68%) were aged <18 years and 13,002 (32%) were aged ≥18 years
 - Of individuals aged <18 years who participated in the URO program, 49% were male and 51% were female, and of individuals aged ≥18 years, 25% were male and 75% were female
- Overall, 5% of URO participants had a genotype consistent with genetic eligibility for setmelanotide therapy either through approved indications (obesity due to biallelic variants in POMC, PCSK1, and LEPR and Bardet-Biedl syndrome [BBS]) or carried an EMANATE-eligible genotype
- Fifty-three genes with ≥1 causal variant were detected, the most common of which were variants in MC4R (n=667; 1.6%), and the most common copy number variant was 16p11.2 deletion duplications (n=108; 0.25%)
- The demographics of individuals with a positive result were generally similar to those of all individuals tested, although notably, the proportion of individuals who were Black or African American was lower for positive individuals (Figure 2)

Figure 2. Race Distribution



- BBS genetic variants of pathogenic relevance, particularly BBS1 and BBS10, were most commonly reported in White individuals (Table 2)
 - Notably, BBS10 was not observed in Black or African American individuals and was generally underrepresented in Hispanic or Latino individuals
 - URO pathogenic/likely pathogenic homozygous results (n=51) were found to be enriched in individuals with Hispanic or Latino ethnicity, and this enrichment was found not to be related to geographic location
 - There were an additional 136 cases with biallelic compound heterozygous variants that were of uncertain significance but suspected likely pathogenic or pathogenic
 - Of those 136 indeterminate cases, 5 were biallelic BBS1 and 9 were biallelic BBS10 cases

Table 2. Bardet-Biedl Syndrome Genetic Results of Clinical Relevance

Gene	White	Hispanic or Latino	Black or African American	Asian
BBS1	18	14	1	0
BBS10	10	2	0	0
BBS12	0	6	1	0
BBS2	6	0	1	2
BBS4	0	1	0	0
BBS5	0	1	1	1
BBS7	3	1	0	3
BBS9	1	2	2	0
CEP290 (BBS14)	2	2	1	0
MKKS (BBS6)	1	3	0	0
ARL6 (BBS3)	0	2	0	0

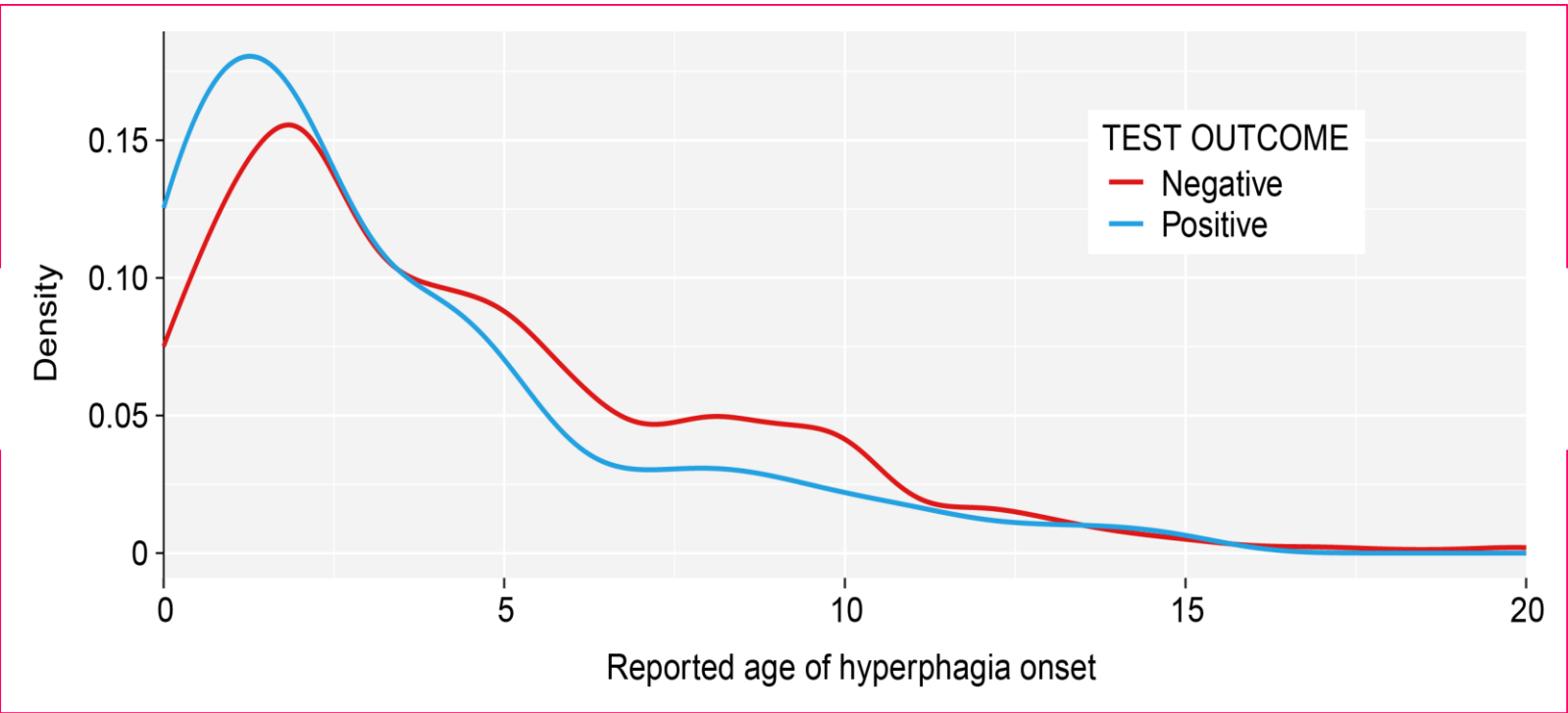
- The mean (standard deviation [SD]) age of onset of obesity in individuals who had a positive genetic test result was significantly lower (3.5 [3.5] years) than in those individuals who tested negative (4.8 [3.9] years; P<0.0001) (Figure 3)

Figure 3. Age of Obesity Onset Over Time



- The proportion of individuals with hyperphagia who tested positive (650/1,132; 57%) was significantly higher than in those who tested negative for a variant of interest (6,786/13,708; 49%) (chi-square 2-tailed P=0.0010)
- The mean (SD) age of onset of hyperphagia in individuals who were reported to have a positive result was significantly lower (3.4 [3.4] years) than in those individuals who tested negative (4.5 [3.9] years; P<0.0001) (Figure 4)

Figure 4. Age of Hyperphagia Onset Over Time



- For individuals who tested positive and were reported to have hyperphagia, when stratified by age, the youngest age category (<3 years old) was found to have the highest positive rate (42/650; 6.5%)
- Positive genetic test results indicating an underlying genetic cause of obesity by age are shown in Table 3

Table 3. Positive Genetic Test Results Indicating an Underlying Genetic Cause of Obesity by Age

	0-<3 y	3-<6 y	6-<11 y	11-<18 y	≥18 y	All ages
ACMG positive, %	5.17	3.79	2.66	2.45	2.11	2.63
EMANATE genotype, %	4.95	5.24	4.55	4.82	4.68	4.76
ACMG & EMANATE combined, %	10.12	9.03	7.21	7.27	6.79	7.39

- Family history of genetic disease was also significantly associated with the likelihood of a positive test result (P<0.0001), with 15.7% of individuals with a positive test result having a family history of genetic disease versus only 5.3% in individuals with no genetic finding

Conclusions

- The URO results in >40,000 individuals continue to demonstrate the importance of genetic testing in the diagnosis of individuals with a genetic cause underlying their obesity
- Clinical characteristics strongly associated with the positive results include earliest onset obesity and hyperphagia, as well as family history of genetic disease
- Even in a cohort selected for early-onset obesity and the presence of hyperphagia, individuals who tested positive according to ACMG criteria had a mean onset over 1 year earlier than those for whom no genetic cause could be found; onset ranged from birth to peaking at 3 years of age
- Results in the BBS genes demonstrate an ancestry-specific distribution of variants including an enrichment of BBS1 homozygous individuals of Hispanic or Latino ancestry
- As of July 2024, the URO program gene panel has been expanded to include 7 additional genes related to BBS and the agouti-signaling (ASIP) gene and continues to be available to eligible individuals

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Disclosures: PS, RN, and JCG, are employees of Rhythm Pharmaceuticals, Inc. and have company-awarded RSU and options. EB was an employee of Rhythm Pharmaceuticals, Inc. at the time of contribution to the study.

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