Variants in Obesity-Related Genes in a Population With Early-Onset Obesity

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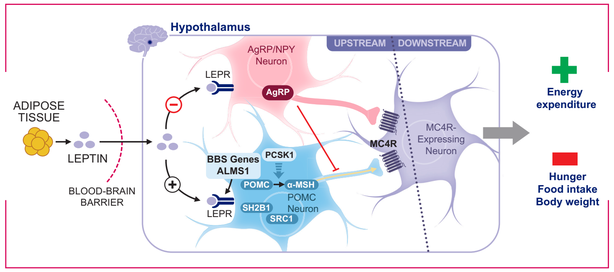
Summary

- **The prevalence of rare genetic diseases of obesity may be underreported given a deficit in genetic testing[1,2]**
- **Individuals with early-onset, severe obesity were evaluated in a US-based cohort of the Uncovering Rare Obesity® genetic testing program; 64.8% of those tested carried potentially clinically relevant variants**
- **The etiology of rare genetic diseases of obesity and subsequently care of individuals within this population may be improved with genetic testing of individuals who have severe obesity[3-7]**

Introduction

- Hyperphagia, or pathological 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 factors[4]
  - Variants in key genes of the melanocortin-4 receptor (MC4R) pathway, a regulator of energy balance, have been associated with obesity and hyperphagia (Figure 1)[2,4,8,9]
- Diagnosis of patients with rare genetic diseases of obesity may be improved by routine genetic testing, allowing for specialized therapeutic approaches and identification of eligibility for clinical trials[3-7]
- Low rates of genetic testing may result in rare genetic diseases of obesity being underdiagnosed in individuals with obesity[1,2]
- The goal of the Uncovering Rare Obesity® testing program (www.UncoveringRareObesity.com) is to enhance access to genetic testing for patients with suspected rare genetic diseases of obesity in the United States[10]

Figure 1. Key components regulating obesity.



AgRP, agouti-related peptide; ALMS1, centrosome and basal body associated protein; BBS, Bardet-Beidl syndrome; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, SH2B adaptor protein 1; SRC1, steroid receptor coactivator 1.

Objective

- To use data from the Uncovering Rare Obesity® program to assess the frequency of select rare variants in individuals with early-onset, severe obesity

Methods

Design of the Uncovering Rare Obesity® program

- The Uncovering Rare Obesity® program began in May 2019 with a panel of 40 genes related to obesity; in July 2021, the panel was expanded to include 79 genes and 1 chromosomal region (Table)
- Individuals within the United States and Canada may be eligible to receive a no-charge genetic test and 2 genetic counseling sessions if they
  - Are ≤18 years of age and have a body mass index ≥97th percentile, or
  - Are ≥19 years of age and have a body mass index ≥40 kg/m^2 with a history of childhood obesity, or
  - Are a relative of someone previously tested, or
  - Show clinical symptoms related to Bardet-Biedl syndrome

Table. Uncovering Rare Obesity® Genetic Panel–Included Genes and Regions

Original 40-gene panel			
ADCY3	*ALMS1*	*ARL6 (BBS3)*	*BBIP1 (BBS18)*
BBS1	*BBS10*	*BBS12*	*BBS2*
BBS4	*BBS5*	*BBS7*	*BBS9 (PTHB1)*
BDNF	*CPE*	*C8ORF37 (BBS21)*	*CEP290 (BBS14)*
GNAS	*IFT172*	*IFT27 (BBS19)*	*IFT74 (BBS20)*
KSR2	*LEP*	*LEPR*	*LZTFL1 (BBS17)*
MC3R	*MC4R*	*MKKS (BBS6)*	*MKS1 (BBS13)*
NCOA1 (SRC1)	*NTRK2*	*PCSK1*	*PHF6*
POMC	*RAI1*	*SDCCAG8 (BBS16)*	*SH2B1*
SIM1	*TRIM32 (BBS11)*	*TTC8 (BBS8)*	*WDPCP (BBS15)*
Genes or region added to expanded panel			
AFF4	*CREBBP*	*CUL4B*	*DNMT3A*
DYRK1B	*EP300*	*HTR2C*	*INPP5E*
ISL1	*KIDINS220*	*MAGEL2*	*MECP2*
MRAP2	*NR0B2*	*NRP1*	*NRP2*
PCNT	*PHIP*	*PLXNA1*	*PLXNA2*
PLXNA3	*PLXNA4*	*PPARG*	*PROK2*
RAB23	*RPGRIP1L*	*RPS6KA3*	*SEMA3A*
SEMA3B	*SEMA3C*	*SEMA3D*	*SEMA3E*
SEMA3F	*SEMA3G*	*TBX3*	*TRPC5*
TUB	*UCP3*	*VPS13B*	16p11.2[a]

[a]Assessment for rearrangement of the 16p11.2 chromosomal region.

- Evaluations of blood or buccal samples submitted for testing are performed by a Clinical Laboratory Improvement Amendments–accredited laboratory

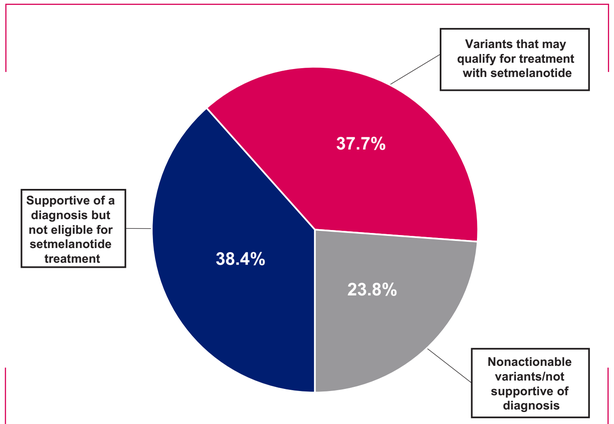
Frequency analysis

- Sequencing results were analyzed from patients who were tested with both the 40-gene panel and the expanded 79-gene (plus 1 chromosomal region) panel
- Data were integrated across the 2 panels, and yield estimates were weighted by the number of individuals sequenced for each gene

Results

- As of April 14, 2022, the program had analyzed sequences from 16,061 individuals (40-gene panel: n=8,230; expanded panel: n=7,831)
- Overall, 64.8% of individuals carried potentially clinically relevant variants in obesity-related genes or the chromosomal region analyzed (Figure 2)

Figure 2. Weighted sequencing yield estimates of individuals carrying clinically relevant variants evaluated in the Uncovering Rare Obesity® program (N=7,831).



- 37.7% of individuals had genetic variants that are either indicated for treatment in the United States with the MC4R agonist setmelanotide or that are currently being investigated for setmelanotide efficacy in clinical trials
- An additional 38.4% of individuals had variants that might support a diagnosis of genetically related obesity but were not indicated for setmelanotide treatment or being investigated for setmelanotide efficacy in clinical trials
- The remaining 23.8% of individuals did not have pathogenic variants or variants of uncertain significance

Conclusions

- Variants related to the MC4R pathway were identified in 64.8% of 16,061 individuals in this large cohort of individuals with early-onset, severe obesity tested through the Uncovering Rare Obesity® program
- Genetic testing can help inform diagnostics for individuals with variants related to obesity and subsequently guide therapeutic approach within this population
- Rare Obesity Advanced Diagnosis is a similar program assessing rare genetic diseases of obesity that is available in the European Union; more information is available at www.roadgenetic.unilabsweb.com

LEARN MORE ABOUT THE UNCONVERING RARE OBESITY® PROGRAM

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your new destination to order kits, view results, and access educational materials.

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Disclosures: Uncovering Rare Obesity is a registered trademark of Rhythm Pharmaceuticals, Inc. RN and PK are employees of and stockholders in Rhythm Pharmaceuticals, Inc. EB's institution receives payment from Rhythm Pharmaceuticals, Inc.

References: 1. Ayers et al. *J Clin Endocrinol Metab*. 2018;103:2601-2612. **2.** Clément et al. *Physiol Behav*. 2020;227:113134. **3.** Gregoric et al. *Front Endocrinol (Lausanne)*. 2021;12:689387. **4.** Huvenne et al. *Obes Facts*. 2016;9:158-173. **5.** Styne et al. *J Clin Endocrinol Metab*. 2017;102:709-757. **6.** van der Valk et al. *Obes Rev*. 2019;20:795-804. **7.** Zorn et al. *Mol Cell Pediatr*. 2020;7:15. **8.** Yang et al. *Nat Commun*. 2019;10:1718. **9.** Yazdi et al. *PeerJ*. 2015;3:e856. **10.** Uncovering Rare Obesity®. Updated July 2021. https://uncoveringrareobesity.com/. Accessed August 8, 2021.