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

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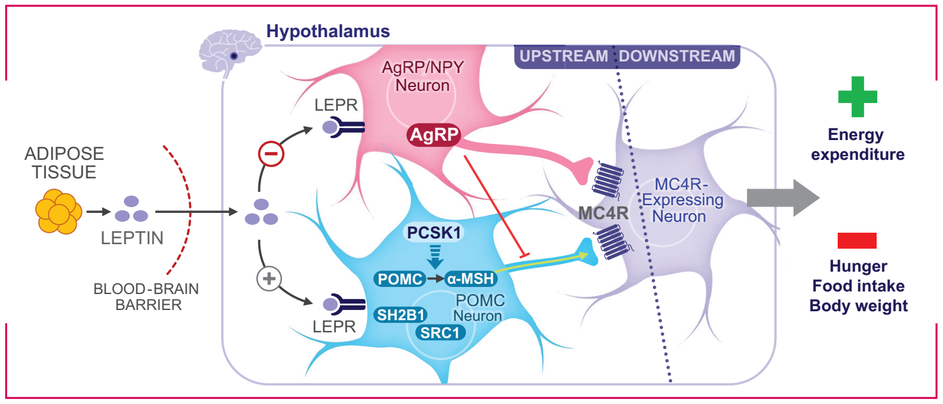
Summary

- **The prevalence of rare genetic diseases of obesity is likely underestimated because of a lack of routine testing in individuals with obesity and hyperphagia**
- **In a United States–based cohort of the Uncovering Rare Obesity® genetic testing program, 64.5% of individuals evaluated with early-onset, severe obesity carried ≥1 potentially clinically relevant variants**
- **Genetic testing in individuals with severe obesity and hyperphagia may be an important component of understanding the etiology of the clinical characteristics of rare genetic diseases of obesity and may improve the course of care for this population**

Introduction

- Rare genetic variants that disrupt key energy and hunger regulatory signaling pathways can lead to early-onset, severe obesity and hyperphagia, irrespective of environmental factors[1]
  - The melanocortin-4 receptor pathway is a key regulator of energy balance, and variants in one of the various genes in this pathway have been associated with obesity and hyperphagia (Figure 1)[1-4]
- Routine genetic testing can improve identification and diagnosis of patients with various rare genetic diseases of obesity and may inform specialized management strategies or eligibility for clinical trials[1,5-8]
- Rare genetic diseases of obesity are likely underdiagnosed, which may be because of low rates of genetic testing in individuals with obesity[2,9]
- The Uncovering Rare Obesity® testing program aims to enhance genetic testing access for patients with suspected rare genetic diseases of obesity in the United States[10]

Figure 1. Key genes involved in the MC4R pathway.[1,3,4,11-13]



AgRP, agouti-related peptide; 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 analyze the frequency of rare variants in selected genes in individuals with early-onset, severe obesity sequenced as part of the Uncovering Rare Obesity® program

Methods

Uncovering Rare Obesity® Program Design

- The testing program was launched in May 2019 with a panel of 40 genes associated with obesity; the panel was expanded in July 2021 to include 79 genes and 1 chromosomal region (Table)
- Individuals may be eligible to receive a no-charge genetic test and 2 genetic counseling sessions if they are located in the United States and its territories, and
  - Are ≤18 years of age with body mass index ≥97th percentile, or
  - Are ≥19 years of age with body mass index ≥40 kg/m^2 and have a history of childhood obesity, or
  - Have a select family member who was previously tested
- In the expanded program, individuals showing clinical symptoms of Bardet-Biedl syndrome were also eligible
- Blood or buccal samples submitted for testing are evaluated by a Clinical Laboratory Improvement Amendments–accredited laboratory

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*	*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*)	*CPE*
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.

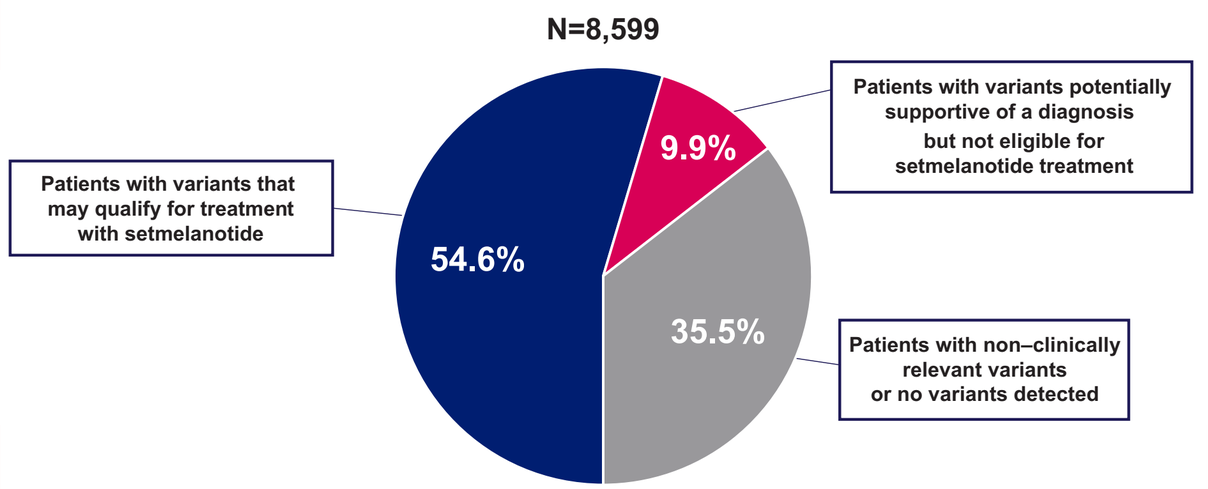
Frequency Analysis

- Sequencing data were analyzed from patients tested with 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

- Sequences from 8,599 individuals were analyzed
  - In total, 7,811 individuals were sequenced using the 40-gene panel, and 788 were sequenced using the expanded panel
- Overall, 64.5% of individuals carried potentially clinically relevant variants (Figure 2)
  - 54.6% of individuals had variants that may qualify them for commercial or investigational treatment with the melanocortin-4 receptor agonist setmelanotide
  - 9.9% of individuals had variants that may support a genetic diagnosis of obesity but were not eligible for setmelanotide treatment
- Of the total population, 2.7% of individuals carried pathogenic or likely pathogenic variants that also met the mode of inheritance criteria
  - Mode of inheritance criteria were defined as ≥2 alleles in autosomal recessive conditions or ≥1 allele in autosomal dominant conditions

Figure 2. Weighted sequencing yield estimates of individuals carrying potentially clinically relevant obesity-associated variants evaluated in the Uncovering Rare Obesity® program.



Conclusions

- In a large cohort of individuals with early-onset, severe obesity, 64.5% carried potentially clinically relevant variants
  - These estimates may change as additional data about the investigational genes and obesity become available
- Routine genetic testing in individuals with obesity and hyperphagia may be a useful tool for diagnosing rare genetic diseases of obesity

*Ilia Ichetovkin and Ida H. Moeller were employees of Rhythm Pharmaceuticals, Inc., at the time of abstract submission.

Uncovering Rare Obesity is a registered trademark of Rhythm Pharmaceuticals, Inc.

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