Uncovering Rare Obesity Genetic Testing Program: Utility of Genetic Testing in Adults With Obesity

Patrick Kleyn,[1] Patrick Sleiman,[1] Elliot Bromberg,[2] Rick Norton[1]

[1]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [2]Beghou Consulting Inc., Rockville, MD, USA

Presenting Author:
Patrick Kleyn
pkleyn@rhythmtx.com

Summary

- **Among patients with obesity tested through the Uncovering Rare Obesity® program, 39.7% of adults had a rare genetic variant associated with the melanocortin-4 receptor (MC4R) pathway**
- **Genetic testing may promote improved care in adults with severe obesity who have not received a prior diagnosis of a rare genetic disease of obesity associated with the MC4R pathway[1-5]**

Introduction

- Rare MC4R pathway diseases associated with obesity can arise because of variants in one of multiple genes involved in the pathway, which regulates hunger and energy expenditure[5,6]
  - Rare variants in this pathway are associated with early-onset, severe obesity and hyperphagia (an insatiable, pathologic hunger)[5,6]
- Genetic testing for obesity-associated variants is recommended in patients with early-onset (ie, before 5 years of age), severe obesity and clinical features of genetic obesity, including hyperphagia or a family history of severe obesity[1]
  - Genetic testing is not commonly recommended in treatment guidelines for adults with obesity[7]
- Genetic testing can help identify, diagnose, and inform specialized management strategies or clinical trial eligibility for patients with suspected rare MC4R pathway diseases of obesity[1-5]
- The Uncovering Rare Obesity® testing program aims to provide genetic testing access for all patients with suspected rare variants associated with MC4R pathway diseases, regardless of age[8]

Objective

- To describe the frequency of rare MC4R pathway variants in adult patients tested as part of the Uncovering Rare Obesity® program

Methods

Uncovering Rare Obesity® program

- Launched in May of 2019, the testing program provides no-charge genetic testing and 2 genetic counseling sessions to eligible patients in the United States and Canada
- Individuals may be eligible for the program if they
  - Are ≤18 years of age with body mass index (BMI) ≥97th percentile, or
  - Are ≥19 years of age with BMI ≥40 kg/m^2 and have a history of childhood obesity, or
  - Are an immediate family member of select, previously tested patients, or
  - Demonstrate clinical symptoms suggestive of Bardet-Biedl syndrome (BBS)
- As of July 2021, the testing panel includes 79 genes and 1 chromosomal region
- Tests are run by a Clinical Laboratory Improvement Amendments–accredited clinical laboratory, with results available ~3 weeks following sample receipt
- Full details about the program can be found at www.UncoveringRareObesity.com
- Variants were classified according to the American College of Medical Genetics framework[9]

Analysis in the adult cohort

- In this analysis, we evaluated the proportion of patients ≥18 years old compared with those <18 years old with rare, potentially pathogenic variants in 57 MC4R pathway genes; the evaluated variants were
  - Biallelic variants in *POMC*, *PCSK1*, or *LEPR*; *NCOA1*; or *SH2B1*
  - Biallelic variants in 22 BBS-associated genes
  - Genes eligible for enrollment in the Phase 3 EMANATE clinical trial[10] (heterozygous variants in *POMC*, *PCSK1*, or *LEPR*; *NCOA1*; and *SH2B1*)
    - Variants in *POMC*, *PCSK1*, and *LEPR* were included if classified as pathogenic (P), likely pathogenic (LP), or suspected pathogenic (VUS-SP)
    - Variants in *SH2B1* were included if classified as P/LP or variants of uncertain significance; no *NCOA1* variants were classified as P/LP because the gene is classified as of uncertain significance clinically[11]
  - Thirty genes eligible for enrollment in the Phase 2 DAYBREAK clinical trial[12] (ie, *CPE*, *CREBBP*, *DNMT3A*, *HTR2C*, *ISL1*, *KSR2*, *LEP*, *MAGEL2*, *MC3R*, *MECP2*, *MRAP2*, *NRP1-2*, *PHIP*, *PLXNA1-4*, *RPGRIP1L*, *SEMA3A-G*, *SIM1*, *TBX3*, *TRPC5*, *TUB*)
    - Variants in DAYBREAK-relevant genes were included if classified as P/LP or VUS; results for this cohort are reported as a raw yield rather than being divided into individual subcategories

Results

- As of May 2022, 9,680 patients were sequenced in the Uncovering Rare Obesity® program, of which 3,160 were aged ≥18 years
- Overall, 1,256 adults (39.73%) carried variants in ≥1 of the 57 genes analyzed (Figure)
- Variant yields for genes relevant to the EMANATE and DAYBREAK studies are shown in the Table
- Results in the adult cohort were generally consistent with pediatric patients

Figure. Proportion of patients with identified variants in **(A)** adult patients and **(B)** pediatric patients sequenced in the Uncovering Rare Obesity® program.

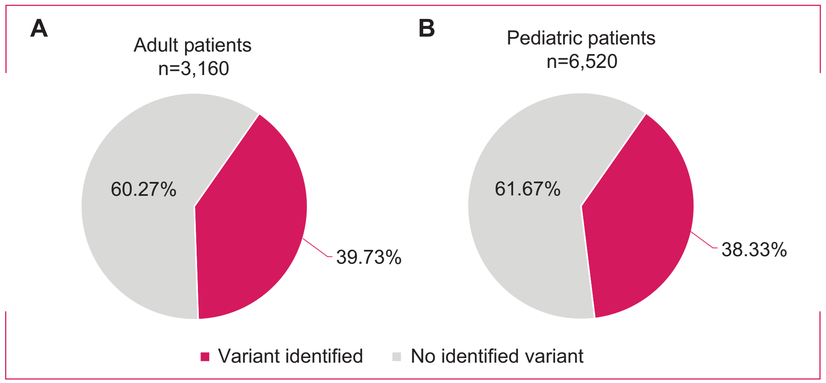

Table. EMANATE and DAYBREAK Eligible Gene Variants in the Uncovering Rare Obesity Program®

	P/LP, n (%)	VUS-SP,[a] n (%)	VUS, n (%)	Raw yield,n (%)
Adult patients (n=3,160)				
EMANATE-relevant genes				
Heterozygous *POMC*/*PCSK1*	8 (0.25)	2 (0.06)	–	
Heterozygous *LEPR*	3 (0.09)	2 (0.06)	–	
NCOA1[b]	–	–	66 (2.09)	
SH2B1	2 (0.06)	–	68 (2.15)	
DAYBREAK-relevant genes[c]	NA	NA	NA	1,080 (34.18)
Total	25 (0.79)	4 (0.13)	147 (4.65)	
Pediatric patients (n=6,520)				
EMANATE-relevant genes				
Heterozygous *POMC*/*PCSK1*	11 (0.17)	5 (0.08)	NA	
Heterozygous *LEPR*	9 (0.14)	6 (0.09)	NA	
NCOA1[b]	–	–	131 (2.01)	
SH2B1	20 (0.31)	–	144 (2.21)	
DAYBREAK-relevant genes[c]	NA	NA	NA	2,092 (32.09)
Total	62 (0.95)	11 (0.17)	331 (5.08)	

"–" indicates not applicable. [a]No *NCOA1* variants are deemed P/LP because of the gene being classified as a gene of uncertain significance clinically.[11] [b]Only heterozygous *POMC*/*PCSK1* and *LEPR* variants were classified as VUS-SP. [c]Predicted pathogenicity not evaluated for DAYBREAK-relevant genes.
NA, not available; P/LP, pathogenic or likely pathogenic; VUS, variant of uncertain significance; VUS-SP, VUS-suspected pathogenic.

Conclusions

- In this update on data from patients sequenced in the Uncovering Rare Obesity® program, a substantial proportion of adult patients (39.7%) carried rare genetic variants associated with the MC4R pathway, with 0.8% of adults carrying a pathogenic or likely pathogenic variant
- Genetic testing was more frequently done in pediatric patients compared with adults, but the proportion of patients in each age category with P/LP, VUS-SP, or VUS variants was similar
- Genetic testing in adults is an important diagnostic step to consider because it may promote improved care in adults with severe obesity who have not received a prior diagnosis of a rare genetic disease of obesity associated with the MC4R pathway

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