Frequency of MC4R Pathway Variants in a Large US Cohort of Patients With Severe Obesity

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521

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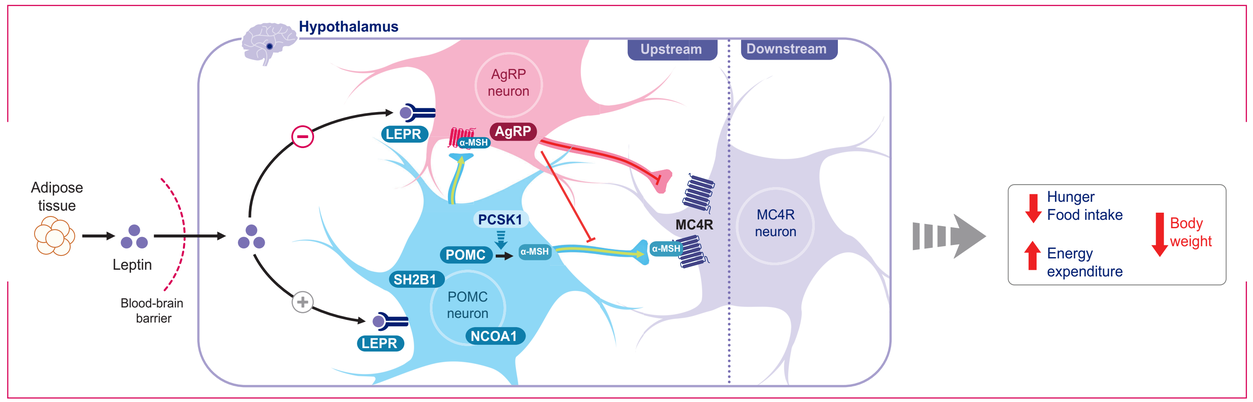
Summary

- **Overall, in our large US-based cohort of individuals with severe obesity, 8.2% carried a potentially clinically relevant variant in the melanocortin-4 receptor (MC4R) pathway genes *POMC*, *PCSK1*, *LEPR*, *SH2B1*, and *NCOA1***
- **Understanding the role of these variants in the pathophysiology of obesity may improve the clinical care of individuals living with rare genetic diseases of obesity**

Introduction

- MC4R tone in the central nervous system is important for regulation of hunger and energy balance[1-4]
- In the hypothalamus, leptin binds the leptin receptor (LEPR) on proopiomelanocortin (POMC) neurons
  - The protein encoded by *PCSK1* cleaves POMC to form α–melanocyte-stimulating hormone, which activates the MC4R receptor, leading to decreased hunger and increased energy expenditure (Figure)[2-4]
- Rare genetic variants that disrupt key energy and hunger regulatory signaling pathways, such as the hypothalamic MC4R pathway, can lead to early-onset, severe obesity and hyperphagia, irrespective of environmental factors
  - Variants within genes comprising this pathway, including *POMC*, *PCSK1*, *LEPR*, *SH2B1*, and *NCOA1* (also known as *SRC1*), have a well-established association with severe obesity[2,3,5]
- A clear understanding of the true prevalence of these rare variants is needed

Figure. Key genes involved in the MC4R pathway.[2-5]



AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; α-MSH, α–melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, SH2B adaptor protein 1; NCOA1, nuclear receptor coactivator 1.

Objective

- To analyze the frequency of rare variants in 5 selected genes of the MC4R pathway in individuals with severe obesity sequenced across multiple initiatives, including the Uncovering Rare Obesity® program

Methods

- Through January 25, 2022, we sequenced *POMC*, *PCSK1*, *LEPR*, *SH2B1*, and *NCOA1* exons and intron–exon boundaries in 45,866 US individuals with severe obesity (Table 1)
  - <18 years old: BMI ≥97th percentile
  - ≥18 years old: BMI ≥40 kg/m^2
  - This analysis included 2,831 individuals sequenced globally and 43,035 individuals sequenced within the United States
  - This cohort comprised individuals sequenced across multiple initiatives, including the Uncovering Rare Obesity® diagnostic testing program, the Genetic Obesity Identification (GO-ID) study, and several biobank collaborations, including 10,604 patients from the Children's Hospital of Philadelphia (CHOP) biobank
- We assessed rare variants classified as pathogenic/likely pathogenic (P/LP) or as a variant of uncertain significance (VUS) according to the American College of Medical Genetics (ACMG) criteria
- We also evaluated 1 *PCSK1* variant, p.N221D, a "Risk" variant considered too prevalent to be classified as P/LP or VUS by ACMG criteria, but that has been associated with obesity

Results

- 8.2% of individuals with severe obesity carried ≥1 rare variant in ≥1 of the 5 studied genes, including 0.3% who carried a P/LP variant and 7.9% who carried a VUS variant
  - An additional 4.8% carried the *PCSK1* p.N221D variant (Table)
- In the total population, 7.4% of individuals carried only 1 variant, while 0.8% carried >1 variant in ≥1 genes
- The gene with the highest variant frequency was *POMC*, followed by *LEPR*, *SH2B1*, *PCSK1*, and *NCOA1* (Table)
- Within the context of a community-focused clinical diagnostic tool, Uncovering Rare Obesity® results demonstrated a higher frequency of P/LP (0.6%), VUS (10.0%), and *PCSK1* p.N221D (6.7%) genotypes

Table. Variant Frequencies

	Total cohort (N=45,866)			Uncovering Rare Obesity® only (N=13,857)		
Gene	**P/LP**	**VUS**	**Risk[d]**	**P/LP**	**VUS**	**Risk[d]**
Total[a]	0.30%	7.87%	4.77%	0.65%	9.96%	6.65%
POMC	0.04%	2.00%		0.08%	2.14%	
PCSK1	0.06%	1.41%	4.77%	0.12%	1.70%	6.65%
LEPR	0.07%	1.73%		0.15%	2.06%	
NCOA1	NA[b]	1.33%		NA[b]	2.12%	
SH2B1	0.13%[c]	1.40%		0.30%[c]	1.94%	

[a]Removes individuals present in multiple genes/variant categories. Prioritized for P/LP/>VUS>Risk. [b]No *NCOA1* variants are deemed P/LP because of the gene being classified as a "gene of uncertain significance" clinically. [c]All P/LP *SH2B1* variants are 16p11.2 deletions, including deletion of *SH2B1*. [d]The only variant classified as Risk is p.N221D in *PCSK1*. NA, not applicable; P/LP, pathogenic/likely pathogenic; VUS, variant of uncertain significance.

Conclusions

- Overall, in our large cohort of individuals with severe obesity, ~8% of individuals carried ≥1 potentially clinically relevant rare variants in one of the 5 MC4R pathway genes (*POMC*, *PCSK1*, *LEPR*, *SH2B1*, or *NCOA1*)
  - There was a slightly higher rate of variant frequency in individuals sequenced through the course of clinical care as part of the Uncovering Rare Obesity® diagnostic genetic testing program than the overall cohort
- The majority of observed variants were of uncertain pathologic significance
  - Studies characterizing VUS and their role in genetic obesity are needed to better understand the etiology of rare MC4R pathway diseases
- Treatment with the MC4R agonist setmelanotide is being studied in the Phase 3 EMANATE clinical trial (NCT05093634) to determine potential weight management benefit in patients with obesity and rare variants impacting the MC4R pathway (ie, heterozygous variants in *POMC*, *PCSK1*, and *LEPR*; variants in *SH2B1*; variants in *NCOA1*)
- Understanding the role of these variants in the pathophysiology of obesity may improve the clinical care of individuals living with these rare genetic diseases of obesity

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