# Identification of MC4R Pathway Variants in Individuals With Extreme Obesity

T-P-3429

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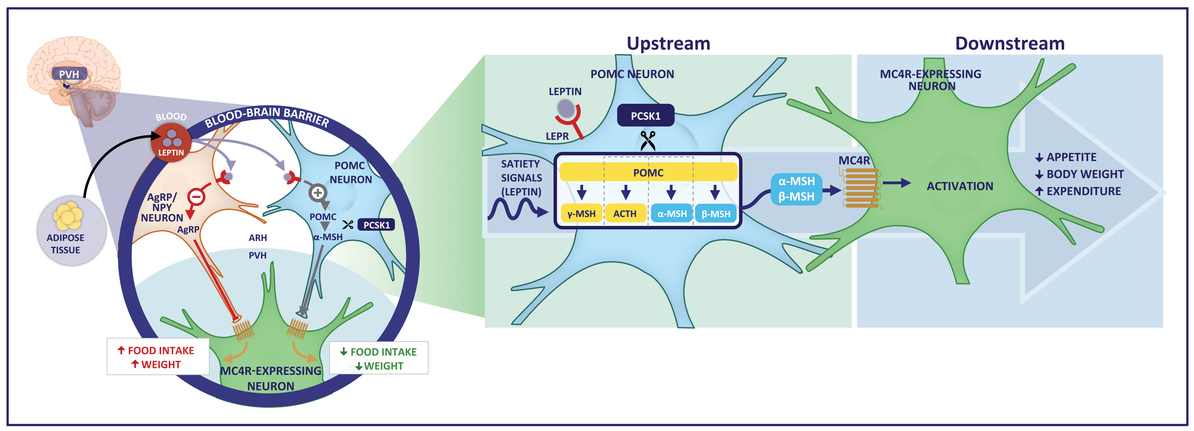
## Summary

- **On the basis of a literature and computational search, the analyses identify a collection of *POMC*, *PCSK1*, and *LEPR* gene variants predicted to be associated with dysfunction within the melanocortin-4 receptor (MC4R) pathway that may cause a rare genetic disorder of obesity**
- **Sequencing data demonstrate that ~0.9% of obese individuals are likely to have a rare genetic disorder of obesity due to a homozygous loss-of-function (LOF) mutation in *POMC*, *PCSK1*, or *LEPR***
- **The identification of these gene variants defines a patient population in which treatment designed to compensate for low MC4R activity is hypothesized to reduce insatiable hunger and obesity**

## Background

- The hypothalamic MC4R pathway, which is a component of the central melanocortin pathway, regulates energy balance and appetite (Figure 1)[1,2]
- Genetic mutations in components comprising the MC4R pathway may cause early-onset insatiable hunger (hyperphagia) and severe obesity[1]
  - Rare genetic disorders of obesity characterized by MC4R pathway dysfunction include *LEP*, *LEPR*, *POMC*, *PCSK1*, and *MC4R* genetic deficiencies; Bardet-Biedl syndrome; and Alström syndrome[1,3]
- Because the prevalence of these disorders of obesity may be underestimated,[4] the relevance of variants in genes within the MC4R pathway remains unknown, and studies are ongoing

**Figure 1.** The hypothalamic MC4R signaling pathway regulates appetite and energy balance, and mutations in this pathway can result in rare genetic disorders of obesity.[4,5]




AgRP, agouti-related protein; ARH, arcuate nucleus of the hypothalamus; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, pro-protein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; PVH, paraventricular nucleus of hypothalamus.

## Objectives

- To generate a compendium of variants within the *POMC*, *PCSK1*, and *LEPR* genes
- To identify individuals who have variants in genes within the MC4R pathway and are affected by rare genetic disorders of obesity

## Methods

- A list of LOF mutations in *POMC*, *PCSK1*, and *LEPR* was compiled from the published literature and supplemented with unpublished computationally predicted deleterious missense mutations (WuXi DeepCode score >0.9)[4]
- On the basis of confidence and likely impact, variants were bucketed into 2 groups[4]
  - Group 1: literature-validated variants and variants arising from high-impact mutations (nonsense, frameshift indel, and splice alterations)
  - Group 2: predicted LOF missense variants expected to have a high functional impact based on the DeepCODE algorithm, and absent or present at <0.1% in the Genome Aggregation Database (gnomAD)
- Individuals with severe early-onset obesity and hyperphagia were sequenced for *POMC*, *PCSK1*, and *LEPR*
  - Participants include 1886 individuals with biobanked DNA samples from 8 clinical obesity centers and 918 participants in the Genetic Obesity Identification genotyping prospective study (GO-ID; NCT02849977)

**Table 1.** GO-ID Inclusion Criteria for the First Cohort[6]

| **BMI and hyperphagia cohort, >2 years of age** | |
|---|---|
| • Adult: BMI >40 kg/m$^2$ | • Hyperphagia |
| • Child: BMI >1.4 × 95th percentile | • Evidence of pediatric onset |

BMI, body mass index; GO-ID, Genetic Obesity Identification.

## Results

- 6863 known or suspected LOF variants were identified

**315**
High-confidence LOF variants in *POMC*, *PCSK1*, and *LEPR* from the published literature and in genetic databases (Group 1)

**6548**
Computationally predicted deleterious missense variants (419 observed at <0.1% prevalence in gnomAD) (Group 2)

From sequenced biobank and GO-ID first cohort samples

- **6.2%** of individuals with early-onset severe obesity and hyperphagia carried ≥1 LOF allele
- **1.5%** carried a Group 1 (high-impact and/or published) LOF allele
- **4.7%** carried a Group 2 (computationally defined) LOF allele
- **~0.9%** were homozygous for either a Group 1 or Group 2 LOF allele (24 patients [n=2804]; Table 2)

- 5 individuals carried mutations in 2 of the 3 MC4R pathway genes assessed; previous analyses have demonstrated an association between carrying multiple MC4R pathway mutations and increased body mass index[4]

**Table 2.** Number of Homozygous LOF Variants Found in the Sequenced Biobank and GO-ID First Cohort Samples From Obese Individuals

| Sequenced sample study | Group 1 homozygotes | Group 2 homozygotes |
|---|---|---|
| GO-ID first cohort, n/N (%) | 6/918 (0.65%) | 11/918 (1.20%) |
| Biobank, n/N (%) | 6/1886 (0.32%) | 1/1886 (0.05%) |
| Total, n/N (%) | 12/2804 (0.43%) | 12/2804 (0.43%) |
| *POMC*, n | 2 | 2 |
| *PCSK1*, n | 4 | 4 |
| *LEPR*, n | 6 | 6 |

GO-ID, Genetic Obesity Identification.

**Acknowledgments:** This study was sponsored by Rhythm Pharmaceuticals, Inc. Assistance with preparation of this poster was provided by Scott Baver, Rhythm Pharmaceuticals, Inc., and Ali Rosenberg, PhD, and David Boffa, ELS, MedThink SciCom, and funded by Rhythm Pharmaceuticals Inc.

**References: 1.** da Fonseca ACP et al. *J Diabetes Complications*. 2017;31:1549-1561. **2.** Shen W-J et al. *Biochim Biophys Acta*. 2017;1863:2477-2485. **3.** Huvenne H et al. *Obes Facts*. 2016;9:158-173. **4.** Ayers KL et al. *J Clin Endocrinol Metab*. 2018;103:2601-2612. **5.** Yazdi FT et al. *PeerJ*. 2015;3:e856. **6.** Shoemaker et al. Overcoming Obesity 2018. September 26-30, 2018; Washington, DC.