# Rare Genetic MC4R Pathway Diseases

Rhythm PHARMACEUTICALS

*Rhythm is dedicated to transforming the lives of patients and their families living with rare neuroendocrine diseases*

## Not All Obesity Is the Same

Causes of obesity are multifactorial, representing a wide range of etiologies and phenotypes influencing disease progression.[1,2] Understanding the underlying causes of obesity is essential for early diagnosis and optimal disease management, particularly in the case of unique obesities such as those caused by rare MC4R pathway impairment.[2-6]

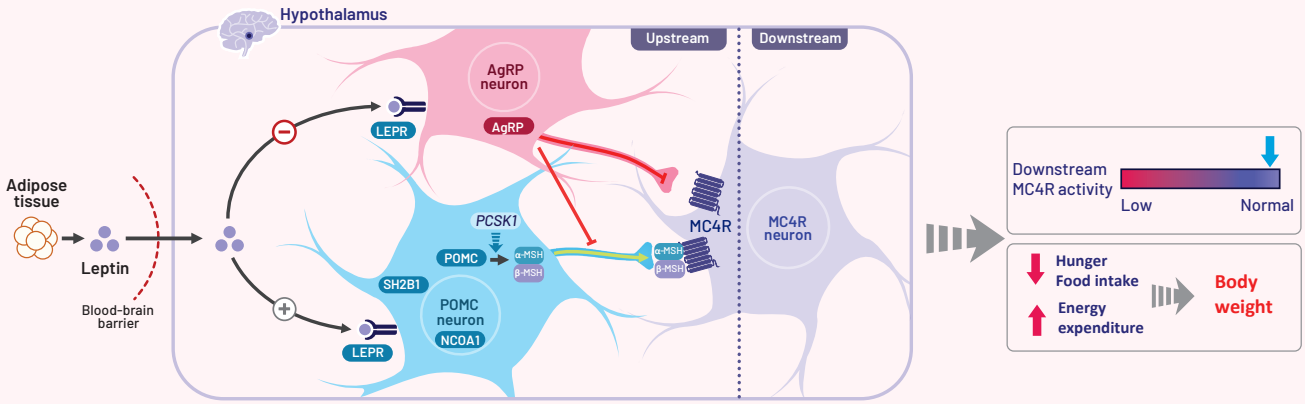
### Differentiating Rare Genetic MC4R Pathway–Associated Obesity From General Obesity

| General Obesity[2-5,7] | | Obesity Associated With Rare Genetic MC4R Pathway Impairment[2,4-11] |
|---|---|---|
| Influenced by common variants in multiple genes and/or environmental factors | Etiology | Caused by rare genetic variants in a single gene affecting the MC4R pathway |
| Weight gain–promoting medications, sleep disruption, and stress are associated with worsening of obesity | Contributing factors | Condition is inherited |
| Any age | Age of onset | As early as a few months of age; often appears during early childhood |
| Weight/BMI | Diagnosis | Distinct clinical features, genetic testing |
| Hyperphagia is not a hallmark | Hyperphagia | Hyperphagia is a hallmark |

## Understanding Rare Genetic MC4R Pathway Diseases

The MC4R signaling pathway controls hunger, satiety, and energy expenditure, which in turn regulates body weight.[1,3,4,6,8,11-13]

### The MC4R Pathway




Impairment of the hypothalamic MC4R pathway due to genetic variants often results in rare MC4R pathway diseases, which present with 2 key clinical characteristics: hyperphagia and early-onset obesity[1,2,4,5,7,11,14]

### Key Clinical Characteristics of Rare Genetic MC4R Pathway Diseases

#### Hyperphagia[2,14]

Pathologic, insatiable hunger and impaired satiety differentiated from other types of overeating by its severity and persistence

#### Early-Onset, Severe Obesity[3-5,7,9]

Severe obesity is defined as BMI ≥120% of the 95th percentile and usually occurs before the age of 5 years

# Rare Genetic MC4R Disease Education Handout

## Hyperphagia in Rare MC4R Pathway Diseases[2,4,5,14-16]

### Hyperphagia is characterized by

- Persistent preoccupation with food
- Prolonged time to satiation and shortened duration of satiety
- Heightened and prolonged feelings of hunger
- Specific abnormal behaviors

### Behaviors range in severity and may include

- Eating extremely quickly
- Waking up at night for food
- Eating more than optimal quantities of food
- Distress if food is unavailable
  - Children may exhibit tantrums or persistent negotiation/demand for food
  - Adults may experience emotional effects including sadness, frustration, irritability, anxiety, and/or guilt
- Abnormal food-seeking behaviors such as hiding, stealing, or sneaking food
- Eating excessively; not to be confused with binge eating

## Common Clinical Presentations of Rare Genetic MC4R Pathway Diseases

| | Monogenic Obesity | | | | Syndromic Obesity |
|---|---|---|---|---|---|
| | POMC deficiency[1,3-9,13,18] | LEPR deficiency[1,3-9,13,18] | SRC1 (NCOA1) deficiency[4,5,19] | SH2B1 deficiency[1,4,5,7,13] | Bardet-Biedl syndrome[4-7,9-11] |
| US prevalence[17,*] | 100-500 individuals | 500-2,000 individuals | 20,000 individuals | 23,000 individuals | 4,000-5,000 individuals |
| Hyperphagia | ✓ | ✓ | ✓ | ✓ | ✓ |
| Early-onset obesity | ✓ | ✓ | ✓ | ✓ | ✓ |
| Endocrine abnormalities | ✓ | ✓ | ✓ | ✓ | ✓ |
| Growth abnormalities | ✓ | ✓ | | ✓ | |
| Additional features | Light pigmentation/ red hair† | Frequent bacterial infections due to defective T-cell immunity, hypogonadism | Fractures from minor incidents, liver fibrosis, insulin resistance or diabetes | Delayed speech and language development | Visual impairment, renal impairment, hypogonadism, cognitive disabilities, polydactyly |
| Genetic testing[3,5-7,9,10] | Genetic testing is **necessary** for the diagnosis of genetically identifiable rare MC4R pathway diseases | | | | Genetic testing **can aid** in diagnosis of clinically identifiable syndromic rare MC4R pathway diseases |

*Estimated prevalence of US patients based on company estimates. Calculations rely on internal and proprietary sequencing data and current estimated responder rates for therapy. Estimations are based on a US population of 327 million, of which 1.7% have early-onset, severe obesity.[20] †Light pigmentation and red hair may be present in only the subset of individuals with POMC deficiency.

**If you think your patient may have obesity due to a rare genetic variant and would like more information on diagnosing and genetic testing, please visit UncoveringRareObesity.com**

**Abbreviations:** α-MSH, α-melanocyte-stimulating hormone; AgRP, agouti-related peptide; BMI, body mass index; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; NCOA1, nuclear receptor coactivator 1; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, SH2B adaptor protein 1; SRC1, steroid receptor coactivator 1.

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