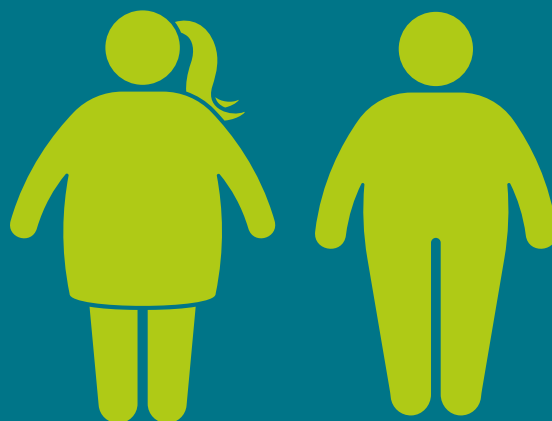


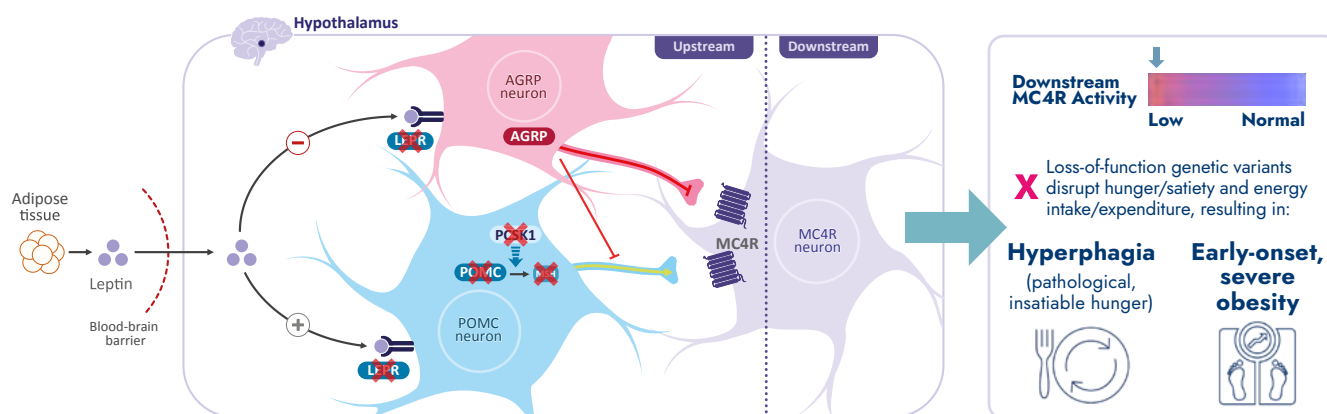
# Leptin receptor deficiency and proopiomelanocortin deficiency

Leptin receptor (LEPR) deficiency and proopiomelanocortin (POMC) deficiency are caused by rare genetic variants within the melanocortin-4 receptor (MC4R) pathway - a key pathway responsible for regulating hunger.<sup>1-3</sup>

They are autosomal recessive diseases caused by variants of the *LEPR* or *POMC* genes.<sup>1</sup>



## Impaired MC4R pathway<sup>1-3</sup>



### Abbreviations:

**AGRP**, agouti-related protein; **LEPR**, leptin receptor; **MC4R**, melanocortin-4 receptor; **MSH**, melanocyte-stimulating hormone; **PCSK1**, proprotein convertase subtilisin/kexin type 1; **POMC**, proopiomelanocortin.

A link and QR code for Prescribing Information and Adverse Event reporting information can be found on page 4

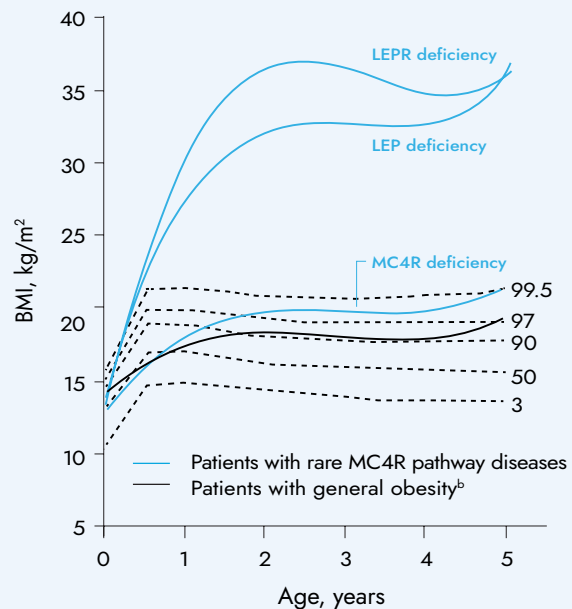
## Primary cardinal symptoms of LEPR and POMC deficiency

### Hyperphagia<sup>4</sup>

Characteristics and behaviours include:

-  Heightened and prolonged hunger
-  Longer time to reach satiety
-  Shorter duration of satiety
-  Severe preoccupation with food (hyperphagic drive)
-  Food-seeking behaviours (sneaking and stealing food)
-  Distress and inappropriate behavioural response if denied food

### Early-onset, severe obesity<sup>5,6,a</sup>

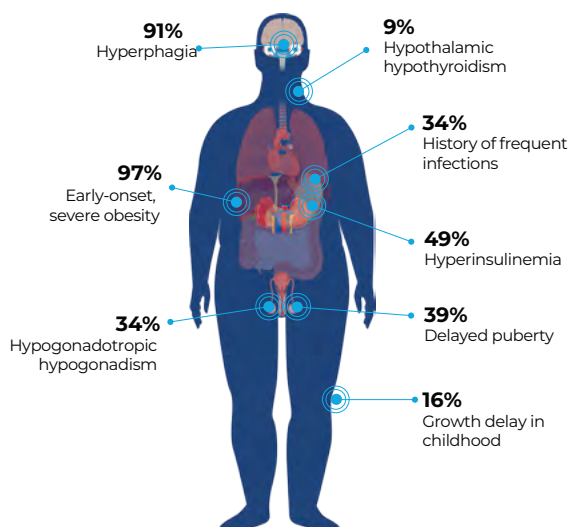


a) Defined as having a BMI  $\geq 120\%$  of the 95th percentile and onset before the age of 5.

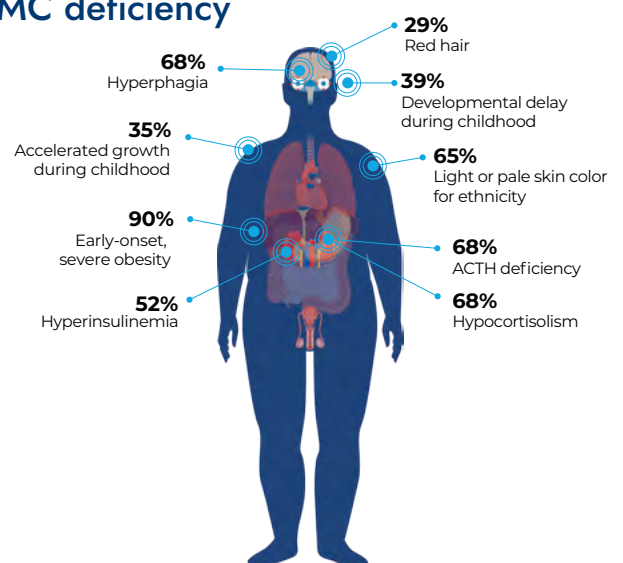
b) Patients with general obesity have a BMI  $>30$  kg/m<sup>2</sup> by age 14-16 years and do not have a variant in *LEPR*, *LEP*, or *MC4R*. Reprinted with permissions from Springer Nature from Kohlsdorf K, et al. *Int J Obes (Lond)*. 2018;42(9):1602–1609.

## Clinical characteristics of LEPR and POMC deficiency<sup>7,c</sup>

### LEPR deficiency



### POMC deficiency



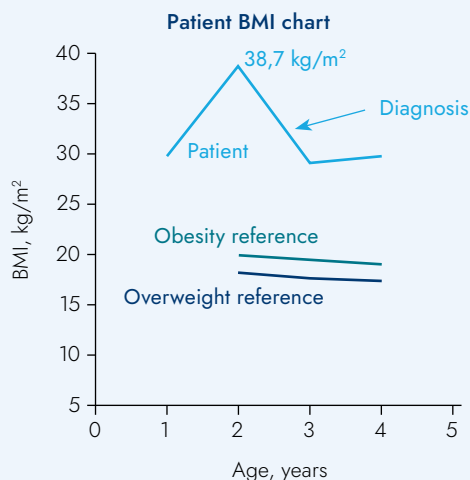
c) Percentages calculated as the number of cases with the characteristic divided by the total number of cases.

### Prevalence:

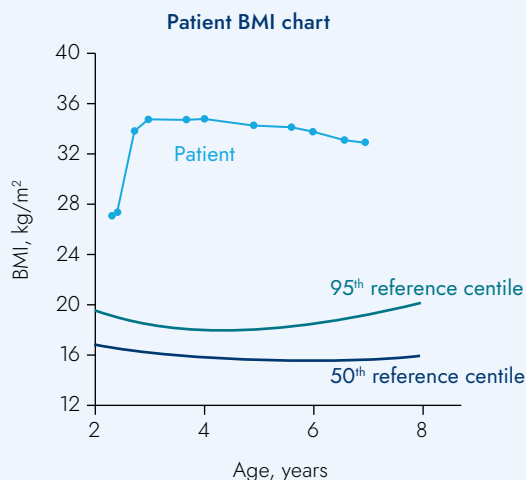
**LEPR:** 1.34 per million people<sup>8</sup>

**POMC/PCSK1:** fewer than 50 cases described worldwide for both indications<sup>9</sup>

## Example BMI chart: LEPR deficiency<sup>10</sup>



## Example BMI chart: POMC deficiency<sup>11</sup>



## How are LEPR and POMC deficiency diagnosed?

Diagnosis of LEPR and POMC deficiency may be suspected on the basis of clinical manifestations and is confirmed by genetic testing.<sup>10,12</sup>



### Paediatric patients

Genetic testing is recommended in paediatric patients with:<sup>4,10,12</sup>

- Early-onset, severe obesity
- Family history of severe obesity
- Features of syndromic obesity
- History of food-seeking behaviours
- Hyperphagia
- Neurodevelopmental abnormalities



### Adult patients

Characteristics of patients diagnosed in adulthood include:<sup>12-14</sup>

- Endocrine abnormalities
- History of early-onset, severe obesity
- Hyperphagia from early age
- Resistant to obesity management approaches
- Red hair

Clinical characteristics can vary on an individual basis and between gene variants. It's therefore important to:<sup>10,12,13</sup>

- Take a detailed clinical history
- Record family history, if available
- Monitor resistance to traditional obesity management strategies

### References:

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Adverse events should also be reported to Rhythm  
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Tel: +31 20 8546071.