

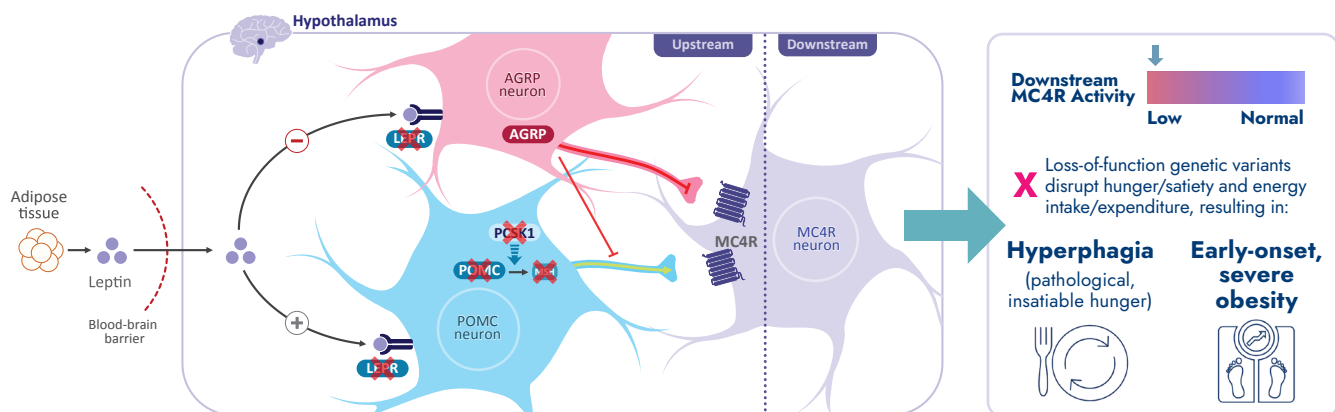
# Leptin receptor deficiency and proopiomelanocortin deficiency

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.

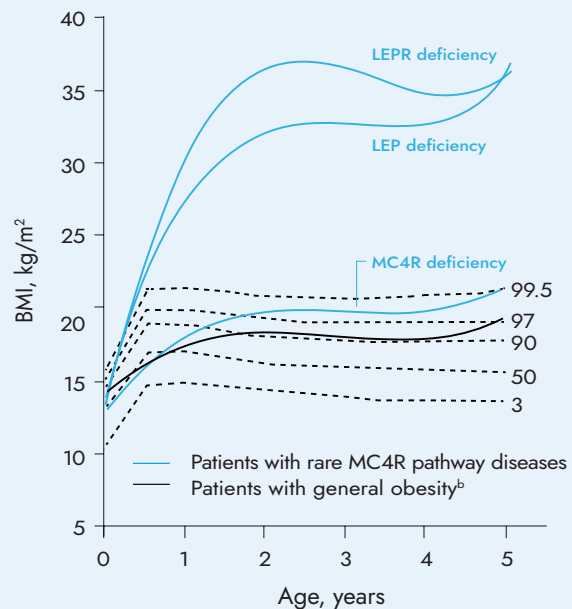
## Primary cardinal symptoms of LEPR and POMC deficiency

### 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>

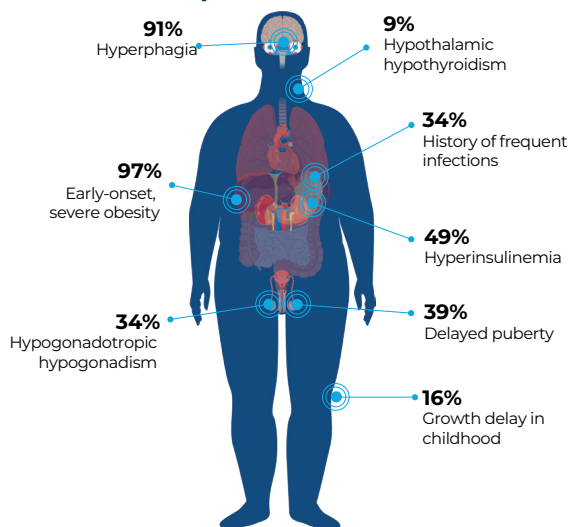


a) Defined as having a BMI  $\geq 120\%$  of the 95th percentile and onset before the age of 5.

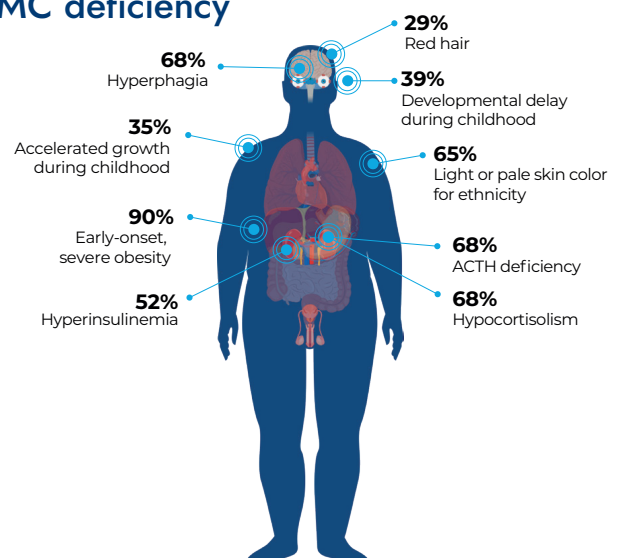
b) Patients with general obesity have a BMI  $>30$  kg/m<sup>2</sup> by age 14-16 years and do not have a variant in *LEPR*, *LEP*, or *MC4R*. Reprinted with permissions from Springer Nature from Kohlsdorf K, et al. *Int J Obes (Lond)*. 2018;42(9):1602–1609.

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

### LEPR deficiency



### POMC deficiency



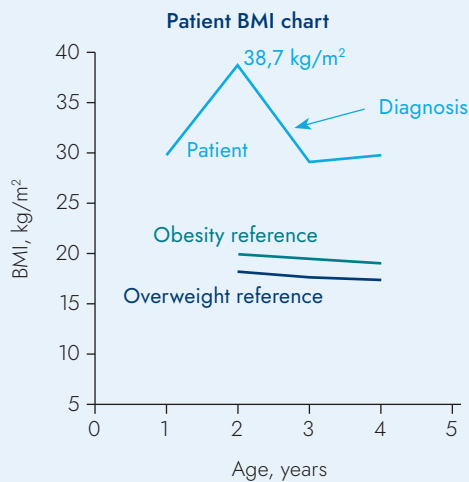
c) Percentages calculated as the number of cases with the characteristic divided by the total number of cases.

### Prevalence:

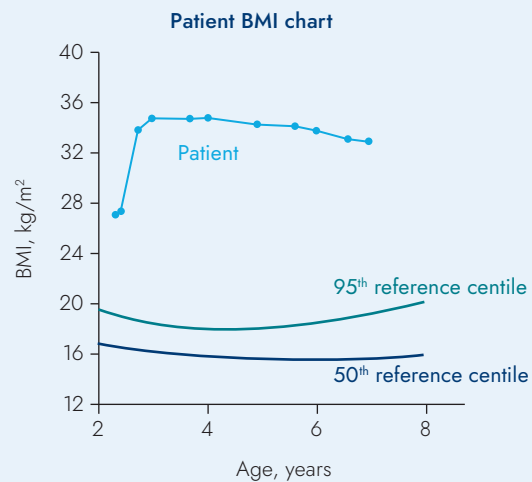
**LEPR:** 1.34 per million people<sup>8</sup>

**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:** 1. Huvenne H, et al. *Obes Facts*. 2016;9(3):158–173. 2. Yazdi FT, et al. *Peer J*. 2015;3:e856. 3. Loos RJF and Yeo GSH. *Nat Rev Genet*. 2022;23:120–13. 4. Heymsfield BS, et al. *Obesity (Silver Spring)*. 2014;22(suppl 1):S1–S17. 5. Kohlsdorf K, et al. *Int J Obes*. 2018;42:1602–1609. 6. Hampl SE, et al. *Pediatrics*. 2023;151(2):e2022060640. 7. Argente J, et al. Poster presented at: 21st European Congress of Endocrinology; May 18–21, 2019; Lyon, France. 8. Kleinendorst L, et al. *Eur J Endocrinol*. 2020;182(1):47–56. 9. Malhotra S, et al. *J Pediatr Genet*. 2021;10:194–204. 10. Kleinendorst L, et al. *BMJ Case Rep*. 2017. 11. Hilado MA and Randhawa SR, *J Pediatr Endocrinol Metab*. 2018;31(7): 815–819. 12. Styne DM, et al. *J Clin Endocrinol Metab*. 2017;102(3):709–757. 13. Zorn S, et al. *Mol Cell Pediatr*. 2020;7(15). 14. Gregoric N, et al. *Front Endocrinol (Lausanne)*. 2021;12:689387.

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