

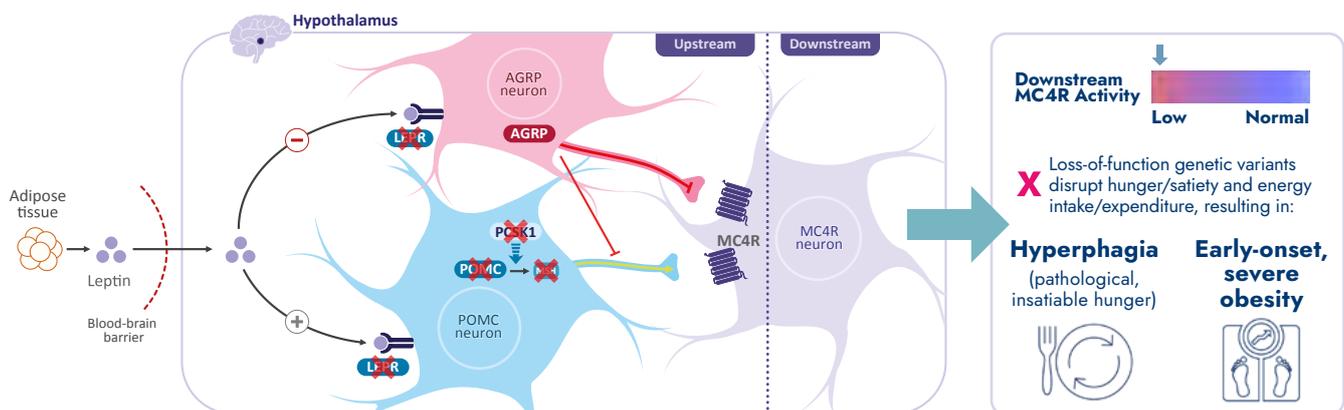
Leptin receptor deficiency and proopiomelanocortin deficiency

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.¹⁻³

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



Impaired MC4R pathway¹⁻³



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

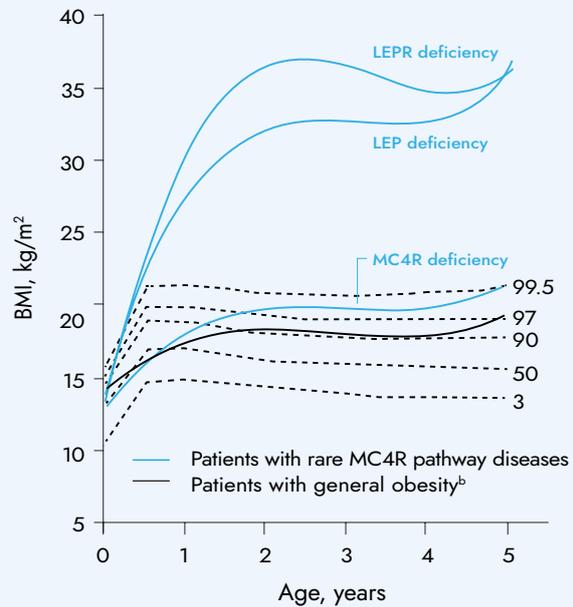
Primary cardinal symptoms of LEPR and POMC deficiency

Hyperphagia⁴

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^{5,6,a}

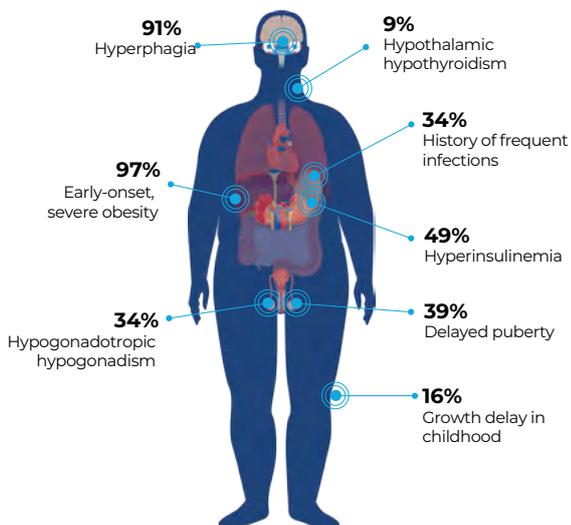


a) Defined as having a BMI $\geq 120\%$ of the 95th percentile and onset before the age of 5.

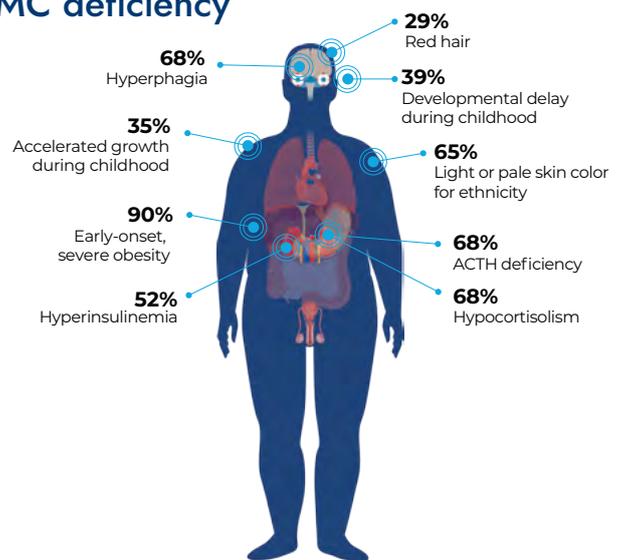
b) Patients with general obesity have a BMI >30 kg/m² by age 14-16 years and do not have a variant in *LEPR*, *LEP*, or *MC4R*. Reprinted with permissions from Springer Nature from Kohlsdorf K, et al. *Int J Obes (Lond)*. 2018;42(9):1602–1609.

Clinical characteristics of LEPR and POMC deficiency^{7,c}

LEPR deficiency



POMC deficiency



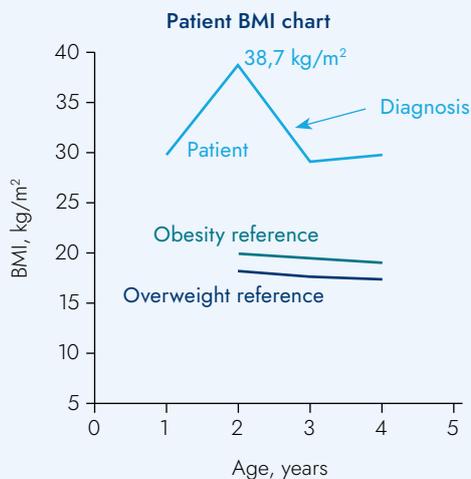
c) Percentages calculated as the number of cases with the characteristic divided by the total number of cases.

Prevalence:

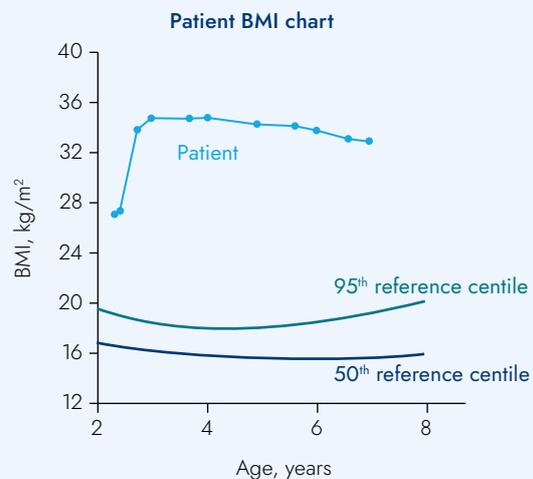
LEPR: 1.34 per million people⁸

POMC/PCSK1: fewer than 50 cases described worldwide for both indications⁹

Example BMI chart: LEPR deficiency¹⁰



Example BMI chart: POMC deficiency¹¹



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.^{10,12}



Paediatric patients

Genetic testing is recommended in paediatric patients with:^{4,10,12}

- 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:¹²⁻¹⁴

- 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:^{10,12,13}

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

References:

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for Prescribing Information for
IMCIVREE▼ (setmelanotide)

Adverse events should be reported.

Reporting forms and information can be found at:
yellowcard.mhra.gov.uk

Adverse events should also be reported to Rhythm
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